Mammoscintigraphy with Technetium-99m-Sestamibi in Suspected Breast Cancer

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Our goal was to determine the clinical usefulness of ^{99m}Tc-sestamibi to identify breast cancer in patients prior to biopsy. **Methods:** We studied 66 patients who received 20 mCi ^{99m}Tc-sestamibi intravenously. Lateral and anterior planar images were gathered within 30 min of the injection. Only focal increased uptake was interpreted as positive. Confirmatory pathologic diagnoses were obtained within 2 mo. The prevalence of breast cancer in our sample was 54%. **Results:** We report an overall sensitivity of 83% and specificity of 93% for the diagnosis of breast cancer. In palpable lesions, the sensitivity was of 94% with a specificity of 91%, while in nonpalpable abnormalities the sensitivity was of 64% with a 100% specificity. Six patients with a malignancy had negative scans, four of these lesions were nonpalpable. Only two of 31 patients with benign lesions had an abnormal scan. **Conclusion:** Mammoscintigraphy with ^{99m}Tc-sestamibi has high specificity and adequate sensitivity for the noninvasive diagnosis of breast carcinomas.

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

J Nucl Med 1996; 37:926–930

Approximately 180,000 new cases of breast cancer occur in the U.S. yearly. The incidence of breast cancer is growing and it is estimated that 12% of all women will be given the diagnosis of breast cancer and 3.5% will die of the disease (*1*). Early detection includes breast self-exams, breast exams by a physician and sequential mammograms after age 40 yr.

The sensitivity of breast examination plus mammography for cancer detection is around 90% for fatty breasts and is significantly less in dense or abnormal breasts (*2*). Some patients at high risk for the development of breast cancer may be difficult to evaluate because of a dense fibroglandular pattern, augmentation or reduction surgery and post-therapy changes. The combination of physical examination, mammography and ultrasonography is highly accurate when all the tests give the same result (*3*). Unequivocal assurance requires a biopsy. The distinction of malignant from benign lesions by mammography is difficult, and its specificity for the diagnosis of breast cancer is low, between 20% and 51% (*4–6*).

The purpose of our study is to characterize benign and malignant lesions by using ^{99m}Tc-sestamibi for breast imaging. Technetium-99m-sestamibi is a myocardial imaging agent and has similar indications as ^{201}Tl-chloride. Technetium-99m-sestamibi accumulates in tumor cells cultures up to nine times more than in normal cells (*7*). Preliminary clinical reports show that ^{99m}Tc-sestamibi concentrates in breast tumors with high specificities in the range of 90%–95% (*8–18*). Our goal was to further evaluate the role of ^{99m}Tc-sestamibi in breast cancer detection on factors that affect sensitivity and specificity.

Received Jul. 13, 1995; revision accepted Nov. 27, 1995.
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MATERIAL AND METHODS

Patients

Sixty-six female patients participated in this study between February of 1993 and June of 1995. They were consecutive patients recruited the same day they had mammograms. Specific written informed consent approved by the Institutional Review Board of UTMB in February 1993 was obtained from all patients. Inclusion criteria were: age (19+ yr), presence of a mammographic abnormality with or without palpable mass and candidate for surgical biopsy. Exclusion criteria were nonconsenting patients, pregnancy and concomitant severe medical condition. The patients' age ranged from 35 to 80 yr, with an average of 52 ± 10 yr. Twenty patients were premenopausal, two were perimenopausal and 44 were postmenopausal. Forty-seven patients had palpable breast masses and 19 had mammographic abnormalities only. All patients underwent excisional biopsy or mastectomy. Only three patients had fine needle aspiration biopsies and they each had a subsequent mastectomy. The patients who had only mammographic abnormalities without palpable changes required wire needle localization with excisional biopsy mammogram to assure excision of the abnormalities.

Imaging Procedure

A dose of 740 MBq (20 mCi) ^{99m}Tc-sestamibi was used for each study. The radiochemical purity of the compound was tested prior to each injection by instant thin-layer chromatography and was >97%. After the injection, a nuclear medicine technologist positioned the patient in the prone, breast-dependent position as described by Khalkhali et al. (*11*). Imaging started within 15 min of the injection. We imaged one breast at a time, gathering right and left lateral views for a preset time of 10 min. The patient's breast was positioned as close as possible to the camera: in most instances the lateral aspect of the breast touched the collimator face. Also, we gathered a third planar view in the anterior projection with the patient supine and the arms elevated above the head. We included the tail of the breast in the field of view. Some large patients whose chests were not completely in the field of view required anterior planar views for each side of the chest. We used a large field of view gamma camera equipped with high-resolution collimation. The study consisted of two lateral breast images and one or two anterior views. Technetium-99m-sestamibi breast imaging took about 1 hr to complete, considering the time for obtaining consent, starting the intravenous line, preparing ^{99m}Tc-sestamibi, injecting and imaging.

The images were interpreted by two nuclear medicine physicians blinded to the clinical, mammographic and pathology results. The report included location of the abnormality and presence or absence of focal increased uptake. All patients underwent open surgical biopsy or mastectomy within 2 mo of the nuclear medicine procedure.

RESULTS

We report an overall sensitivity of 83%, specificity of 93%, positive predictive value of 94% and negative predictive value

TABLE 1
Pathological and Nuclear Medicine Correlations

	All lesions		
	Breast cancer	Benign	Totals
Sestamibi +	29	2	31
Sestamibi −	6	29	35
Total	35	31	66
	Palpable lesions		
	Breast cancer	Benign	Totals
Sestamibi +	22	2	24
Sestamibi −	2	20	22
Totals	24	22	46
	Nonpalpable lesions		
	Breast cancer	Benign	Totals
Sestamibi +	7	—	7
Sestamibi −	4	9	13
Totals	11	9	20
	All	Palpable	Nonpalpable
Sensitivity	83%	94%	64%
Specificity	93%	91%	100%
Positive predictive value	94%	92%	100%
Negative predictive value	83%	91%	69%

of 82% for the diagnosis of breast cancer. For palpable lesions the sensitivity was 94% and 64% for nonpalpable lesions (Table 1). The correlation with pathology is shown in Table 2. The prevalence of breast carcinoma in our sample was 54%. Technetium-99m-sestamibi showed focal abnormal increased uptake in 29 of 35 patients with breast cancer. Only 2 of 31 patients with benign lesions showed abnormal focal uptake. Six patients with breast cancer showed no uptake of ^{99m}Tc-sestamibi; their characteristics are described in Table 3. The false-negative studies occurred in older and postmenopausal patients (Table 4). Mammography showed a fatty pattern in 16 patients, predominantly glandular or fibroglandular in 29 patients and dense in 21 patients (Table 5). Fifty patients had a dominant mass with or without calcifications by mammogram. Fifteen patients had calcifications only, and one had a normal mammogram.

Examples of a negative ^{99m}Tc-sestamibi breast study in a patient with a fibroadenoma are shown in Figure 1. Focal increased uptake in a breast cancer patient is shown in Figure 2. A patient with a nonpalpable mammographic density and a negative ^{99m}Tc-sestamibi scan is illustrated in Figure 3. The final pathologic diagnosis in this patient was invasive ductal carcinoma.

DISCUSSION

Thallium-201 was used for the evaluation of breast masses by Waxman et al. (*19*) who reported a sensitivity of 96% and specificity of 91% in the diagnosis of breast cancer in a series of 81 patients. Interestingly, in that series, none of the 19 patients with fibrocystic disease showed uptake in their breasts. Lee et al. (*20*) report using ^{201}Tl in the diagnosis of breast cancer with a sensitivity of 80% and specificity of 95% for malignant breast disease. Cimitan et al. (*21*), in a prospective study, compared ^{201}Tl breast imaging, mammography and ultrasonography to pathology for the diagnosis of breast cancer. They found a sensitivity of 91% and specificity of 94% for scintimammography.

Technetium-99m-sestamibi has improved imaging characteristics with a different mechanism for tissue uptake when compared to ^{201}Tl. Thallium-201 enters into viable cells using the sodium-potassium pump mechanism and accumulates twice as avidly in malignant cells as in normal cells. Technetium-99m-sestamibi accumulates in cells in relation to perfusion, viability and mitochondrial activity. Technetium-99m-sestamibi is a lipophilic cationic compound such as rhodamine-123 and tetraphenylphosphonium and has high affinity for myocites and carcinoma cells (*22–24*). In tumor cells, ^{99m}Tc-sestamibi is clustered in the cytoplasm around the nucleus in relation to the

TABLE 2
Pathological and Nuclear Medicine Findings

Result	No. of patients	Pathologic diagnosis	Tumor size (cm)
True-Negative (29/31 patients)	12	Fibrocystic changes	
	5	Normal	
	4	Fibroadenoma	
	2	Atypical ductal hyperplasia	
	1	Florid epithelial hyperplasia	
	1	Fibrocystic changes and florid epithelial hyperplasia	
	1	Fibroadenoma and epithelial hyperplasia	
	1	Stromal sclerosis	
	1	Sclerosed fibroadenoma and mild epithelial hyperplasia	
	1	Complex sclerosing lesion	
True-Positive (29/35 patients)	18	IDC	0.5–6.0
	2	DCIS comedo type	n/a
	4	IDC and DCIS	2.3–3.5
	2	DCIS	n/a
	3	ILC	3.0–4.5
False-Positive (2/31 patients)	2	fibrocystic changes and fibroadenoma	
False-Negative (6/35 patients)	1	IDC, minimal papillary	0.9
	1	DCIS	n/a
	1	ILC	2.0
	1	DCIS and IDC, low grade	0.7
	1	IDC	1.7
	1	ILC	5.0

IDC = invasive ductal carcinoma; DCIS = ductal carcinoma in-situ; ILC = infiltrating lobular carcinoma.

TABLE 3
False-Negative Technetium-99m-Sestamibi Breast Scans*

Age (yr)	Breast exam	Mammographic breast pattern and finding		Pathologic diagnosis	Tumor size (cm)
75	Mass	Fatty	Mass	IDC	0.9
52	Normal	Dense	Calcifications	DCIS	n/a
60	Normal	Fibrogland	Mass and arch dist	ILC	2.0
44	Normal	Fibrogland	Calcifications and arch dist	DCIS and IDC	0.7
58	Normal	Fibrogland	Mass	IDC	1.7
68	Mass	Dense	Normal	ILC	5.0

*Characteristics of six patients with breast cancer and a negative ^{99m}Tc-sestamibi breast study. Two of these patients presented with a palpable mass, two had calcifications and two had masses detected by mammography.

Fibrogland = mammographic fibroglandular breast pattern; arch dist = architectural distortion; IDC = invasive ductal carcinoma; DCIS = ductal carcinoma in situ; ILC = infiltrating lobular carcinoma.

plasma and mitochondrial membrane potential (*25*). Technetium-99m-sestamibi uptake also appears to be an in vivo marker of P-glycoprotein activity which is associated with multi-drug resistance (*26*).

In this group of 66 patients, the overall sensitivity of ^{99m}Tc-sestamibi breast imaging for the diagnosis of breast cancer was 83%, with a specificity of 93%. Our sensitivity was lower than reported in two studies with a larger number of patients (Table 5). One of the reasons might be the ratio of palpable-to-nonpalpable breast abnormalities. We found a 94% sensitivity for palpable and 64% for nonpalpable abnormalities. The smallest lesion detected was an invasive ductal carcinoma of 0.5 cm. We identified 29 of 35 patients with breast cancer. Of the six false-negative patients, only two had a distinct palpable mass and four had a normal clinical exam. Five of six patients were postmenopausal. The age of the patients with false-negative studies was 60 ± 11 yr and they were older than the patients with true-positive studies (Table 4). The largest two nonvisualized breast cancers corresponded to the less aggressive lobular carcinoma. Three small invasive ductal carcinomas (1.7, 0.9 and 0.7 cm, respectively) were not visualized (Table 3). Also, one ductal carcinoma in situ was not visualized. A hypothesis for nonvisualization of breast cancer includes the lack of stromal reaction around the tumor. Technetium-99m-sestamibi may accumulate in the desmoplastic or stromal reaction of the tumor as well as in the tumor. Tumors with minimal desmoplastic reaction (as lobular carcinoma) may be more difficult to visualize with ^{99m}Tc-sestamibi (*27*). Another possibility for nonvisualization is overexpression of the multi-drug resistance gene (*26*). Technetium-99m-sestamibi may enter into the tumor cell but be rapidly extruded; this mechanism could be important in assessing the development of resistance to chemotherapeutic agents. Scopinaro et al. (*28*) suggest that ^{99m}Tc-sestamibi may be a marker of breast cancer invasiveness: its uptake may be related to angiogenesis and, possibly, to oxidative metabolism of the tumor. Other possibilities for nonvisualization are tumor size, tumor location within the breast, size and density of the breast tissue, distance of the tumor from the camera and soft-tissue attenuation. Each of these variables requires further study. The presence of false-negative studies reported in this and other series preclude the use of this technique for screening. However, ^{99m}Tc-sestamibi visualization could be very valuable in the diagnostic setting when conventional radiographic methods are inconclusive.

TABLE 4
Age, Menopausal State, Mammographic Finding and Technetium-99m-Sestamibi Study

	TN	TP	FN	FP	Total
Age (yr)	50 ± 11	53 ± 11	60 ± 11	47 ± 9	—
Menopausal state					
Pre-	11	7	1	1	20
Peri-	2	—	—	—	2
Post-	16	22	5	1	44
Totals	29	29	6	2	66
Mammographic breast pattern					
Fatty	6	8	1	1	16
Fibroglandular	13	12	3	1	29
Dense	10	9	2	—	21
Primary mammographic finding					
Mass	22	23	3	2	50
Calcification	7	6	2	—	15

TN = true-negative; TP = true-positive; FN = false-negative; FP = false-positive.

We report a 94% overall specificity for the noninvasive diagnosis of breast cancer with ^{99m}Tc-sestamibi. For palpable abnormalities, the specificity was 91% and for nonpalpable 100%. Very high specificities have been a consistent finding in previous reports (*9–16*). In our series, only 2 of the 30 patients with benign lesions, fibrocystic changes and fibroadenomas had an abnormal scan. The two false-positive lesions corresponded to palpable abnormalities.

In this report, we focused on breast imaging only. Abnormal increased axillary uptake could be evaluated from the anterior views. Our impression is that anterior and lateral planar views are adequate for breast imaging but not sufficient projections to image the axillae. Probably, anterior oblique views with the axillae in the center of field of view and close to the detector surface are better to define abnormal axillary uptake.

Radionuclide tracers described for breast cancer imaging include ^{99m}Tc-methylene dyphosphonate (*29*), ^{111}In-octreotide (*30*) and ^{18}F-(2)-deoxyglucose (FDG) (*31–32*). There is evidence from in vitro studies that FDG may accumulate more avidly in breast cancer cells than ^{99m}Tc-sestamibi (*33*). Estrogen receptor markers (*34*) and monoclonal antibodies (*35*) may provide specific agents for diagnosis and follow-up. Also, MRI may have a variety of roles in the detection and management of breast disease. Because study methods and imaging are not standard, there is still much uncertainty about MRI's place in clinical practice. MRI is potentially useful for detection, localization and guiding biopsy in the management of breast cancers (*36*). Probably a combination of studies rather than one study alone may be the most efficacious way to noninvasively

TABLE 5
Sensitivity and Specificity of Scintimammography for Breast Cancer Diagnosis

Investigator	No. of patients	Prevalence of breast cancer n (%)	Sensitivity (%)	Specificity (%)
^{201}Tl studies				
Waxman et al. (*19*)	81	44 (54)	96	91
Lee et al. (*20*)	39	15 (38)	80	96
Cimitan et al. (*21*)	72	56 (72)	81	95
Total/Average	192	115 (55)	89	94
^{99m}Tc-sestamibi studies				
Khalkhali et al. (*21*)	100	32 (32)	94	88
Taillefer et al. (*23*)	65	47 (72)	92	94
Palmedo et al. (*37*)	54	24 (44)	88	93
This report	66	35 (53)	83	93
Total/Average	285	138 (50)	89	90

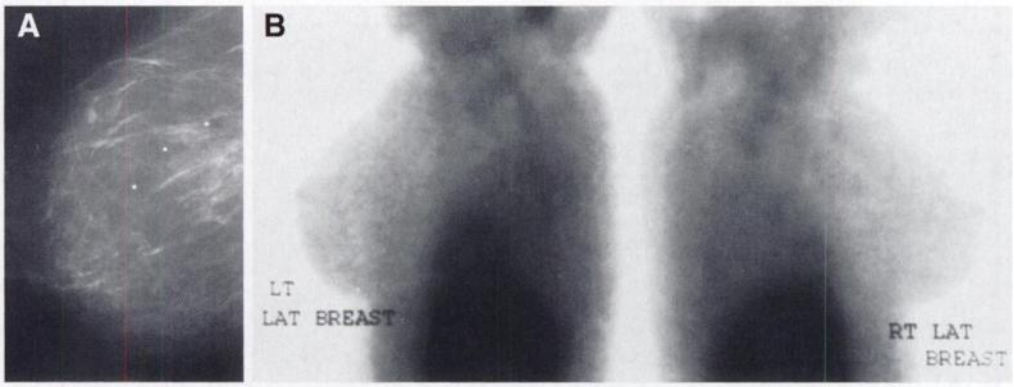

FIGURE 1. Fibrocystic changes. A 59-yr-old patient with a screening mammogram showing an ill-defined density. She had a normal physical exam. The markers on this mammogram identified a skin scar (A). Technetium-99m-sestamibi breast scan showed homogeneous distribution of tracer without focal abnormality (B). Right breast biopsy showed fibrocystic changes, stromal sclerosis, adenosis, microcalcifications and focal mild epithelial hyperplasia.

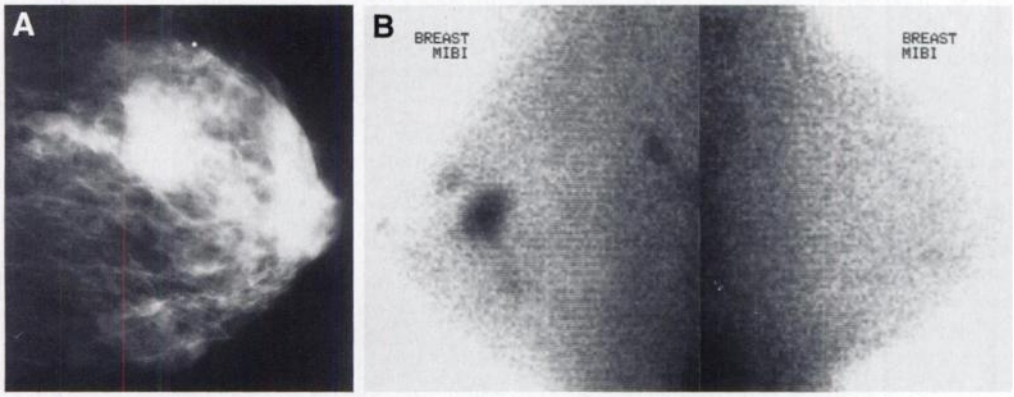

FIGURE 2. Breast cancer, true-positive ^{99m}Tc-sestamibi. A 50-yr-old woman presented with a palpable left breast mass and multifocal mammographic densities. The mammogram showed dense fibroglandular tissue and a 4-cm spiculated mass with calcifications (A). Technetium-99m-sestamibi showed abnormal increased uptake in one lesion in the left breast with two satellite lesions (B). Biopsy demonstrated infiltrative ductal carcinoma in a 3-cm nodule and atypical ductal hyperplasia. The tumor was positive for estrogen and progesterone receptors.

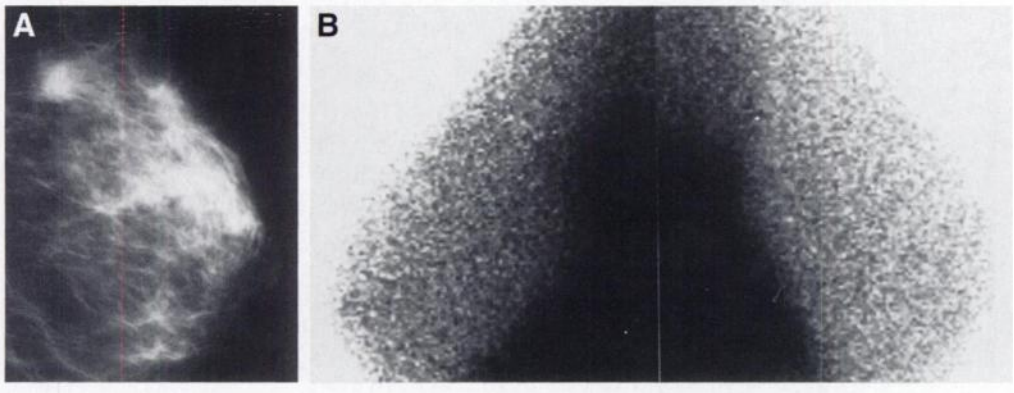

FIGURE 3. Breast cancer, false-negative ^{99m}Tc-sestamibi. A 58-yr-old woman with a normal breast exam. The left mediolateral oblique view (A) from a screening study showed a 2-cm, ill-defined density in the left breast. Technetium-99m-sestamibi study showed homogeneous distribution in both breasts (B). Biopsy findings corresponded to a 1.7-cm infiltrating ductal carcinoma. This tumor was positive for estrogen and progesterone receptors.

diagnose breast cancer. As two studies complement each other, it is possible to obtain high sensitivities and maintain high specifities.

CONCLUSION

Our report confirms that planar ^{99m}Tc-sestamibi breast imaging has a high specificity of 93% and an adequate sensitivity of 83% for the diagnosis of breast carcinoma. The sensitivity is highest (94%) in patients with palpable breast abnormalities. In patients with nonpalpable abnormalities, the sensitivity could be improved with high contrast or spatial resolution imaging with SPECT imaging or a dedicated breast imaging camera. Potential applications of ^{99m}Tc-sestamibi are as a complement to conventional imaging in the evaluation of dense breasts, multiple mammographic or palpable abnormalities, after breast surgery or biopsy, in patients with breast implants and in the follow-up of breast cancer patients.

ACKNOWLEDGMENT

Supported in part by DuPont Merck grant CG93019.

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