Diagnostic Value of ^{99m}Tc-Methylene Diphosphonate and ^{99m}Tc-Pentavalent DMSA Compared with ^{99m}Tc-Sestamibi for Palpable Breast Lesions

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Different radiopharmaceuticals have been used to detect breast cancer. Among them, sestamibi has been extensively studied and has come to have a well-recognized role in the evaluation of palpable breast lesions. The goal of this study was to compare the diagnostic value of ^{99m}Tc-labeled compounds, such as methylene diphosphonate (MDP) and pentavalent dimercaptosuccinic acid (DMSA-V), with sestamibi for palpable breast lesions, in the scope of a multicenter trial sponsored by the International Atomic Energy Agency. **Methods:** Patients from 7 countries were included: 47 women (mean age, 54 ± 13 y) examined with MDP and sestamibi and 111 women (mean age, 55 ± 12 y) examined with DMSA-V and sestamibi. Cancer was diagnosed in 41 of 49 lesions from the MDP group and in 78 of 113 lesions from the DMSA-V group. Axillary lymph node involvement was observed in 18 of 30 patients from the first group and in 27 of 53 patients from the second group. Prone scintimammography was performed using a dose of 740 MBq of each tracer, and diagnostic values were calculated from a masked interpretation of scans. **Results:** In the first group, the sensitivity for sestamibi and MDP studies was 82.9% and 65.9%, respectively, with a specificity of 87.5% and 50%, respectively. In the second group, the sensitivity for sestamibi and DMSA-V studies was 87.2% and 65.4%, respectively, with a specificity of 77.1% and 74.3%, respectively. Regarding axillary involvement, the sensitivity was 33.3% for sestamibi in both groups, whereas the values for MDP and DMSA-V were 16.7% and 7.4%, respectively. In contrast, the specificity for sestamibi was 83.3% and 92.3% for the first and second groups, respectively, and the specificity for MDP and DMSA-V was 91.7% and 100%, respectively. **Conclusion:** Sestamibi is the most adequate alternative among the mentioned ^{99m}Tc-labeled radiopharmaceuticals for the evaluation of palpable breast lesions.

Key Words: ^{99m}Tc-sestamibi; ^{99m}Tc-methylene diphosphonate; pentavalent ^{99m}Tc-DMSA; scintimammography; breast cancer

J Nucl Med 2002; 43:882–888

The role of ^{99m}Tc-labeled radiopharmaceuticals for the diagnosis of breast cancer is still under evaluation. It is accepted that nuclear techniques are not appropriate for screening but may be helpful for the evaluation of specific subgroups as complementary techniques to radiologic mammography (*1–5*). After the initial studies with ^{201}Tl, several tracers have been used with variable results. Furthermore, they have been used in populations with different characteristics and lesion types (*6,7*). ^{99m}Tc-radiotracers including sestamibi, methylene diphosphonate (MDP), tetrofosmin, radiolabeled antibodies, and pentavalent dimercaptosuccinic acid (DMSA-V), as well as ^{111}In-octreotride and ^{18}F-FDG, have been evaluated in breast cancer patients by various investigators (*7–12*).

^{99m}Tc-Sestamibi is postulated as an appropriate tracer for evaluating primary breast lesions for malignancy, especially in women with palpable lumps, dense breasts, or mammographically indeterminate lesions > 1 cm (*2,13,14*). Sensitivity values have ranged from 72% to 100%, with higher values obtained for patients with palpable or large lesions (*3,6*). Sestamibi is a lipophilic molecule, and its cellular uptake is related to mitochondrial activity and electric transmembrane potential. Sestamibi has also been described as a substrate of P-glycoprotein, which is associated with the multidrug resistance phenotype (*15–17*).

Received Sep. 11, 2001; revision accepted Feb. 21, 2002.

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Diphosphonates such as MDP and DMSA-V, because of their easier availability and lower cost, were proposed by some investigators as interesting alternatives to sestamibi. MDP is widely used to scan for bone metastases from breast cancer. Encouraging results were initially reported for early-phase MDP scintimammography (*10*). Although less studied, DMSA-V scanning was used in breast cancer patients as a complementary procedure to MDP scanning for the evaluation of suggestive bone lesions (*18–20*). This radiopharmaceutical is currently used in the evaluation of medullary thyroid cancer. Tumor uptake has also been described for other lesions, such as hepatocellular carcinoma (*21–23*). Recently, DMSA-V was used to assess primary lesions and axillary involvement in breast cancer patients (*11*,*24*). Several mechanisms have been advocated as responsible for the uptake of both radiopharmaceuticals. DMSA-V seems to be a pH-sensitive agent related to glucose-mediated acidosis. Therefore, acidification appears to mediate its tumor accumulation (*25*).

The aim of this study was to investigate the clinical value of 2 ^{99m}Tc-labeled radiopharmaceuticals (MDP and DMSA-V) and to compare them with sestamibi in the framework of a prospective, open, multicenter trial by the International Atomic Energy Agency on women with palpable breast lesions.

MATERIALS AND METHODS

Population

We included, as a first group, 47 women (mean age, 54 ± 13 y) with palpable breast lesions examined with ^{99m}Tc-MDP and ^{99m}Tc-sestamibi and, as a second group, 111 women (mean age, 55 ± 12 y) examined with ^{99m} Tc-DMSA-V and ^{99m}Tc-sestamibi. They were recruited from countries in Asia (China and India), Europe (Greece), the Middle East (Turkey), and South America (Chile, Colombia, and Uruguay). The countries had different prevalences of breast cancer, with breast cancer age-standardized annual incidences (estimated in 1990 by Parkin (*26*)) ranging from 11.77 (China) to 87.59 (Uruguay), with a median of 28.66.

Inclusion and Exclusion Criteria

To be included in the study, a participant had to be a nonpregnant woman older than 18 y; have a palpable breast lesion that was diagnosed by an experienced surgeon; have undergone x-ray mammography within 4 wk of nuclear scans, with films available; have received a recommendation for excisional biopsy, with histopathology report available; and have given informed consent. A participant was excluded from the study if she underwent prior surgery of the breast because of a palpable lesion, underwent fine-needle biopsy within 1 wk before scintigraphy or core biopsy during the previous 4 wk, received prior chemo- or radiotherapy, or had no histopathology report available.

Radionuclide Study Protocol

The same protocol was used in all countries.

Sestamibi and MDP or DMSA-V paired studies were performed within 1 wk of each other and at least 48 h apart, with 10-min images being acquired 10 min after injection. Sestamibi delayed images were acquired 1 h after injection. DMSA-V delayed images were also acquired, but only early-phase scans were selected for this presentation.

All breast images were acquired with the patient prone. A low-energy, high-resolution collimated gamma camera was used, with appropriate zooming for lateral views to include the axilla, breast, and chest wall and with minimization of the distance between the breast and the detector. A special breast holder (Pinestar Technology, Greenville, PA) designed to support the patient's head, shoulders, and arms while allowing a pendent imaged breast and compressing the opposite breast was provided to all centers and used for lateral views. After the lateral views, 10-min anterior thoracic views of all patients were acquired for axillary evaluation.

^{99m}Tc-Sestamibi Scintimammography. Labeling and quality control of ^{99m}Tc-sestamibi were performed according to the manufacturer's instructions (DuPont Radiopharmaceuticals, North Billerica, MA). The radiochemical purity of the radiopharmaceutical was always ≥90%.

^{99m}Tc-Sestamibi was injected into the arm through an indwelling catheter, on the side opposite the palpable breast lesion, followed by a 10-mL saline flush. In patients with bilateral lesions, the injection was into a dorsal vein of the foot. The dose ranged from 740 to 1,110 MBq (20–30 mCi).

DMSA-V and MDP were also labeled according to manufacturer's instructions, using a mean dose of 740 MBq.

Histologic Confirmation. The median interval between scintimammography and histologic confirmation by biopsy was 18 and 11 d for the first and second groups, respectively. Histopathologic reports showed 41 malignant and 8 benign lesions in the first group and 78 malignant and 35 benign lesions in the second group. Table 1 summarizes the histologic characteristics of all lesions. Two patients in each group had bilateral palpable lesions. The mean lesion size was 26 ± 13 mm (range, 5–70 mm) and 25 ± 13 mm (range, 7–65 mm) for the first and second groups, respectively.

Axillary dissection was performed for 30 patients of the first group and for 53 patients of the second group. Axillary metastases were found in 18 of the 30 and in 27 of the 53.

TABLE 1
Histologic Features of Breast Biopsy Samples from All Patients

Histology	MDP-sestamibi	DMSA-V-sestamibi
Benign	8	35
Fibroadenoma	3	16
Fibrocystic disease/adenosis	3	8
Lipoma	0	2
Papilloma	0	2
Hamartoma	0	1
Mastitis/inflammation	2	1
Not specified	0	5
Malignant	41	78
Ductal carcinoma	28	67
Lobular carcinoma	3	3
Mucinous carcinoma	1	2
Intraductal carcinoma	1	0
Ductal carcinoma in situ	1	2
Phyllodes	0	1
Fibroadenocarcinoma	1	0
Infiltrating carcinoma (not specified)	6	3

Analysis and Statistics. All studies were read by 2 independent and experienced observers, with a third acting as a referee in cases of discordant opinions. The observers were unaware of the clinical status of the patients and of the results of physical examination, mammography, other nuclear scans, and histopathology. A scan was considered to indicate malignancy if it showed an accumulation of tracer that was well defined, focal, and higher than the background level, regardless of uptake intensity. Sensitivity, specificity, and likelihood ratios for positive and negative studies, with their respective 95% confidence intervals, were calculated for the different radiotracers and groups of patients. Differences among diagnostic values were analyzed using the McNemar test. To obtain a homogeneous sample, we excluded technically inappropriate scans (9%), such as those that had confusing labeling, included only 1 breast, or were too pale or too dark.

RESULTS

Breast Cancer Involvement

Tables 2 and 3 show the results for lesion classification.

Sestamibi Versus MDP. Sensitivity tended to be higher for sestamibi than for MDP. Specificity and likelihood ratios were similar for both tracers (Table 4). In 7 cases (6 of ductal invasive carcinoma and 1 of ductal in situ carcinoma), assignment was correct only for sestamibi. A case of inflammatory process and ductal ectasia was false-positive for both methods.

Sestamibi Versus DMSA-V. Sestamibi was more sensitive than DMSA-V ($P < 0.0005$; Table 5). A higher number of false-negative findings was observed with DMSA-V (all for tumors > 11 mm in diameter), mostly for cases of invasive ductal carcinoma (22 cases) but also for 2 cases of ductal noninvasive cancer, 1 case of lobular carcinoma, 1 case of mucinous carcinoma, and 1 case of in situ carcinoma. Additionally, a higher positive likelihood ratio was obtained with sestamibi scans. Diffuse bilateral uptake of DMSA-V was observed in 75% of patients. Nipple uptake was also a common finding.

Axillary Involvement

Sestamibi Versus MDP. The sensitivity of both radiopharmaceuticals was suboptimal (without significant differences) for detecting axillary node involvement. Specificity was high for both (Table 6).

Sestamibi Versus DMSA-V. Although sensitivity was low for both radiopharmaceuticals, the value was significantly higher for sestamibi than for DMSA-V ($P = 0.023$). Specificity was high for both, without significant differences (Table 7).

In different countries, interobserver concordance for breast lesion interpretation ranged from 77% to 97% for sestamibi, from 83% to 93% for MDP, and from 75% to 98% for DMSA-V. For axillary evaluation, the values ranged from 82% to 100% for sestamibi, from 75% to 100% for DMSA-V, and from 66% to 90% for MDP. A special case, evaluated with all 3 radiopharmaceuticals, is displayed in Figure 1.

TABLE 2
Comparison of MDP and Sestamibi Results for Palpable Breast Lesions

Result	MDP	Sestamibi
True-positive	27	34
False-negative	14	7
True-negative	4	7
False-positive	4	1
Total	49	49

TABLE 3
Comparison of DMSA-V and Sestamibi Results for Breast Lesion Detection

Result	DMSA-V	Sestamibi
True-positive	51	68
False-negative	27	10
True-negative	26	27
False-positive	9	8
Total	113	113

DISCUSSION

The diagnostic value of ^{99m}Tc-sestamibi scintimammography has been extensively reviewed by Waxman (*13*), who compared several published studies that found sensitivities ranging from 84% to 94%. Better results were reported for palpable lesions (84%–100%) than for nonpalpable lesions (25%–57%). Global specificity ranged from 72% to 94%, with values between 74% and 87% and between 86% and 90% for palpable and nonpalpable lesions, respectively. The prevalence of cancer ranged from 39% to 84% in the studied populations. Sestamibi scintimammography had appropriate diagnostic values for lesions > 12 mm, whereas its diagnostic accuracy was low for lesions < 7 mm (*2*,*9*,*13*,*27*). Early images proved to be more sensitive than delayed ones. Taillefer (*6*) published an analysis of 20 reports including 2,009 patients scanned with sestamibi. The proportion of palpable to nonpalpable lesions was 2 to 3, with the following mean values and ranges: 85% (67%–95%), 89% (58%–100%), 86% (73%–92%), 89% (67%–100%), and 84% (55%–97%) for sensitivity, specificity, accuracy, positive predictive value, and negative predictive value, respectively. In contrast, the combined use of mammography and scintimammography with sestamibi for suspected primary breast cancer appeared to be better than the use of either technique separately, with a potential for reducing the number of unnecessary breast biopsies (*5*,*14*).

For axillary evaluation, sestamibi showed a high specificity (approximately 90%) but a relatively low sensitivity ranging from 55% to 85%, with an acceptable positive predictive value but a low negative predictive value (*6*,*13*).

DMSA-V showed uptake not only in tumors but also in normal breast glands—a major drawback of the technique (*28*). Few studies have evaluated breast lesions with this

TABLE 4
Comparison of MDP and Sestamibi Diagnostic Value for Palpable Breast Lesions

Index	MDP	Sestamibi	*P*
Sensitivity	65.9% (45.5%–79.9%)	82.9% (68%–92%)	0.11, NS
Specificity	50.0% (15.7%–84.3%)	87.5% (47.3%–99.7%)	0.24, NS
LR, positive lesion	1.3 (0.8–3.3)	6.6 (1.7–37.1)	
LR, negative lesion	0.7 (0.3–1.7)	0.2 (0.09–0.4)	

NS = not statistically significant; LR = likelihood ratio.
Values in parentheses are confidence intervals.

TABLE 5
Comparison of DMSA-V and Sestamibi Diagnostic Value for Palpable Breast Lesions

Index	DMSA-V	Sestamibi	*P*
Sensitivity	65.4% (53.8%–75.8%)	87.2% (77.7%–93.7%)	<0.0005
Specificity	74.3% (56.8%–87.5%)	77.1% (59.9%–89.6%)	>0.99, NS
LR, positive lesion	2.54 (1.50–4.70)	3.81 (2.21–7.26)	
LR, negative lesion	0.47 (0.32–0.67)	0.17 (0.09–0.30)	

NS = not statistically significant; LR = likelihood ratio.
Values in parentheses are confidence intervals.

TABLE 6
Comparison of MDP and Sestamibi Diagnostic Value for Axillary Nodes

Index	MDP	Sestamibi	*P*
Sensitivity	16.7% (3.8%–41.4%)	33.3% (13.4%–59.0%)	0.24, NS
Specificity	91.7% (61.5%–99.8%)	83.3% (51.6%–97.9%)	NE
LR, positive lesion	2.0 (0.3–13.39)	2.0 (0.6–7.9)	
LR, negative lesion	0.9 (0.7–1.3)	0.8 (0.5–1.3)	

NS = not statistically significant; NE = not evaluable; LR = likelihood ratio.
Values in parentheses are confidence intervals.

TABLE 7
Comparison of DMSA-V and Sestamibi Diagnostic Value for Axillary Tumor Detection

Index	DMSA-V	Sestamibi	*P*
Sensitivity	7.4% (0.91%–24.3%)	33.3% (16.5%–54.0%)	0.023
Specificity	100% (86.8%–100%)	92.3% (74.9%–99.1%)	0.47, NS
LR, positive lesion	NE	4.33 (1.20–16.9)	
LR, negative lesion	0.93 (0.78–1.11)	0.72 (0.51–0.95)	

NS = not statistically significant; LR = likelihood ratio; NE = not evaluable.
Values in parentheses are confidence intervals.

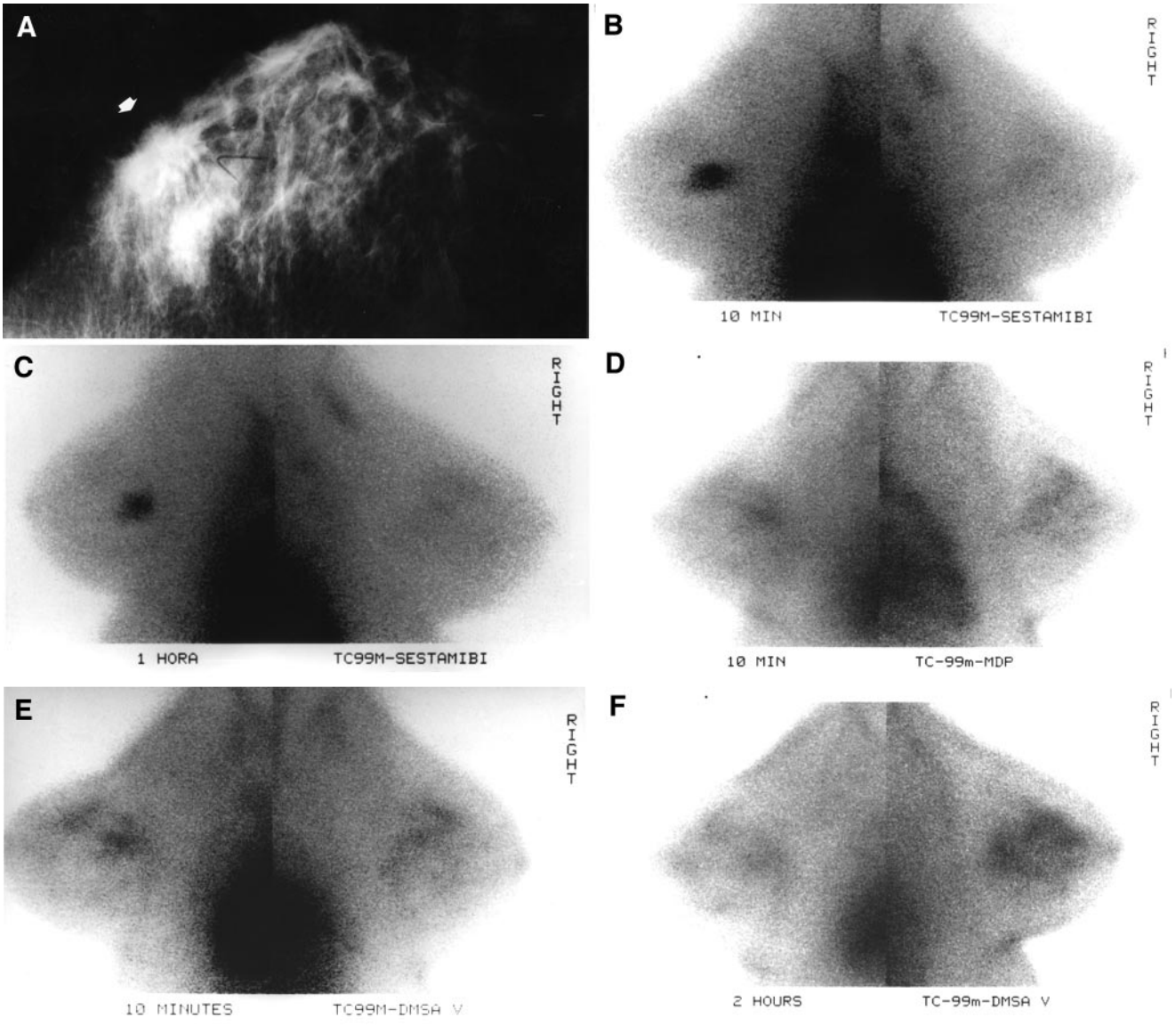

FIGURE 1. A 51-y-old woman with approximately 19-mm palpable lesion of left breast. Craniocaudal mammogram showed probable malignancy (A, arrow). Scintimammograms are displayed in lateral views. Early sestamibi scan at 10 min (B) and delayed sestamibi scan at 1 h (C) showed clear, focal lesion in left breast (true-positive finding). Early MDP scan at 10 min (D) also showed focal uptake in left breast, reported as positive finding and diffuse activity. Early DMSA-V scan at 10 min (E) and delayed DMSA-V scan at 2 h (F) showed focal and diffuse uptake in left breast, reported as positive finding for early scan. Compared with other 2 radiopharmaceuticals, sestamibi showed net focal uptake and almost no contralateral activity. Histopathology showed ductal infiltrating carcinoma in left breast, with 11 of 19 lymph nodes in left axilla positive for cancer. HORA = hour.

tracer. Ambrus et al. (*11*) compared sestamibi with DMSA-V in 51 women with palpable breast lesions (22% of them benign). DMSA-V was not helpful for differentiating breast lesions and was no better than sestamibi using visual evaluation and quantitative data with receiver operating characteristic analysis. For axillary evaluation, these investigators found a sensitivity of 53% for both tracers and a specificity of 81% and 95% for sestamibi and DMSA-V, respectively. Papantoniou et al. (*24*), in a recent report, compared DMSA-V with sestamibi in 41 patients with palpable and nonpalpable breast lesions using early (10–20 min) and delayed (60–70 min) imaging; they obtained a sensitivity of 88.4% and a specificity of 93.3% for both radiopharmaceuticals. For lymph node involvement also, their values were similar for both tracers; sensitivity was 78.9% and specificity was 86.3%. In our experience, the diagnostic value of DMSA-V for breast cancer was significantly lower than that of sestamibi. Our observation of diffuse uptake of DMSA-V in normal breasts agrees with data published by Nakamato et al. (*28*). DMSA-V has also been proposed as an alternative to sestamibi for the evaluation of in situ ductal carcinomas (*29*); the value of that

specific use needs to be confirmed with more data. However, according to our unbiased experience, sestamibi has greater value in the diagnosis of breast cancer in patients with palpable lesions.

Regarding diphosphonates, Piccolo et al. (*10*) reported a high diagnostic value for MDP scintimammography in 200 patients with suspicion of breast cancer (14% with benign lesions). That study also had a control group (including 80 women with other breast and nonbreast solid tumors). Sensitivity was 92% for early images, whereas delayed scanning detected fewer lesions. The same group of investigators (*30*) reported later data comparing the technique with mammography in 400 patients. In the subgroup of women with indeterminate mammograms, MDP scintimammography had a diagnostic accuracy of 84%. A larger series, with 2,000 patients, showed overall sensitivity of 92%, specificity of 90%, and accuracy of 91% (*31*). Sensitivity was affected by lesion size, and specificity was affected by sclerotic or hyaline or myxoid fibroadenomas, which may yield false-positive results. Lee et al. (*32*) reported, for 65 patients (23% with benign lesions), a sensitivity of 88%, a specificity of 93%, and an accuracy of 89% for MDP. Atasever et al. (*33*), studying 96 patients, concluded that MDP was helpful if used in conjunction with mammography to preclude unnecessary biopsies. In a subgroup of 52 palpable lesions, MDP revealed 12 of 13 malignant lesions.

Arslan et al. (*34*) recently performed a comparative study with sestamibi and MDP on a small sample of 20 patients and, for early images, found an overall sensitivity and specificity of 71.4% and 62.5%, respectively, for MDP and 90.4% and 62.5%, respectively, for sestamibi. Delayed MDP scans showed 100% specificity but only 23.8% sensitivity. Moreover, the sensitivity of MDP was lower than that of sestamibi in detecting metastatic axillary involvement (50% vs. 67%). Wilczek et al. (*35*) studied a series of 20 women with large breast masses and proposed that MDP SPECT may be helpful only for postmenopausal patients without hormone replacement. This proposal was based on the visualization of normal parenchyma for 8 of 20 lesions, indicating a very low specificity.

Our MDP scintimammography results and the results of others (*10*,*31*–*33*) are discrepant. Our diagnostic values were much lower than those reported for nonpaired studies. Our data showed lower diagnostic values for MDP than for sestamibi. Nevertheless, a significant difference was not reached, probably because of the sample size. The explanation for this difference could be an acquisition that was too delayed. Piccolo (*10*) observed that tumoral uptake decreased significantly after 40–60 min after injection as soft-tissue activity increased; however, our protocol was designed accordingly, with images taken early after injection. Even though we found only a trend toward better diagnostic values for sestamibi scintimammography than for MDP, our data agree with the reports of Arslan et al. (*34*) and Wilczek et al. (*35*). Nishiyama et al. (*36*) also recently reported a lower value for hydroxymethylene diphosphonate than for sestamibi on quantitative analysis of breast and axillary lesions; their sample size was similar to ours (44 palpable tumors and 6 nonpalpable tumors, but all proven priorly through fine-needle aspiration). Even more, our findings coincide with those of Inoue et al. (*37*) in that the increased parenchymal activity of bone-seeking agents disturbed visualization of primary breast cancer, especially in patients younger than 50 y.

This study clearly showed that sestamibi is superior to DMSA-V for breast cancer detection. Halac et al. (*38*), in a comparison of both radiopharmaceuticals in 31 patients, also found a lower diagnostic accuracy for DMSA-V. This fact could be explained by breast tracer accumulation of DMSA-V in nonpathologic conditions (*28*,*39*). Our results with DMSA-V showed a good specificity only for axillary node evaluation, but the sensitivity was too low for DMSA-V to be considered clinically useful. The important discrepancy with the good results reported previously for DMSA-V in breast cancer evaluation indicates a need for caution in applying the tracer widely.

The principal strength of this study was its use of a head-to-head comparison of different radiopharmaceuticals in patients with palpable breast lesions. For analysis, we chose only early sestamibi images on the basis of our own experience (*40*) and that of others.

A possible disadvantage of this study could be the relatively moderate number of patients in the group scanned with MDP and sestamibi. A larger number of cases could improve the observed difference between both tracers. In contrast, an adequate number of patients was included in the DMSA-V group. The high prevalence of malignant cases in the MDP group (83.6%) reflects, in part, the relatively higher prevalence of breast cancer in the countries supplying most of the cases in this group but also a trend for clinicians to perform fine-needle aspiration instead of open surgery if benign disease was probable.

CONCLUSION

Among the proposed ^{99m}Tc-labeled radiopharmaceuticals, sestamibi is the best choice for the evaluation of patients with palpable breast lesions. MDP and DMSA-V had less diagnostic value.

ACKNOWLEDGMENTS

The authors thank Dr. Dimitri Papantoniou, Alexandria University Hospital, Greece, for providing us with cases and Dr. Jamshed Bomanji, University College of London Medical School, England, for his suggestions. The authors are also grateful to all staff clinicians and technologists in the participant countries who contributed to the success of this coordinated work. This study was supported by a grant (IAEA E1.30.17) from the International Atomic Energy Agency, in the framework of the coordinated research project "Evaluation of ^{99m}Tc-Radiopharmaceuticals in the Diagnosis and Management of Breast Cancer Patients."

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