Technetium-99m-Tetrofosmin SPECT Imaging of Lung Masses: A Negative Study

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Technetium-99m-tetrofosmin has emerged as a new radiopharmaceutical for myocardial imaging, in competition with ^{201}Tl and ^{99m}Tc-MIBI. In this study, ^{99m}Tc-tetrofosmin was evaluated for its ability to detect malignant and benign lesions from single solid lung masses. **Methods:** Forty-nine patients with a single solid lung mass based on chest radiograph findings received ^{99m}Tc-tetrofosmin SPECT of the chest to evaluate the value of ^{99m}Tc-tetrofosmin SPECT for detecting malignant and benign lesions. **Results:** Only 61% of the lung malignancies were detected by ^{99m}Tc-tetrofosmin SPECT of the chest, including 53% of epidermoid carcinoma (ca), 67% of adeno ca, 75% of small-cell ca, 0% of undifferentiated large-cell ca and 100% of other lung malignancies. In addition, 50% of the benign lesions were detected by chest ^{99m}Tc-tetrofosmin SPECT. The probability of tetrofosmin uptake in the mass was not related to mass size. The diagnostic sensitivity, specificity and accuracy were 61%, 50% and 59%, respectively, for differentiating malignant and benign lesions when diagnosing a single solid lung mass. **Conclusion:** Technetium-99m-tetrofosmin SPECT of the chest is of little or no value for the detection of lung ca from single solid lung masses.

Key Words: single solid lung masses; technetium-99m-tetrofosmin; SPECT

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Lung cancer is a leading cause of death in many countries. The majority of lung carcinomas are readily classified into four main types: epidermoid carcinoma (ca), adeno ca, small-cell ca and undifferentiated large-cell ca. Overall, the 5-yr survival rate for lung carcinomas is very low (*1,2*).

The number of radiopharmaceuticals proposed for tumor imaging is in the hundreds, but only two simple cations, ^{67}Ga and ^{201}Tl, have achieved widespread acceptance in clinical imaging. From 1970 to 1985, a tremendous amount of data were accumulated on ^{67}Ga scanning for the clinical evaluation of oncology patients. Positive ^{67}Ga scans have been reported to occur in between 70% and 100% of patients with lung carcinoma (*3*). However, the use of ^{67}Ga as a tumor-imaging agent is limited due to its lack of tumor specificity and inability to detect tumors smaller than 2 cm in diameter (*4*). Salvatore et al. (*5*) and Cox et al. (*6*) first reported the use of ^{201}Tl for lung cancer diagnosis in 1979. The sensitivity and specificity of ^{201}Tl for the detection of lung cancers have been reported to be 71%–100% and 30%–100%, respectively (*7–9*). However, uptake of ^{201}Tl also has been reported in benign lesions (*10*).

Radiolabeled monoclonal antibodies (MAbs) directed against tumor antigens are potentially of great value for cancer diagnosis. Several MAbs have been used as alternatives to lung cancer associated antigens, but few have been used for scintigraphic detection (*11*). One of the main difficulties in using MAbs is the lack of specificity that they provide. Biggi et al. (*12*) showed that nonspecific uptake of antibody was possible in nonlung cancer patients. Recently, octreotide compounds and PET have been introduced to oncology (*13,14*). However, there are many theoretical and practical problems associated with their use in clinical imaging, such as high cost and lack of availability.

Technetium-99m-MIBI provides good imaging quality and is better suited for SPECT imaging than ^{67}Ga or ^{201}Tl. It is also more readily available and practical than monoclonal antibody imaging, octreotide compounds. Also, PET is available in kit form ready to be labeled with ^{99m}Tc. In addition, ^{99m}Tc-MIBI has been tested as a potential tumor imaging agent for the detection of malignancies from single solid lung masses. However, its diagnostic accuracy has varied (*15–17*). Kao et al. (*15*) reported poor sensitivity (65%) and specificity (57%) for ^{99m}Tc-MIBI.

Technetium-99m-tetrofosmin has been used as an alternative to ^{201}Tl and ^{99m}Tc-MIBI for myocardial imaging. Technetium-99m-tetrofosmin also has been used to detect thyroid (*18–20*), breast (*21–23*) and brain cancers (*24*). In this study, we evaluated ^{99m}Tc tetrofosmin for its ability to differentiate between malignant and benign lesions in single solid lung masses.

MATERIALS AND METHODS

Materials

Forty-nine patients (10 women, 39 men; ages 19–85 yr) with single solid lung masses in their lungs based on the findings of chest radiographs and without histories of chemo- or radiotherapy were included in this study. All of the patients received ^{99m}Tc-tetrofosmin (^{99m}Tc-tetrofosmin) SPECT of the chest to evaluate ^{99m}Tc-tetrofosmin SPECT for the detection of benign lesions and lung cancers of different cell types. Then, all of the patients had bronchoscopic biopsies or operations to prove the pathological diagnosis. There were 41 malignancies (including 19 epidermoid carcinoma (ca), 15 adeno ca, 4 small-cell ca, 1 undifferentiated large-cell ca, 1 sarcoma, 1 metastasis) and 8 benign lesions (Table 1). Ten normal control subjects also received ^{99m}Tc-tetrofosmin SPECT of the chest for comparison.

Image Analysis

All SPECT images were interpreted by at least two nuclear medicine physicians. SPECT results were classified as positive (focal abnormal accumulation at the tumor site) or negative (no abnormal focus of activity at the tumor site). The SPECT images of 10 cardiology patients without lung lesions were also interpreted for comparison (Fig. 1).

Technetium-99m-Tetrofosmin SPECT of the Chest

Tetrofosmin was obtained commercially. The labeling and quality-control procedures were performed according to the man-

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TABLE 1
Patient Data

Patient no.	Age (yr)	Sex	Location	^{99m}Tc-tetrofosmin SPECT	Pathology	Size (cm)
1	69	M	RLL	P	Epidermoid ca	1.5 × 2
2	62	M	RML	P	Epidermoid ca	2 × 3
3	71	M	RUL	P	Epidermoid ca	3 × 4
4	76	M	RML	P	Epidermoid ca	3 × 5
5	72	M	LLL	P	Epidermoid ca	4.5 × 5
6	72	M	RUL	P	Epidermoid ca	4 × 11
7	65	M	RUL	P	Epidermoid ca	5 × 5.5
8	76	M	RUL	P	Epidermoid ca	5 × 6
9	54	M	RUL	P	Epidermoid ca	6 × 8.5
10	71	M	RUL	P	Epidermoid ca	7.5 × 8.5
11	65	M	LUL	N	Epidermoid ca	1 × 1
12	85	M	LLL	N	Epidermoid ca	1.5 × 3
13	78	M	RUL	N	Epidermoid ca	2 × 3
14	65	F	LUL	N	Epidermoid ca	2.5 × 3
15	70	M	LLL	N	Epidermoid ca	2 × 4
16	65	M	RUL	N	Epidermoid ca	2.5 × 4
17	63	F	RUL	N	Epidermoid ca	3.5 × 5
18	70	M	RUL	N	Epidermoid ca	4 × 5
19	76	M	RUL	N	Epidermoid ca	4 × 6
20	81	M	LUL	P	Adenocarcinoma	2 × 3
21	76	M	RLL	P	Adenocarcinoma	3 × 3
22	77	F	RML	P	Adenocarcinoma	3 × 4
23	74	M	LUL	P	Adenocarcinoma	3 × 4
24	67	F	RML	P	Adenocarcinoma	3 × 7
25	83	F	LUL	P	Adenocarcinoma	4 × 5
26	64	F	RUL	P	Adenocarcinoma	4 × 8
27	77	F	LLL	P	Adenocarcinoma	5.5 × 6.5
28	69	M	RUL	P	Adenocarcinoma	6 × 7
29	78	M	RUL	P	Adenocarcinoma	8 × 15
30	65	M	LLL	N	Adenocarcinoma	1 × 1.5
31	73	M	RML	N	Adenocarcinoma	2 × 2
32	66	F	LUL	N	Adenocarcinoma	2 × 4
33	54	M	LLL	N	Adenocarcinoma	4.5 × 5
34	76	M	LLL	N	Adenocarcinoma	4 × 5
35	71	M	RML	P	Small-cell ca	3 × 7.5
36	65	M	LLL	P	Small-cell ca	4.5 × 5
37	63	M	LUL	P	Small-cell ca	5.5 × 5.5
38	71	M	RLL	N	Small-cell ca	3.5 × 5
39	66	M	RUL	N	Undiff. large-cell ca	2 × 3
40	63	M	LUL	P	Sarcoma	7 × 8
41	19	M	LUL	P	Lung metastasis of seminoma	3 × 3
42	63	M	LUL	P	Granulation tissue	3 × 4
43	58	M	LUL	P	Mucormycosis	3 × 5.5
44	73	F	RLL	P	Fungal abscess	5 × 10
45	67	M	RUL	P	Intrathoracic goiter	6 × 15
46	72	M	RLL	N	Organizing pneumonitis	2 × 3
47	21	M	RLL	N	Angiofollicular hyperplasia	4 × 3
48	67	M	LLL	N	Pneumonia	3 × 5
49	46	F	RUL	N	Hemothorax	4.5 × 1

ufacturer's instructions. The radiochemical purity of ^{99m}Tc-tetrofosmin used in this study was consistently higher than 90%.

Chest SPECT was performed 15–30 min after intravenous injection of 740 MBq (20 mCi) ^{99m}Tc-tetrofosmin. The patient was positioned supine on the imaging table with the chest strapped to prevent motion. The equipment consisted of a rotating, large field of view gamma camera fitted with a low-energy, high-resolution collimator. Sixty images were acquired for 20 sec each, during a 360° camera rotation. Each image was stored in a 64 × 64 pixel matrix. Reconstruction of the image was performed with attenuation correction, using Hanning filters. Transaxial slices were reoriented parallel to the base of the lungs, and sagittal and coronal reconstructions were then obtained.

RESULTS

The results showed that only 61% (25 of 41) of the lung malignancies were detected by ^{99m}Tc-tetrofosmin SPECT of the chest, including 53% (10 of 19) of the epidermoid ca (Fig. 2), 67% (10 of 15) of the adenocarcinoma, 75% (3 of 4) of the small-cell ca, 0% (0 of 1) of the undifferentiated large-cell ca and 100% (2 of 2) of the other lung malignancies. However, 50% (4 of 8) of the benign lesions (Fig. 3) were detected by ^{99m}Tc-tetrofosmin SPECT (Table 2). The diagnostic sensitivity, specificity and accuracy were 61%, 50% and 59%, respectively, for differentiating malignant and benign lesions from single solid lung masses (Table 3).

The minimum and maximum sizes of ca that could be

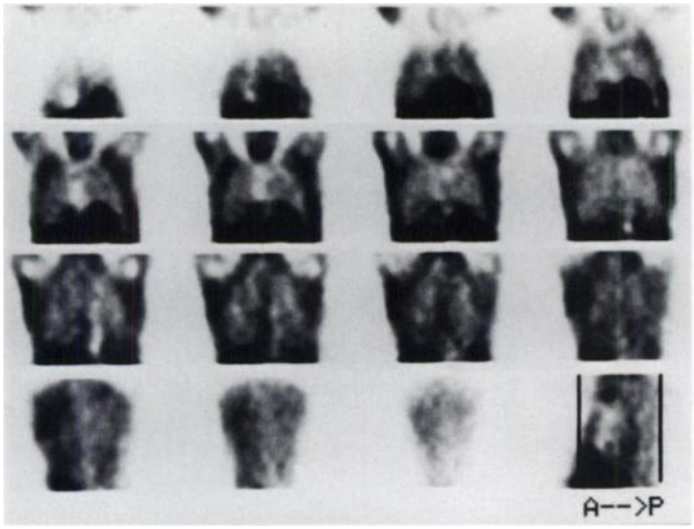

FIGURE 1. In a 70-yr-old male control subject, ^{99m}Tc-tetrofosmin SPECT (coronal sections) revealed only normal tetrofosmin uptake in the heart and the liver. No definite evidence of abnormal uptake in the lungs is demonstrated.

detected were 1.5 × 2 cm and 8 × 15 cm, respectively. The minimum and maximum sizes of ca that escaped detection were 1 × 1 cm and 4 × 6 cm, respectively. In conclusion, the probability of positive tetrofosmin uptake in the mass was not related to mass size (Table 1).

DISCUSSION

There has been a continuous effort to find a tracer for lung ca imaging that can be labeled with ^{99m}Tc, as ^{99m}Tc is readily available and has attractive nuclear properties for SPECT imaging. Among the ^{99m}Tc-labeled tumor imaging agents for lung ca, ^{99m}Tc-MIBI is considered to have the largest potential (*13,14*). Technetium-99m-tetrofosmin is a new myocardial imaging agent. Although the tumor uptake mechanism of ^{99m}Tc tetrofosmin is not clearly understood, it does appear to have a similar myocardial uptake mechanism to ^{99m}Tc-MIBI (*25–28*). It has been suggested that ^{99m}Tc-tetrofosmin binds to cytosol in the tumor cell, as in the myocardium (*25–28*). The cationic charge and lipophilicity of ^{99m}Tc-tetrofosmin, mitochondria and plasma membrane potentials of the tumor cell, as well as cellular mitochondria content, can play significant roles in the tumor uptake of this agent (*25–28*). Or, the uptake may be caused by an indirect phenomenon, such as increased tumor blood flow or capillary permeability.

TABLE 2
Results of Chest Technetium-99m-Tetrofosmin SPECT

Lesions	Pathologic type	Detection rate
Malignancies 61% (25/41)	Epidermoid ca	53% (10/19)
	Adenoid ca	67% (10/15)
	Small-cell ca	75% (3/4)
	Undiff. large-cell ca	0% (0/1)
	Other malignancies	100% (2/2)
Benign 50% (4/8)		

Numbers in parentheses are number of patients.

Recently, it has been reported that the retention of ^{99m}Tc-MIBI in cells depends on the activity of the 170 kDa P-glycoprotein (P-gp) coded by MDR1 (multidrug-resistance gene), which functions as an ATP-dependent efflux pump for many cytotoxic substances, mostly lipophilic cations. Technetium-99m-MIBI is reported to be a ligand for this MDR1 P-gp (*29*), as accumulation of the complex in cells has been reported to be inversely related to the level of P-gp. Other reports also have shown that verapmil and cyclosporin A, multidrug-resistant reversal agents, enhance accumulation of ^{99m}Tc-MIBI many fold. Similar findings have been reported in clinical human tumor imaging of breast cancer (*30*) and metastatic renal cell carcinoma (*31*). Negative ^{99m}Tc-MIBI tumor uptake and positive ^{99m}Tc-MIBI tumor uptake are thought to be consistent with relative high and low expression of P-gp, respectively (*30,31*). It has also been reported that ^{99m}Tc-tetrofosmin is a ligand for the same P-gp protein (*32*).

A previous research project, which was similar to this study in dosage and scanning protocol, used ^{99m}Tc-MIBI SPECT to differentiate malignant and benign lesions of the lungs (*15*). Their results showed that only 65% (30 of 46) of the lung malignancies could be detected by ^{99m}Tc-MIBI SPECT. However, 75% (6 of 8) of the benign lesions was also detected. The diagnostic accuracy for differentiating malignant and benign lesions was 70% (*15*). Technetium-99m-tetrofosmin replaced ^{99m}Tc-MIBI in this study, and the results showed that 61% (25

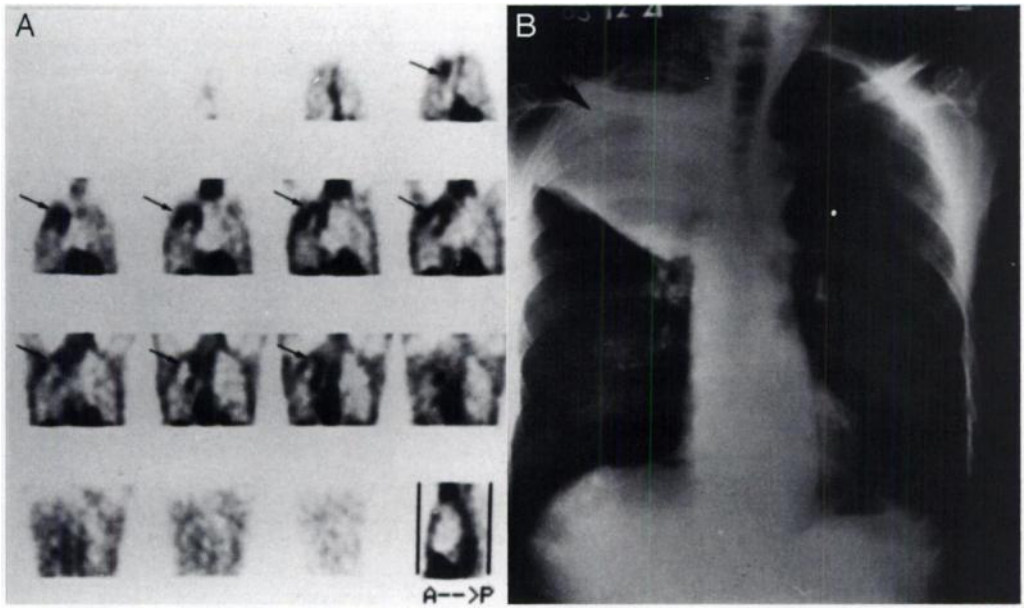

FIGURE 2. In Patient 10, a 71-yr-old man with epidermoid lung ca ^{99m}Tc-tetrofosmin SPECT of the chest (A, coronal sections) revealed increased tetrofosmin uptake in the right lower lobe of the lungs (arrows). (B) Chest radiograph showed a lesion in the same area (arrow).

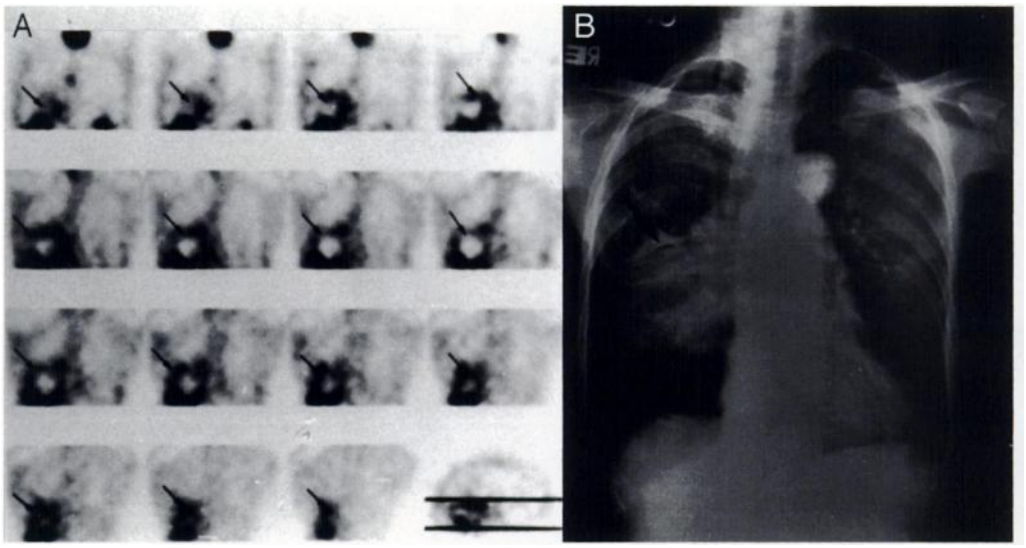

FIGURE 3. In Patient 44, a 73-yr-old woman with a fungal abscess, ^{99m}Tc-tetrofosmin SPECT (A, coronal sections) revealed increased tetrofosmin uptake in the right lower lobe of the lungs (arrows). (B) A chest radiograph showed a lesion in the same area (arrow).

of 41) of the malignancies in the lungs were detected by ^{99m}Tc-tetrofosmin SPECT. In addition, 50% (4 of 8) of the benign lesions were detected by ^{99m}Tc-tetrofosmin SPECT. The diagnostic accuracy was 59%. Technetium-99m-tetrofosmin is considered to have lower uptake than of ^{99m}Tc-MIBI in human breast cancer cells (*33*). Technetium-99m-tetrofosmin also is considered to have higher background radioactivity than ^{99m}Tc-MIBI in one reported case of thyroid carcinoma (*18*). Therefore, we believe that ^{99m}Tc-tetrofosmin is not a good alternative to ^{99m}Tc-MIBI for detecting malignancies from single solid lung masses.

In a review of the literature, only one complete investigation, which studied 30 patients with planar thorax images, reported that the sensitivity, specificity and accuracy of ^{99m}Tc-tetrofosmin were 90%, 55% and 86%, respectively (*34*). Two other brief articles, including a total of 10 patients with lung tumors, have described a preliminary assessment of the usefulness of ^{99m}Tc-tetrofosmin chest planar and SPECT images for detecting malignant lung tumors (*35,36*). In addition, a few abstracts dealing with ^{99m}Tc-tetrofosmin SPECT for the detection of lung cancer have been reported (*37–40*). In these studies, the sensitivity ranged from 73% to 100%, and the specificity has been reported to be 100% (*37–40*). In contrast to our results, the diagnostic sensitivity and specificity seem excessively high. The diagnostic sensitivity and specificity of ^{99m}Tc-tetrofosmin (*34,37–39*) were also higher in these studies than in previous reports using ^{99m}Tc-MIBI (*15–17*) for lung cancer detection. The discrepancies between our results and previous published reports (*34–40*) are difficult to explain, as most of the studies used a similar scanning protocol for dosage (740 MBq or 20 mCi) and imaging time (30 min after intravenous injection of ^{99m}Tc-tetrofosmin). One possible explanation may be due to differences of patient selection with different P-gp expression (*30–32*).

TABLE 3
Decision Matrix for Technetium-99m-Tetrofosmin Chest SPECT Performed in Patients with Single Solid Lung Masses

	Pathology		
SPECT results	Malignant	Benign	Total
Positive	25	4	29
Negative	16	4	20
Total	41	4	49

CONCLUSION

Technetium-99m-tetrofosmin has little or no clinical value in the detection of lung cancers from single solid lung masses.

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Radionuclide-Guided Stereotatic Prebiopsy Localization of Nonpalpable Breast Lesions with Normal Mammograms

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Scintimammography with ^{99m}Tc-sestamibi can be used as a complementary technique to improve the mammogram's sensitivity and specificity for detection of breast carcinoma. We have observed in some patients focal areas of increased ^{99m}Tc-sestamibi uptake with no corresponding abnormalities on physical examination or mammogram. A phantom device and a special needle were designed to stereotactically localize these lesions before biopsy. **Methods:** After intravenous injection of 30 mCi (1110 MBq) of ^{99m}Tc-sestamibi, a prone lateral image of the abnormal breast was obtained. With the patient in the prone position, the breast was compressed with two fenestrated plates in the prone position. The x and y coordinates of the abnormal hot spot of the breast were determined. The z coordinate of focal ^{99m}Tc-sestamibi uptake was determined by advancing a localizer needle through a selected predetermined hole of the fenestrated plate using real-time visualization on the persistence monitor. The tip of the opturator inside the needle is welded with ^{57}Co to determine the depth of the hot spot in the breast. **Results:** Three women, all of whom had normal mammograms and breast physical examinations, were studied using ^{99m}Tc-sestamibi prone breast imaging. Pre-excisional biopsy needle localization of abnormal focal uptake was performed. Two women demonstrated infiltrative ductal carcinoma, and the third had proliferative fibrocystic disease of the breast. **Conclusion:** Our initial experience demonstrates that nuclear medicine-guided stereotactic needle biopsy of the breast in patients with positive scintimammograms is technically feasible. In the future, this technology will enable us to detect breast carcinoma in the absence of clear-cut clinical and mammographic findings.

Key Words: breast biopsy; scintimammography; breast cancer; technetium-99m-sestamibi

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Mammography and physical examination combined have a sensitivity of 85% for the detection of breast carcinoma. Mammography also has a positive predictive value of 15%–30%. (*1*) Initial data indicate that ^{99m}Tc-sestamibi can be used as a complementary technique to improve mammography's sensitivity and specificity for breast cancer detection (*2*).

We have observed that some patients have abnormal focal areas of ^{99m}Tc-sestamibi uptake with no abnormalities on physical examination or mammography to serve as a guide for biopsy. Because of the reported higher specificity of ^{99m}Tc-sestamibi uptake for breast cancer, our experience indicates such uptake is more likely to be due to malignancy than benign lesions and probably requires tissue diagnosis (*3–5*). We designed and manufactured a prototype of a stereotactic-guided prebiopsy needle localization device which enables us to localize the abnormality on the scintimammogram using nuclear medicine techniques (*6*). In this article, we demonstrate the clinical utility of this device in three women with normal mammograms and physical breast examinations who had focal areas of abnormal increased ^{99m}Tc-sestamibi breast uptake. These lesions were subsequently localized and biopsied with our stereotactic device. Two women had invasive ductal carcinoma, and the third had a proliferative type of fibrocystic disease.

MATERIALS AND METHODS

Scintimammography

Five minutes after intravenous injection of 20 mCi (740 MBq) ^{99m}Tc-sestamibi, prone lateral planar images of each breast were acquired followed by an anterior upright image of the chest. The procedure has been previously described in detail (*7*). Focal