Technetium-99m-Methylene Diphosphonate Scintimammography to Image Primary Breast Cancer

Sergio Piccolo, Secondo Lastoria, Ciro Mainolfi, Pietro Muto, Lucio Bazzicalupo and Marco Salvatore

Department of Nuclear Medicine, National Cancer Institute, Fondazione G. Pascale, Napoli, Italy

Technetium-99m-methylene diphosphonate (MDP) uptake within breast lesions was investigated during routine presurgical bone scintigraphy in a cohort of women at high risk for cancer who were candidates for surgery or excisional biopsy. The aim was twofold: (a) to demonstrate positive ^{99m}Tc-MDP uptake in primary breast cancer and (b) to differentiate malignant from benign lesions. **Methods:** Anterior and oblique lateral views of the breasts were acquired 0–4 min, 10–20 min and 2 hr after intravenous injection of 740 MBq of ^{99m}Tc-MDP in 200 women with elevated suspicion or proven diagnosis of breast cancer (Group 1) and in 80 women with other solid tumor types (Group 2). **Results:** Physical examination and mammography revealed breast abnormalities in all Group 1 subjects. The mammographic findings were definitely positive for carcinoma in 120 patients, highly suspicious in 27 and indeterminate in 53. Breast cancer was later histologically diagnosed in 172 women (86%) and benign disease found in 28 women (14%). Of these patients, 158 (92%) showed focal uptake of ^{99m}Tc-MDP in the images collected 10–20 min after injection. This was found to be the best timing for imaging, with tumor-to-background ratios as high as 4.3 (mean ± s.d. = 3.8 ± 0.4). Two hr after injection, only 61 of the 158 (38%) malignant lesions were clearly detectable. **Conclusion:** Technetium-99m-MDP is concentrated by primary breast carcinoma 10–20 min after injection, enabling successful external gamma imaging. Scintimammography with ^{99m}Tc-MDP is an accurate test that differentiates malignant from benign breast lesions, particularly in patients with indeterminate mammograms.

Key Words: breast cancer; technetium-99m-MDP; scintimammography

J Nucl Med 1995; 36:718–724

Radionuclide imaging of the skeleton is the most frequently performed procedure in nuclear medicine departments. The majority of bone studies are used to stage patients with breast cancer by detecting skeletal metastases either at diagnosis or during follow-up (*1–3*). Extraskeletal accumulation of ^{99m}Tc-MDP has often been reported in some malignant tumors, including neuroblastoma, sarcoma, osteosarcoma, soft-tissue lymphoma, etc. (*4–6*). Similar results have also been reported for large primary breast tumors, cystosarcoma phyllodes and benign lesions (*7–13*). A wide spectrum of hypotheses for such phenomena has been proposed and in a few circumstances demonstrated. For instance, increased vascularization has been documented to favor imaging of malignant lesions (*14*).

The differential diagnosis between benign and malignant breast lesions has long been a challenge for many researchers using radioisotope-based techniques. Previous studies showed increased accumulation of [^{99m}Tc]pertechnetate and ^{67}Ga-citrate in malignancies (*15–18*). More recently, ^{201}Tl and ^{99m}Tc-sestamibi have provided favorable results in diagnosing cancer among palpable breast masses (*19–22*). Furthermore, sestamibi seems to be useful in diagnosing cancer in nonpalpable breast masses where mammographic results are indeterminate. Mammography provides acceptable sensitivity in the identification of carcinoma occurring in fatty breasts, while it is not reliable in detecting malignant lesions in dense breasts (*23–30*). Unfortunately, one-fourth of women evaluated by mammography have dense breasts (*28–30*). Therefore, targeted biopsies are necessary to achieve an accurate diagnosis, resulting in a high number of biopsies in patients with benign breast lesions. Noninvasive and accurate imaging modalities able to differentiate malignant from benign lesions might spare patients from unnecessary surgical procedures and might play a pivotal role in their management.

This study assesses the efficacy of ^{99m}Tc-MDP scintimammography in detecting breast cancer and differentiating malignant from benign lesions.

MATERIALS AND METHODS

Patients

Scintimammography with ^{99m}Tc-MDP was performed during routine presurgical bone imaging in 200 women at high risk for

Received Aug. 3, 1994; revision accepted Dec. 29, 1994.
For correspondence or reprints contact: Sergio Piccolo, MD, Via A. Garofano 18, Aversa (CE), 81031, Italy.

breast cancer who were scheduled for surgery or excisional biopsy (Group 1) and in 80 women who served as controls during follow-up for other tumors (Group 2).

Group 1. Patients ranged in age from 27 to 80 yr (mean age, 50 ± 11) and were enrolled in the study before surgery. The presurgical workup included mammography, liver ultrasound, chest x-ray and breast ultrasound if necessary. Surgical and/or needle biopsy of the lesions was performed within 1 wk of bone scintigraphy. The pathological findings were considered the gold standard to correctly assess the imaging results. In the 91 premenopausal women with a negative pregnancy test, scintimammography was performed within 10 days from the last menses.

Group 2. The solid tumors in this group included: 17 gynecological tumors, 14 melanoma, 13 lymphoma, 13 lung cancer, 8 sarcoma, 6 gastric or colon adenocarcinoma, 5 carcinoid and 4 renal adenocarcinoma. The subjects were age-matched to the Group 1 members and the same imaging protocol was used in both groups. This group was divided in two subgroups: Subgroup I included 35 women with mammographic and cytologically proven benign breast diseases. Subgroup II included 45 women with no breast abnormalities.

Radiopharmaceutical

Each patient received approximately 740 MBq of ^{99m}Tc-MDP in the arm controlateral to the breast with the abnormality.

Scintimammography Study Protocol

Patients were imaged in an upright position. The imaging protocol included dynamic acquisition (60 frames of 1 sec/each; 6 of 10 sec/each and 4 of 30 sec/each) for a total of 4 min, and repeat planar views at 10–20, 40–60 min and 2–3 hr postinjection using anterior and lateral oblique projections of the breasts. The use of oblique lateral views of the chest enabled positioning of the breast alone in the camera's field of view. A low-energy, general-purpose, parallel-hole collimator was used. The images (matrix 128 × 128 pixels) were stored in a dedicated computer and the photopeak was set at 140 keV with a symmetric window of 20%.

Semiquantitative Analysis of Technetium-99m-MDP Uptake

Irregular regions of interest (ROIs) which circumscribed foci of increased tracer uptake in the oblique/lateral views at different scanning times were manually drawn to define the activity within breast lesions. Similar ROIs were drawn on the normal breast to define the background. In the later scans, superimposition of tumor nodules and bony structures (ribs, sternum) was accurately avoided to ensure correct measurements in the drawn ROIs.

Classification of Mammographic Findings

The mammographic patterns were classified as follows:

- Definitely diagnostic when images had features for breast cancer (i.e., spiculated opacity with or without microcalcification, irregular border of the opacity in fatty breasts, etc.).
- Highly suspicious when images had indirect signs diagnostic for breast cancer (i.e., focal architectural distortion, asymmetric breasts, ductal asymmetry, microcalcification without mass).
- Indeterminate when images were not clear because of the high density of the glands or did not match with the physical examination.
- Definitively negative when no abnormalities were seen.

Statistical Analysis

Scintimammography was evaluated as positive or negative for ^{99m}Tc-MDP localization by two experienced, unbiased nuclear medicine physicians blinded to the patients' clinical work-up findings. Subsequently, these results were compared to mammographic and histological findings. The scintimammography results were classified as true-positive, true-negative, false-positive and false-negative according to histological findings. Sensitivity, specificity, accuracy and positive (PPV) and negative (NPV) predictive values were determined.

RESULTS

Group 1

Mammography and Histology. Mammography documented breast abnormalities in all 200 women, and the results were classified, according to previously reported criteria, as diagnostic for carcinoma in 120 patients (60%), highly suspicious in 27 (13.5%) and indeterminate in 53 patients (26.5%). The maximal diameter was measurable in 183 breast abnormalities, ranging from 3 mm to 70 mm, whereas it was not measurable in 17 patients with inflammatory cancer. Breast cancer was diagnosed in 172 of 200 women (86%); benign breast diseases were documented in the other 28 (14%) by histology and/or cytology of needle aspirate. Tumor types are summarized in Table 1.

MDP Scintimammography. The pattern of ^{99m}Tc-MDP uptake within breast cancers was not constant during the study. In fact, in early images (0–4 min p.i.), 158 of 172 neoplastic lesions (92%) showed focal tracer uptake with a significant gradient over surrounding normal breast (tumor-to-background ratios (T/B) were 2.6 ± 0.5). The pattern was substantially unmodified in the images collected between 10 and 20 min after injection, although the T/B ratio increased up to 3.8 ± 0.4. Conversely, in late images, only 61 of 158 (38%) suspected malignant tumors were still

TABLE 1
Scintimammography Results Versus Histological Classification of 172 Malignant Breast Lesions

Histology	Number of lesions	Scintimammography findings
Infiltrating ductal carcinoma	95	90 TP 5 FN
In situ ductal carcinoma	26	22 TP 4 FN
Mixed ductal/Lobular carcinoma	17	16 TP 1 FN
Ductal carcinoma (indeterminate)	16	15 TP 1 FN
Infiltrating lobular carcinoma	7	6 TP 1 FN
Medullary carcinoma	6	5 TP 1 FN
Colloid carcinoma	5	4 TP 1 FN

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

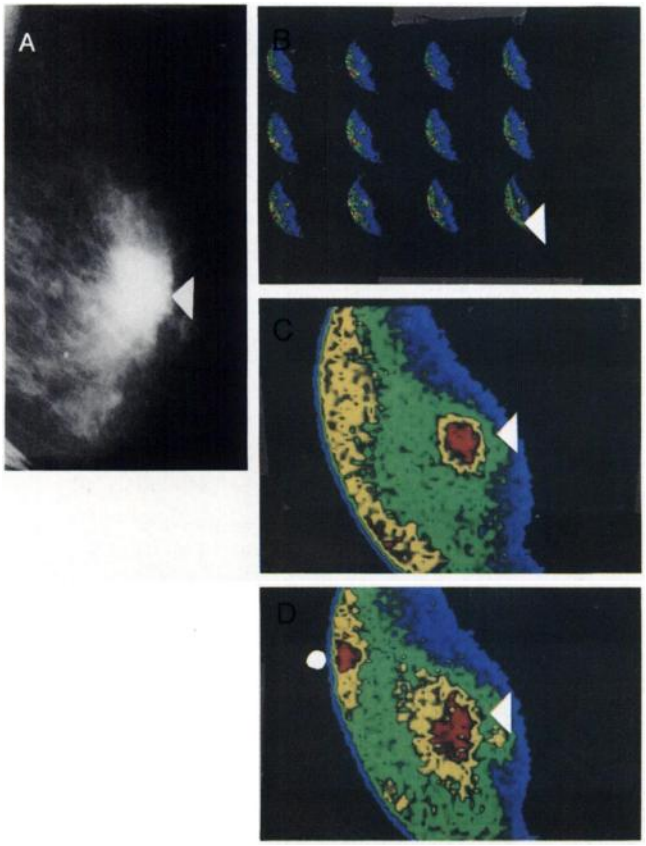

FIGURE 1. Histologically proven infiltrating ductal breast cancer (largest diameter of 35 mm) involving the retroareolar region of the right breast in a 45-yr-old woman appeared on mammography (A) as star-shaped opacity with radiating spicules (arrow). Dynamic scintimammography images acquired immediately after injection (B) and 10 min later (C) show focal uptake of ^{99m}Tc-MDP within the lesion (arrow). The pattern is slightly modified (arrow) on the late scan, and normal rib uptake is evident (dot) (D).

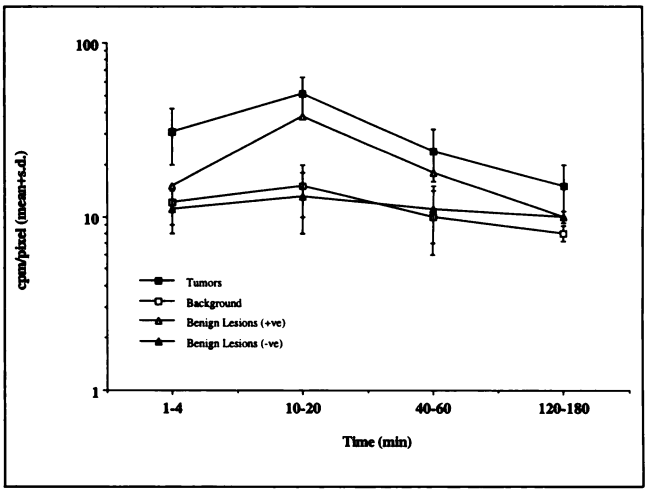

FIGURE 2. Time-activity curves of ^{99m}Tc-MDP in malignant lesions, benign lesions and normal breasts measured as cpm/pixel using ROIs method.

clearly detectable (Fig. 1). The T/B ratios at this time point decreased to 1.3 ± 0.5. The time-activity curves recorded in tumors, benign lesions and normal glands are shown in Figure 2.

The changes in T/B ratios reflected the decrease of ^{99m}Tc-MDP content within tumors. In fact, in the majority of patients, the tracer migrated from the lesion to the surrounding tissue. The best imaging time occurred between 10 and 20 min after tracer injection.

A specific pattern of uptake was found in the 17 patients with inflammatory carcinoma. In the early images, the tumor is recognized as a well-defined focus of increased uptake, which decreased in the late scans; whereas activity delineated infiltrated skin (Fig. 3). Conversely, acute inflammatory processes showed faint, nonhomogeneous uptake of ^{99m}Tc-MDP without signs of skin infiltration. Thus, the sign of activity in infiltrated skin may permit differentiation between malignant and benign inflammatory processes.

Size and site seem to affect successful breast cancer imaging with ^{99m}Tc-MDP scintimammography. Of the 14 false-negative lesions, 10 were nonpalpable (largest cross-sectional diameter <10 mm) and 4 were smaller than 15 mm. These tumors were peripherally located in the inner quadrants of small breasts. In this group, however, 20 breast cancers smaller than 10 mm and 66 smaller than 20 mm were clearly depicted (Fig. 4 and Table 2). These lesions were frequently located in outer quadrants and were superficial. Tumor type did not interfere with ^{99m}Tc-MDP uptake. Histological, mammography and scintimammography findings, classified on the basis of the tumor size, are summarized in Table 2.

Twenty-six of 28 benign lesions did not show focal uptake of ^{99m}Tc-MDP. The biodistribution and the T/B ratios measured during the different time points mirrored those observed in normal breasts (Fig. 2). One sclerotic fibroadenoma with the largest diameter of 22 mm and one mixoid fibroadenomas (18 mm) showed positive uptake (Fig. 5) on the 10–20-min images. The time-activity curves mirrored those encountered in malignant lesions (Fig. 2). The T/B ratios, however, were significantly lower. These differences might aid in differentiating malignant from rare benign lesions that concentrated ^{99m}Tc-MDP.

In the 53 women with indeterminate mammograms, scintimammography findings characterized 43 lesions (81%) correctly. In particular, positive ^{99m}Tc-MDP uptake was seen in 17 of 25 carcinomas (68%), whereas 26 of 28 benign lesions (93%) were negative. Among the eight missed malignant lesions, four were smaller than 10 mm and four smaller than 15 mm. The results in this subset of patients are summarized in Table 3.

Metastatic axillary lymph nodes greater than 3 cm in size avidly concentrated ^{99m}Tc-MDP and were most recognizable on the early images. Skeletal metastases were found in only seven patients with primary breast cancer (4%) after bone scintigraphy.

Group 2

Physical Examination and Mammography. Eighty patients with solid tumors other than breast cancer under-

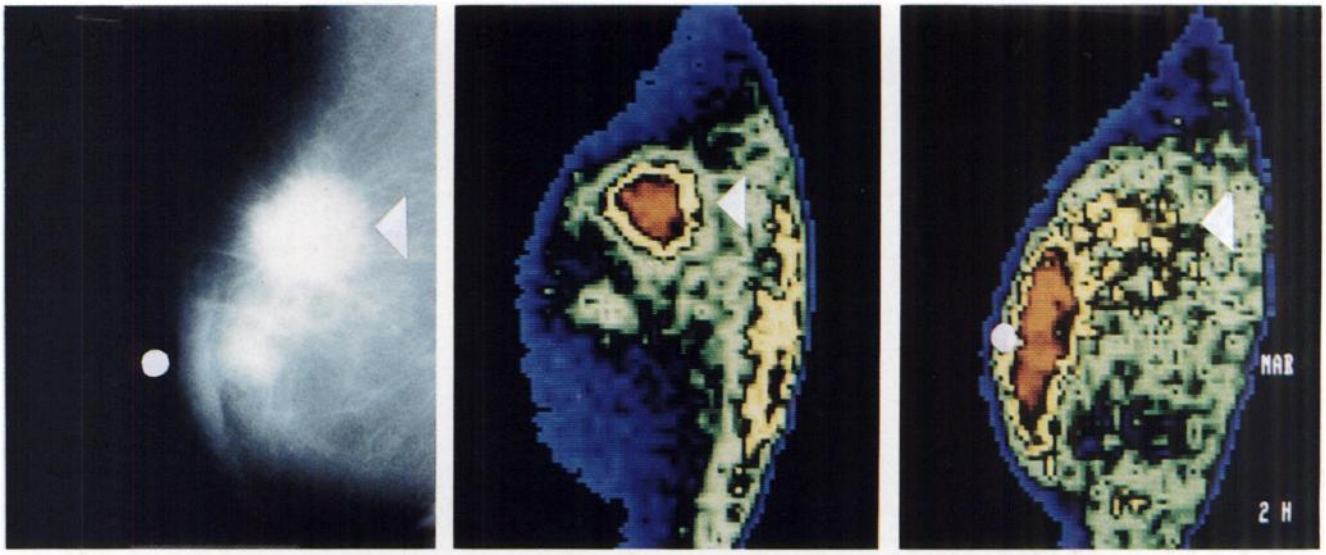

FIGURE 3. Inflammatory cancer of the left breast in a 65-yr-old-woman. A large mass in the upper quadrant (arrow) and skin infiltration are clearly evident (dot) (A). Scintimammography in the early images shows ^{99m}Tc-MDP accumulation in the mass (arrow) (B). Late image demonstrates decreased activity within the lesion (arrows) and tracer appearance in infiltrated skin (circle) (C).

went physical examination and mammography. The presence of breast abnormalities with a definitive diagnostic pattern for benign disease was documented in 35 patients (Subgroup I) and ruled out in 45 (Subgroup II). Cytology of fine needle biopsies corroborated the diagnosis of benign diseases in the Subgroup I (Table 4).

MDP Scintimammography. No or faint uptake of ^{99m}Tc-MDP was detected in patients of Subgroup II, where no clinical or mammographic abnormalities were found. The faint uptake might mirror the parenchymal contents within the breast. Analysis of time-activity curves showed a constant uptake of ^{99m}Tc-MDP during the study.

One patient with a mixoid fibroadenoma (diameter 25 mm) had positive tracer accumulation in Subgroup I. Thus, 3 of 63 benign lesions (28 Group 1 and 35 Subgroup I) were false-positive according to scintimammography.

Statistical Analysis

For images collected at 10–20 min, the sensitivity was 92% in patients with histologically proven breast cancer (158/172) and 4.7% in patients with proven benign lesions (3/63). The specificity was 95%, the accuracy 92%, while the PPV and NPV were 98% and 81%, respectively.

DISCUSSION

The role that mammography plays in diagnosing breast cancer and differentiating malignant from benign lesions, especially in dense breasts, is under debate. Thus, a great interest has been focused on novel approaches which may provide high diagnostic accuracy. Recently, isotope-related techniques have been tested extensively to address

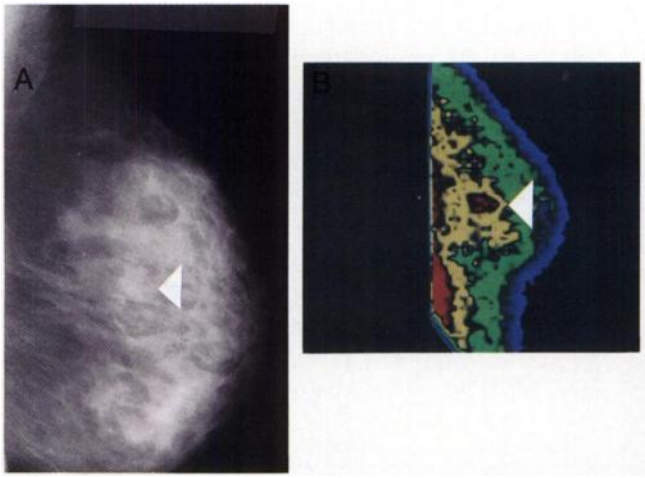

FIGURE 4. Indeterminate mammogram shows opacity (10 mm diameter) with a clear-cut outline in the lower outer quadrant (arrow) of the right breast in a 38-yr-old woman (A). Scintimammography documented focal ^{99m}Tc-MDP uptake corresponding to the mass (arrow) (B). Histological diagnosis was of infiltrating ductal carcinoma.

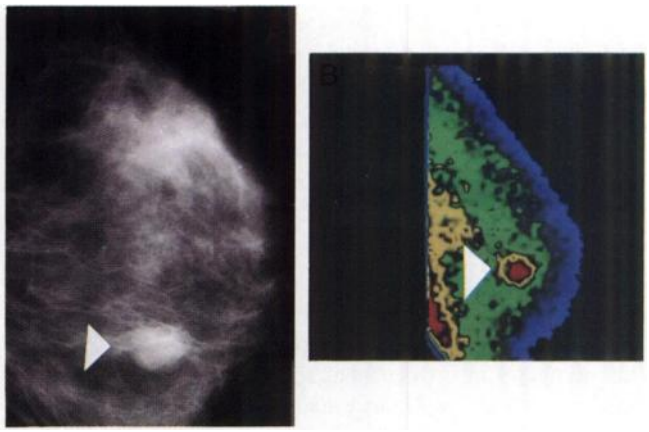

FIGURE 5. Nodular opacity (18 mm diameter) with partly irregular margins in a 50-yr-old woman classified as mammographically indeterminate (A). Scintimammography shows focal uptake (arrow) (B). Histological diagnosis was of myxoid fibroadenoma.

TABLE 2
Results of ^{99m}Tc-MDP Mammoscintigraphy (MMS) Versus Mammographic and Histological Results in Group 1

Histology (size)	Number of lesions	^{99m}Tc-MDP MMS		Mammographic results		
		Positive	Sensitivity (%)	Diagnostic	Suspicious	Indeterminate
Tumors	172	158	92	120	27	25
3–10 mm	30	20	66	15	7	8
10–20 mm	70	66	94	40	17	13
20–50 mm	40	40	100	33	3	4
>50 mm	15	15	100	15	—	—
Inflammatory cancer	17	17	100	17	—	—
Benign lesions	28	2				28

these issues. Scintimammography with ^{201}Tl-chloride showed a sensitivity of 98% in a series of 44 palpable breast tumors, thus allowing correct diagnosis of carcinomas greater than 10 mm. Among benign lesions, only 3 of 13 adenomas were positive, whereas fibrocystic and/or fat necrotic lesions were negative (*19*). Similar findings have also been reported in another series in which ^{201}Tl-chloride scintimammography was used as a complementary test to mammography (*20*). Technetium-99m-sestamibi, a cardiac agent currently used for tumor imaging has identified breast tumors with elevated accuracy (*21,22*). Even more suggestive were preclinical findings with ^{18}F-estradiol, which enabled in vivo definition of the receptor profile within primary and metastatic breast cancer sites (*31,32*). Other receptor studies using ^{111}In-pentetreotide have been performed to define the percentage of breast cancers expressing detectable amounts of somatostatin receptors (*33*).

Previously reported results indicating that extraskeletal uptake of ^{99m}Tc-MDP frequently occurs within primary breast tumors, although with less than acceptable sensitivity, tantalized our interest (*7–12*). Thus, we sought to reevaluate the clinical usefulness of this bone-seeking agent. A few methodological innovations were introduced in the acquisition protocol to overcome the problems which led to the poor results already published (*7–12*). In fact, in previous studies, the images acquired in the anterior and lateral views were collected only 2–3 hr after ^{99m}Tc-MDP infusion. Our series shows that only 38% of primary breast cancers were clearly detectable with elevated T/B ratios. A high rate of detection (92%) was obtained in images collected within the first 20 min. These results reflect increased accumulation of ^{99m}Tc-MDP within malignant lesions. Successively, a progressive decrease was observed because of washout from the lesions. Tracer uptake was not correlated with tumor histotype, grading and status of lymph node involvement. Furthermore, the use of oblique lateral views improved imaging of smaller lesions and lesions located in the inner quadrants.

The mechanism(s) regulating extraskeletal uptake of ^{99m}Tc-MDP are still unclear. Since no binding of ^{99m}Tc-MDP to normal and neoplastic cells has been demonstrated, probably nonspecific phenomena regulate the uptake and dismission from malignant breast lesions. A wide spectrum of reliable hypotheses has been formulated and partly documented (*14*): increased vascularization, inflammatory changes, modifications of local metabolism (Ca^{2+} content, pH) and collagen deposits favor ^{99m}Tc-MDP uptake (*10*). Other factors, common to many tumors, including changes in secretory functions and cell metabolism, enlargement of the interstitial space, cell wall damage and microcalcification in necrotic degenerative tissues, have to be considered (*7,14*). Finally, it has been demonstrated that ^{99m}Tc-MDP uptake in breast cancers might be influenced by hormones, for example, estradiol (*13*). Our results suggest, however, that these proposed mechanisms may only be partially accepted. In fact, if increased ^{99m}Tc-MDP accumulation in the early phases reflects tumor hypervascularization, then trapping within lesions (at 10–20 min) might reflect enlargement of interstitial space. Subsequent tracer disappearance, however, from the majority of tumor nodules is still unclear.

To fully evaluate the diagnostic advantages of scintimammography with ^{99m}Tc-MDP, apart from relative diagnostic accuracy (sensitivity = 92%, specificity = 95%), the role and relative pitfalls of modern mammography need to be discussed briefly. Mammography is the most accurate technique to detect abnormalities, namely nonpalpable masses in fatty breasts (*23–27*). Conversely, it fails in detecting tumors occurring in dense breasts (*29*). Furthermore, mammography lacks adequate specificity (*28*), requiring histology of surgical biopsies for correct diagnosis

TABLE 3
Comparison of Scintimammography Findings in 53 Group 1 Patients with Indeterminate Mammograms

Histology	Number of lesions	Scintimammography findings	
		Positive	Negative
Malignant lesions	25	17	8
<10 mm	8	4	4
10–20 mm	13	9	4
>20 mm	4	4	0
Benign lesions (10–30 mm)	28	2	26

TABLE 4
Rate of ^{99m}Tc-MDP Detection in Overall Benign Breast Lesions

Histology	Number of lesions	Detected lesions
Adenoma	21	0
Fibrocystic dysplasia	20	0
Mastitis	5	0
Intracystic papilloma	4	0
Papillomatosis	4	0
Mixoid fibroadenoma	3	2
Sclerotic fibroadenoma	2	1
Radial scar	2	0
Fat necrosis	2	0

Specificity in this group of patients was 96%.

and resulting in a high rate of biopsies in patients with benign diseases. Therefore, the use of a noninvasive, accurate imaging technique that can discriminate mammographically indeterminate lesions is needed. The results of the present study suggest a role for ^{99m}Tc-MDP scintimammography. In fact, many patients might be spared from unnecessary targeted biopsy or needle aspiration, and short-term periodic mammography may be used during follow-up. Similar high levels of accuracy have been reported for ^{99m}Tc-sestamibi scintimammography (*36–38*). On the other hand, ^{99m}Tc-MDP scintimammography done during routine bone scanning avoids further administration of labeled compounds and is an extremely inexpensive exam. This fact may be considered an advantage over ^{99m}Tc-sestamibi, in which the poor rate for detecting metastatic lymph nodes smaller than 3 cm is the main drawback.

Economic considerations have impacted greatly on implementing new diagnostic procedures because of restrictions in health care programs and significant cuts for expensive exams and procedures (e.g., monoclonal antibodies, color doppler ultrasound, MRI, PET, etc.). Technetium-99m-MDP scintimammography might be a "win-win" situation for both patients and physicians, enabling elevated accuracy and reducing patient stress and cost. Also, no additional expertise or special training is required for nuclear medicine staff since bone scanning is the most frequently performed nuclear medicine procedure. Some concerns might arise from breast surgeons, who usually handle biopsy candidates. They should know, however, that procedures such as ^{99m}Tc-MDP scintimammography may allow a better selection of candidates for surgery.

CONCLUSION

Technetium-99m-MDP scintimammography allows successful, accurate breast carcinoma imaging with elevated PPVs (98%). It is not, however, concentrated in the majority of benign breast lesions. Conversely, the NPV of 81% in our series is affected by tumor size. In fact, for lesions greater than 10 mm, the NPV significantly improved to 94%–100%. The limitations we encountered for detecting lesions smaller than 0.7 cm would probably be avoided by either mammographically or sonographically guided core needle biopsy. Furthermore, placing the patient in the prone position during acquisition, as proposed for ^{99m}Tc-sestamibi scintimammography (*36,37*), or the use of dedicated small field of view gamma cameras, would significantly reduce these limitations. Confirmation of these preliminary results in a larger series might definitely indicate the utility of scintimammography in the management of patients with indeterminate mammograms, aiding in the differential diagnosis between malignant and benign lesions.

ACKNOWLEDGMENTS

Presented in part at the 41st Annual Meeting of the Society of Nuclear Medicine, Orlando, FL, June 5–8, 1994. The authors thank Mr. Aldo Bartiromo for technical assistance and expertise in the acquisition of studies and Mrs. Carmela Imparato for secretarial assistance.

REFERENCES

1. Hahn P, Vikterlof KJ, Rydman H, Beckman KW, Blom O. The value of whole body bone scan in the preoperative assessment of carcinoma of the breast. *Eur J Nucl Med* 1979;4:207–210.
2. O'Connell MJ, Wahner HW, Ahmann DL, Edis AJ, Silvers A. Value of preoperative radionuclide bone scan in suspected primary breast carcinoma. *Mayo Clin Proc* 1978;53:221–226.
3. Coleman RE, Rubens RD, Fogelman I. Reappraisal of the baseline bone scan in breast cancer. *J Nucl Med* 1988;29:1045–1049.
4. Garty I, Friedman A, Sandler MP, Kedar A. Neuroblastoma: imaging evaluation by sequential Tc-99m-MDP, I-131-MIBG and Ga-67-citrate studies. *Clin Nucl Med* 1989;14:515–522.
5. Gordon I, Peters AM, Gutman A, Morony S, Dicks-Mireayx C, Pritchard J. Technetium-99m bone scans are more sensitive than I-123-MIBG scans for bone imaging in neuroblastoma. *J Nucl Med* 1990;31:129–134.
6. Brown ML. The role of radionuclides in the patient with osteogenic sarcoma. *Semin Roentgenol* 1989;24:185–192.
7. Berg GR, Kalisher L, Osmond JD, Pendergrass HP, Potsaid MS. Technetium-99m-diphosphonate concentration in primary breast carcinoma. *Radiology* 1973;109:393–394.
8. Ross McDougall I, Pistenma DA. Concentration of ^{99m}Tc-diphosphonate in breast tissue. *Radiology* 1974;112:655–657.
9. Schmitt GH, Holmes RA, Isitman AT, Hensley GT, Lewis JD. A proposed mechanism for ^{99m}Tc-labeled polyphosphate and diphosphonate uptake by human breast tissue. *Radiology* 1974;112:733–735.
10. Burnett KR, Lyons KP, Theron-Brown W. Uptake of osteotropic radionuclides in the breast. *Semin Nucl Med* 1984;14:48–49.
11. Hobbs S, Neumann RD, Merino MJ, Gunzenhauser J, Carrasquillo JA. Localization of Tc-99m MDP in cystosarcoma phyllodes. *Clin Nucl Med* 1992;17:58–60.
12. Serafini AN, Raskin MM, Zard LC, Watson DD. Radionuclide breast scanning in carcinoma of the breast. *J Nucl Med* 1974;15:1149–1152.
13. Uno K, Uchida Y, Sakata S, et al. Visualization of female breast in bone scintigraphy. *Kaku Igaku* 1992;29:1201–1206.
14. Worsley DF, Lentle BC. Uptake of technetium-99m-MDP in primary amyloidosis with a review of the mechanisms of soft-tissue localization of bone-seeking radiopharmaceuticals. *J Nucl Med* 1993;34:1612–1615.
15. Cancroft ET, Goldsmith SJ. Technetium-99m-pertechnetate scintigraphy as an aid in the diagnosis of breast masses. *Radiology* 1973;106:441–444.
16. Villareal RF, Parkey RW, Bonte FG. Experimental pertechnetate mammography. *Radiology* 1974;111:657–661.
17. Richman SD, Ingle JN, Levenson SM, et al. Usefulness of gallium scintigraphy in primary and metastatic breast carcinoma. *J Nucl Med* 1975;16:996–1001.
18. Richman SD, Brodey PA, Frankel RS, de Moss EV, Tormey DC, Johnston

GS. Breast scintigraphy with Tc-99m pertechnetate and Ga-67 citrate. *J Nucl Med* 1975;16:293–299.
19. Waxman AD, Ramanna L, Memsic LD, et al. Thallium scintigraphy in the evaluation of mass abnormalities of the breast. *J Nucl Med* 1993;34:18–23.
20. Lee VW, Sax EJ, McAneny DB, et al. A complementary role for thallium-201 scintigraphy with mammography in the diagnosis of breast cancer. *J Nucl Med* 1993;34:2095–2100.
21. Waxman AD, Ashok G, Kooba A, et al. The use of Tc-99m methoxy isobutyl isonitrile (MIBI) in evaluation of patients with primary carcinoma of the breast: comparison with Tl-201 (T1) [Abstract]. *J Nucl Med* 1993; 34(suppl):139P.
22. Khalkhali I, Mena I, Jouanne E, Diggles L, Alle K, Klein S. Technetium-99m-sestaMIBI prone breast imaging in patients with suspicion of breast cancer [Abstract]. *J Nucl Med* 1993;34(suppl):140P.
23. American Cancer Society. Mammography guidelines. *Cancer* 1983;33:255.
24. Kopans DB, Mayer E, Cohen AM, et al. Palpable breast masses: the importance of preoperative mammography. *JAMA* 1981;246:2819–2822.
25. Baker LH. Breast cancer detection and demonstration project: five years summary report. *Cancer* 1982;32:194–225.
26. Sickles EA. Mammographic features of early breast cancer. *AJR* 1984;143: 461–464.
27. Sickles EA. Mammographic features of 300 consecutive non-palpable breast cancer. *AJR* 1986;146:661–663.
28. Kopans DB. The positive predicitive value of mammography. *AJR* 1992; 158:521–526.
29. Bird RE, Wallace TW, Yankaskas BC. Analysis of cancer missed at the screening mammography. *Radiology* 1992;184:613–617.
30. Jackson VP, Hendrick RE, Kerg SA, et al. Imaging of the radiographically dense breast. *Radiology* 1993;198:297–301.
31. McGuire AH, Dehdashti F, Siegel BA, et al. Positron tomographic assessment of 16 alpha-[^{18}F]fluoro 17-beta-estradiol uptake in metastatic breast cancer. *J Nucl Med* 1991;32:1526–1531.
32. Mintun MA, Welch MJ, Siegel BA, et al. Breast cancer: PET imaging of estrogen receptors. *Radiology* 1988;169:45–48.
33. Lamberts SWJ, Krenning EP, Reubi JC. The role of somatostatin and its analogs in the diagnosis and treatment of tumors. *Endocrinol Rev* 1991;12: 450–482.
34. Peller PJ, Ho VB, Kransdorf MJ. Extraosseous Tc-99m-MDP uptake: a pathophysiologic approach. *Radiographics* 1993;13:715–734.
35. Yelland A, Graham MD, Trott PA, et al. Diagnosing breast carcinoma in young women. *Br Med J* 1991;302:618–620.
36. Waxman A, Nagaraj N, Ashok G, et al. Sensitivity and specificity of Tc-99m methoxy isobutyl isonitrile (MIBI) in the evaluation of primary carcinoma of the breast [Abstract]. *J Nucl Med* 1994;35(suppl):22P.
37. Khalkhali I, Cutrone J, Mena I, Diggles L. Clinical and pathological follow-up of 100 patients with breast lesions studied with scintimammography (SMM) [Abstract]. *J Nucl Med* 1994;35(suppl):22P.
38. Lastoria S, Varrella P, Mainolfi C, et al. Technetium-99m-sestamibi scintigraphy in the diagnosis of primary breast cancer [Abstract]. *J Nucl Med* 1994;35(suppl):22P.