Scintimammography with 11β-Methoxy-(17α,20Z)-[^{123}I]Iodovinylestradiol: A Complementary Role to ^{99m}Tc-Methoxyisobutyl Isonitrile in the Characterization of Breast Tumors

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The aim of this study was to investigate a possible relationship between ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) uptake and the estrogen receptor (ER) status of breast tumors as determined by 11β-methoxy-(17α,20Z)-[^{123}I]iodovinylestradiol (MIVE) scintimammography. **Methods:** Thirteen patients referred for MIVE scintimammography after abnormal mammography or finding of a suspect mass on physical examination were injected intravenously with MIVE. Planar images of the breasts and axillary region were taken with both radiopharmaceuticals and compared with pathologic examination of the tumor tissue and in vitro ER quantification. **Results:** The presence of cancerous tissue, as indicated by MIBI uptake, is a prerequisite for the accumulation of MIVE by the breast tumors. There was no statistically significant correlation between the MIBI and MIVE tumor uptake ratios. However, the latter correlate well with the presence of ER, as determined by an in vitro assay. **Conclusion:** MIVE scans add unique information concerning the tumor ER status in breast cancer patients, which could contribute to a better characterization of the tumor and aid in the selection of the most appropriate treatment protocol.

Key Words: estrogen receptors; iodovinylestradiol; MIVE; ^{123}I; breast cancer; MIBI

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Diagnostic mammography is the method of choice for breast tumor screening (*1*). However, mammography is frequently incapable of differentiating between malignant and benign lesions (*2*), and most published studies report positive predictive values for mammography ranging between 10% and 40% (*3–5*). This high level of false-positive indicators results largely from breast biopsies performed on benign lesions and represents an unnecessary burden to the patient and a high cost (*5*). Furthermore, conditions such as fibrocystic disease, dense breast tissue and status after biopsy, surgery, or radiotherapy make the interpretation of the mammogram difficult. ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) scintimammography is a useful diagnostic test to differentiate between benign and malignant lesions in patients presenting an equivocal or nondiagnostic mammogram (*6,7*). MIBI exists as a cation, which diffuses freely into tumor cells where they bind primarily to the mitochondria (*8*). Thus, MIBI tissue uptake represents both blood flow and tumor metabolic activity (Fig. 1). A relationship between the initial intensity of MIBI uptake and the aggressiveness of several types of tumors, including breast cancer, has been suggested (*9,10*). Because aggressive breast tumors usually are less differentiated, an inverse relationship between MIBI uptake and estrogen receptor (ER) levels may be expected. However, no relationship between ER expression and MIBI uptake has been reported to date. MIBI is also used to monitor the response to therapy in patients with breast cancer; reduction of MIBI tumor uptake during the course of hormone therapy or chemotherapy indicates a good response to treatment (*11*).

Knowledge of the ER status of the tumor is an important factor in considering the proper management of breast cancer patients (*12–14*), with the likelihood of response to hormone therapy being roughly proportional to the concentration of ER in the tumor (*12*). ER-positive cancers also have a more favorable prognosis than ER-negative cancers. Scintigraphic imaging of the ER, using a radiolabeled estrogen, could provide valuable information on the hormone status of the tumor. ER ligands that have been considered for this purpose include both ^{18}F- (*15–17*) and ^{123}I-labeled estrogens (*18–20*), which exhibit high affinity and specificity for the ER. Recent clinical studies indicate that 11β-methoxy-(17α,20Z)-[^{123}I]iodovinylestradiol (MIVE) uptake by ER-positive breast tumors correlates well with in vitro ER measurements (*21,22*). The aim of this study was to investigate a possible relationship between MIBI uptake and the ER status of the tumor as determined by in vivo MIVE uptake.

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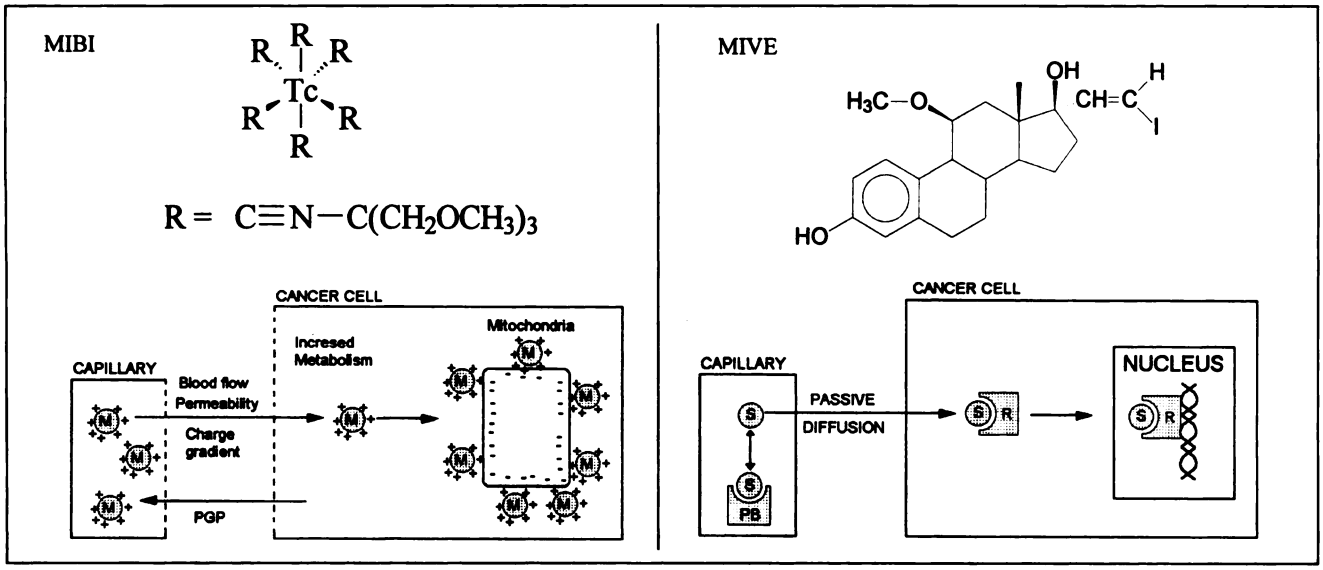

FIGURE 1. Mechanism of MIBI and MIVE uptake. M = ^{99m}Tc-MIBI complex; PGP = P-glycoprotein; R = receptor; S = substrate (MIVE); PB = plasma-binding proteins.

MATERIALS AND METHODS

Patients

The 13 women (mean age, 56 ± 12 y; age range, 40–79 y) participating in the study were referred for MIVE scintimammography after abnormal mammography or finding of a suspect mass on physical examination. All patients also underwent MIBI scintimammography as part of the regular diagnostic protocol to determine the nature of the lesion. In each patient, MIBI and MIVE images were interpreted independently. MIBI-positive patients were referred for histopathologic confirmation by biopsy and subjected to surgery. The MIBI-negative patients also underwent biopsy to confirm the fibrocystic nature of the lesion. Women younger than 18 y old or those who were pregnant (pregnancy test was required of all women of childbearing age) or lactating were excluded from the study. An internal review board approved the clinical protocol, and all participants signed an informed consent.

Radiopharmaceutical Synthesis

MIVE was prepared as described (*22*). The following manipulations were performed in a sterile hood. The freshly synthesized MIVE dissolved in 2 × 1.0 mL ethanol was transferred into a sterile and pyrogen-free vial through a 0.22-μm filter and evaporated to dryness. Ethanol (0.2–0.4 mL) was added to the vials containing the dry MIVE followed by the addition of 2–4 mL of a 20% lipid emulsion (Intralipid; Pharmacia, Mississauga, Ontario, Canada). The Intralipid was added rapidly to the ethanol solution while swirling the vial. An aliquot of the preparation was retained for pyrogenicity testing with the *Limulus* amebocyte lysate kit (Biowhittaker Inc., Walkersville, MD). The content of the vial was transferred to a syringe, and the activity was measured in a dose calibrator. MIBI (Miraluma; DuPont Merck Pharmaceutical, Billerica, MA) was prepared according to the manufacturer's recommendations.

Imaging

Scintigraphic images were recorded with a Starcam 4000i XRT gamma camera (General Electric, Saint Albans, UK) equipped with a parallel-hole, low-energy, high-resolution collimator. The windows of the camera were open at 20% and adjusted at 159 keV for ^{123}I and at 140 keV for ^{99m}Tc. MIBI and MIVE images were recorded as a 256 × 256 pixel matrix. Image analysis was performed on a Genie PNR model nuclear medicine dedicated computer (General Electric). Prone breast scintigraphy was performed with a special table using the technique described by Khalkhali et al. (*23*). The radiopharmaceuticals dissolved in 1–2 mL (740 MBq MIBI; 150 MBq MIVE) were administrated intravenously through the foot vein or the vein contralateral to the patient's breast with the suspected abnormality while she was resting on the imaging table. The injection site was imaged within minutes after administration to ensure that there was no tissue infiltration. The same imaging sequence was performed in all patients beginning with the lateral view of the breast with the suspected abnormality, followed by the lateral view of the contralateral breast and the anterior view of both breasts and of the axillary region. Scintigraphy was performed 10 min and 1 h after injection; for MIVE, late images up to 24 h after injection were also recorded. The day before and 1 h before the administration of MIVE, each subject was given orally 150 mg of a saturated solution of iodine potassium. For all patients, MIBI and MIVE studies were separated by at least 3 d but were scheduled within 7 d of each other and before surgery or treatment.

Image Analysis

Images were interpreted by 3 experienced nuclear medicine physicians, who were unaware of the results of MIBI scintimammography or biopsy analysis. All focal uptake of radioactivity higher than the background uptake of the breast was considered positive. Diffuse and relatively symmetric breast uptake was considered benign. Tumor-to-normal tissue ratios at 1 h after injection were obtained by drawing regions of interest around the tumors and the adjacent normal tissue.

Tumor Characterization

Tumors were characterized by macroscopic and histologic examination after surgical removal. Grading was done according to Bloom and Richardson (*24*). In vitro quantification of ER and

progesterone receptors (PRs) was done on viable, fresh or frozen surgically removed tumor samples. The receptor quantification was done by immunoassay on tumor cytosol using ER-EIA and PR-EIA monoclonal kits (Abbot Laboratories, Abbot Park, IL). A concentration exceeding 9 fmol of receptor per gram of protein was considered positive. In some cases the result of the receptor assay was further confirmed by immunohistochemistry on formalin-fixed tissue sections from the tumor.

Statistical Analysis

Errors of the mean are presented as mean ± SD. MIBI uptake for the MIVE-positive and -negative groups was compared using a unilateral Student *t* test.

RESULTS

Among the 13 patients investigated, 10 were subsequently diagnosed with breast cancer (Table 1). Pathologic examination established that 8 of the 10 patients had invasive, ductal carcinoma and 2 had invasive, lobular carcinoma. The size of the excised breast tumor masses ranged from 2 to 13 cm (median value, 2.5 cm), whereas in 1 case (patient 11) the complete breast was involved. All patients who showed focal uptake of MIBI were subsequently confirmed as having malignant tumors; the remaining 3 patients showed mild diffuse uptake and were diagnosed with fibrocystic disease (Fig. 2). MIVE uptake was optimal at 1 h after injection. Negative MIVE scintigrams were recorded for all patients with noncancerous lesions. Benign lesions appeared as a diffuse and relatively symmetric uptake in both breasts.

The 10 patients diagnosed with cancer can be separated in 2 groups: concordant uptake (MIBI positive/MIVE positive; n = 5 [patients 1, 6, 10, 11, and 13]) and discordant uptake (MIBI positive/MIVE negative; n = 5 [patients 3, 4, 8, 9, and 12]). Among the first group of patients, 3 tumors were determined (in vitro) to be ER positive and PR positive (patients 6, 10, and 13) (Fig. 3) and 2 tumors were ER negative (patients 1 and 11) (Figs. 4 and 5), with 1 of them being PR positive (patient 11). All patients of the second group were ER negative (patients 3, 4, 8, 9, and 12) (Fig. 6),with only 1 being PR positive (patient 4).

The scan for patient 1 was MIVE positive, despite negative in vitro ER results. This patient was treated earlier (1992) for a large ER-positive, invasive, lobular carcinoma of the left breast, which required partial mastectomy. A malignant lymph node was discovered in 1997 in the left axilla; this node gave a MIVE-positive scan (Fig. 4) but was classified as ER negative on the basis of cytosol receptor determination. A few months after this study, patient 1 was again diagnosed with an infiltrating, lobular carcinoma of the left breast, which was ER positive and required complete mastectomy. The scans of patient 11 showed focal uptake of MIVE and the presence of PR, despite a negative ER assay. A large necrotic tumor, involving most of the breast, was found. The necrotic central area of the tumor is clearly visible on both MIVE and MIBI scans (Fig. 5).

The uptake of radiotracer was quantified as tumor-to-normal tissue ratios, which are summarized in Table 1. Uptake ratios were found to be optimal at 1 h after injection

TABLE 1
Clinical and Scintigraphic Findings

Patient no.	Age (y)	Disease status				Biochemistry			Imaging*		Ratio†	
		Pathology	Node	Grade‡	Size (cm)	CA-15.3§ (kIU/L)	ER‖ (fmol/mg protein)	PR‖ (fmol/mg protein)	MIVE	MIBI	MIVE	MIBI
1¶	55	ILC (LB)	—	—	2.0	29.1	Neg.	Neg.	Pos.	Pos.	1.46	1.28
2	43	FD	—	—	—	—	—	—	Neg.	Neg.	—	—
3¶	54	IDC (LB)	0/17	G3	2.0	21.9	Neg.	Neg.	Neg.	Pos.	—	1.30
4	42	IDC (LB)	1/18	G2	2.0	12.4	Neg.	38	Neg.	Pos.	—	1.75
5	40	FD	—	—	—	—	—	—	Neg.	Neg.	—	—
6¶	56	IDC (LB)	0/9	G2	—	13.8	81	30	Pos.	Pos.	1.95	1.25
7	45	FD	—	—	—	—	—	—	Neg.	Neg.	—	—
8¶	69	IDC (LB)	1/12	G2	2.5	31.9	Neg.	Neg.	Neg.	Pos.	—	1.90
9¶	73	IDC (LB)	0/0	G2	2.5	—	Neg.	Neg.	Neg.	Pos.	—	1.74
10¶	79	IDC (LB)	0/0	G3	2	—	60	95	Pos.	Pos.	1.61	2.02
11¶	55	ILC (RB)	0/0	—	13.0	25.4	Neg.	16	Pos.	Pos.	1.86	1.57
12¶	55	IDC (RB)	0/0	G3	4.0	68.7	Neg.	Neg.	Neg.	Pos.	—	2.52
13¶	57	IDC (LB)	2/6	G3	3.0	29.6	30	128	Pos.	Pos.	2.37	1.98

*Focal tumor uptake.
†Tumor-to-normal breast tissue ratio at 1 h after injection.
‡Grading is according to Bloom and Richardson (*24*).
§Values of <36 kilo IU/L (kIU/L) are considered normal.
‖Values of <9 fmol/mg protein are considered negative.
¶Postmenopausal women.
ILC = infiltrating lobular carcinoma; LB = left breast; Neg. = negative; Pos. = positive; FD = fibrocystic disease; IDC = infiltrating ductal carcinoma.

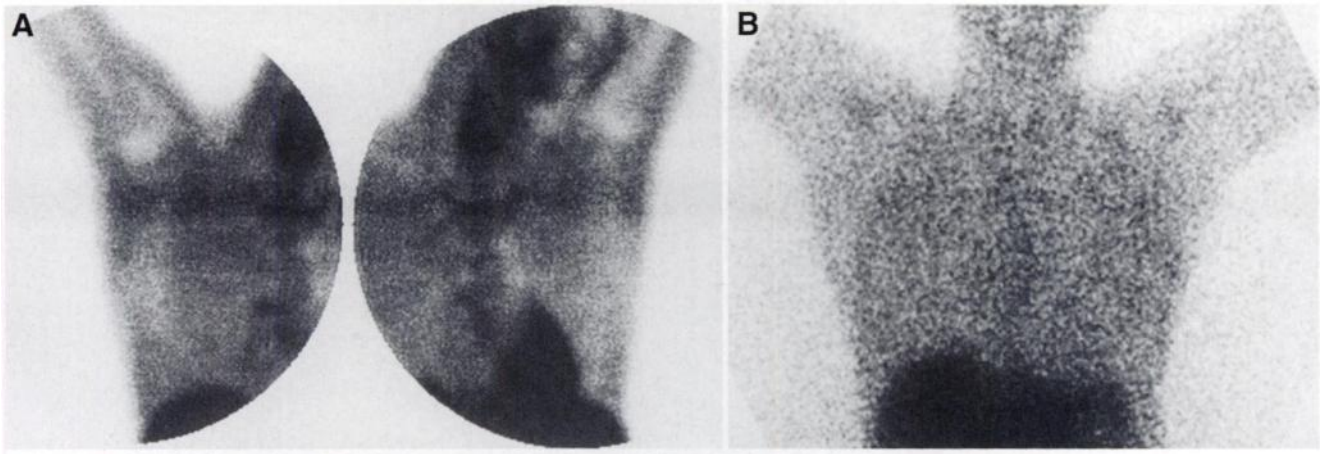

FIGURE 2. Anterior planar scintigram of patient 5 with fibrocystic disease. No focal uptake of either MIBI (A) or MIVE (B) was evident.

with mean values of 1.73 ± 0.40 and 1.85 ± 0.35 for MIBI and MIVE, respectively. Except for 1 patient (patient 10), whose cancer was staged G3, we observed a tendency for higher tumor-to-normal tissue ratios on MIBI scans for MIVE-positive compared with MIVE-negative patients (1.82 ± 0.44 versus 1.62 ± 0.37), although the difference was not statistically significant ($P = 0.2$). The most intense MIBI uptake and highest CA-15.3 (human breast cancer antigen) value (68.7 kilo IU/L [kIU/L]; normal, <36 kIU/L) was observed in patient 12 (Fig. 6), who had a negative MIVE scan and a negative in vitro ER analysis. Overall agreement between in vitro ER status and MIVE uptake is 80% (5 ER negative/MIVE negative; 3 ER positive/MIVE positive) and, likewise, between in vitro PR values and MIVE uptake agreement is 80%. Agreement for MIBI and MIVE uptake values is 69% (5 MIBI positive/MIVE positive and 3 MIBI negative/MIVE negative). Agreement between MIBI uptake and in vitro ER values is only 30% (3 ER positive/MIBI positive).

DISCUSSION

MIBI is commonly used in nuclear medicine imaging procedures. The radiopharmaceutical was originally designed as a myocardial perfusion agent but was soon found to be useful for tumor imaging. MIBI scintimammography is currently used to differentiate between benign and malignant lesions in patients presenting an equivocal or nondiagnostic mammogram (*6*). It is also used to monitor the course of hormone therapy or chemotherapy in patients with breast cancer. A relationship between the initial intensity of MIBI uptake and the aggressiveness of several types of tumors has been suggested (*10*). Some centers have correlated semiquantitative uptake ratios, referencing the level of MIBI uptake in abnormal areas against the normal breast uptake, with pathologic features of breast tumors (*25*). Such ratios are especially useful in monitoring response to therapy (*11*).

Tumor uptake of MIBI is dependent on blood flow and capillary permeability, both factors that are often increased

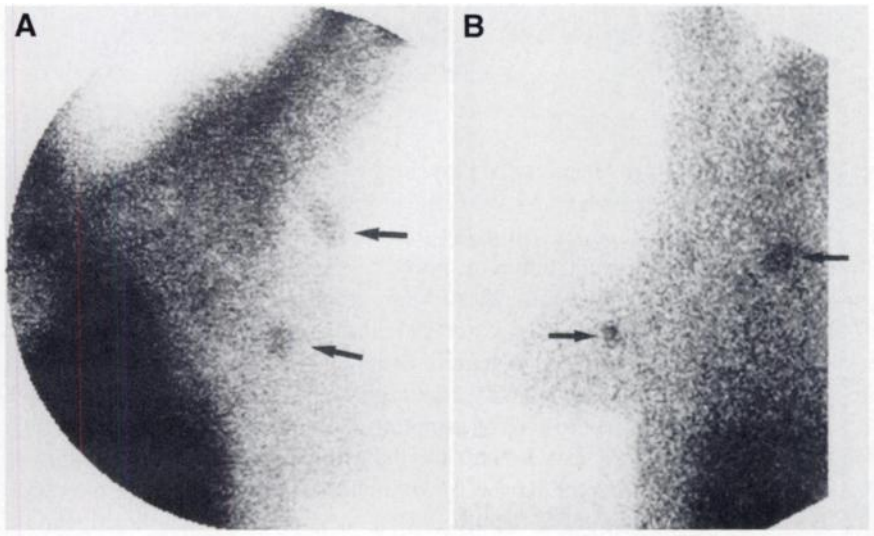

FIGURE 3. (A) Focal MIBI uptake in primary tumor and lymph node (arrows) in left upper quadrant of left breast and left axilla of patient 13. (B) Corresponding MIVE focal uptake of left breast and axilla.

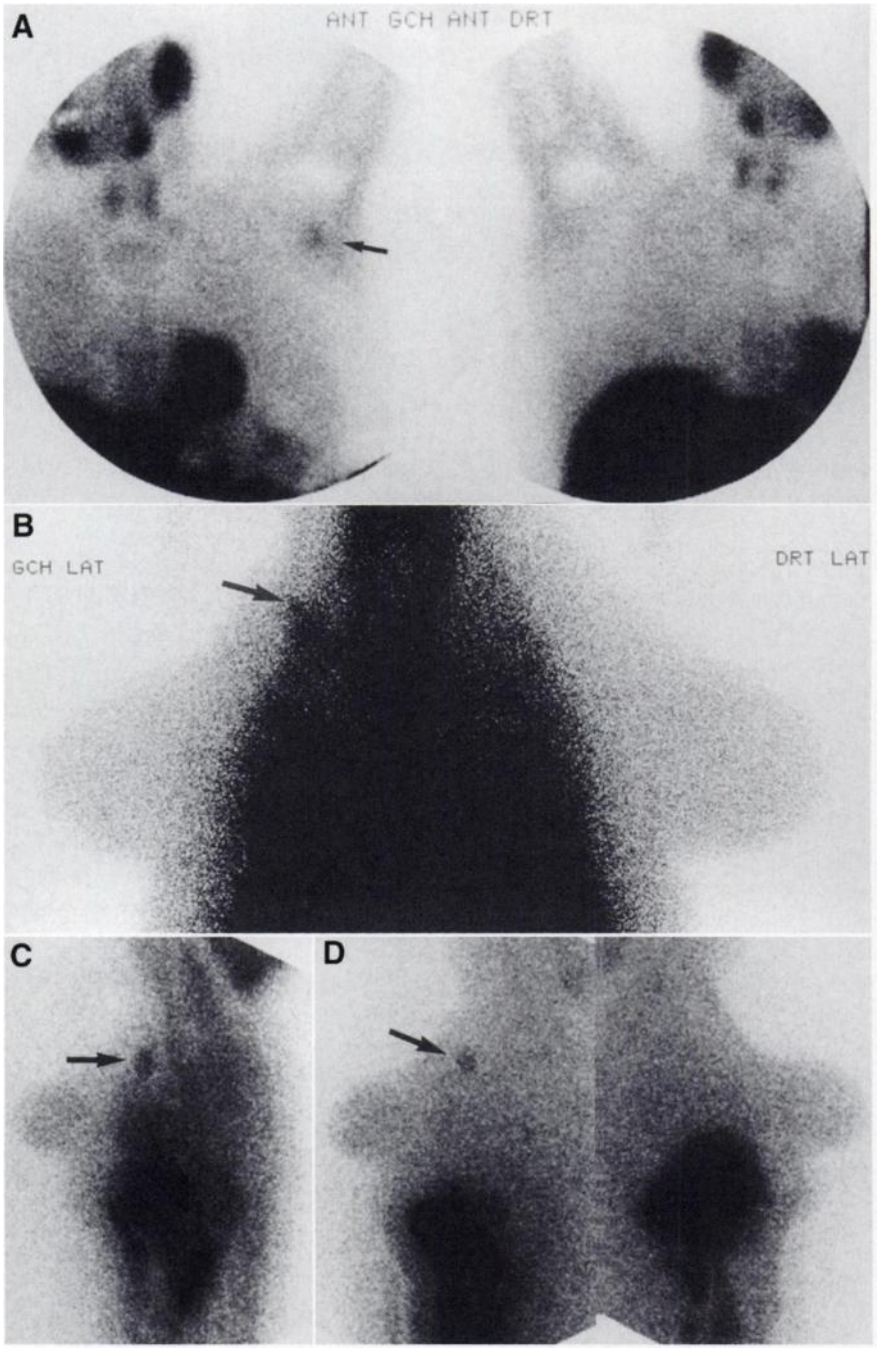

FIGURE 4. Planar images of patient 1 with MIBI show focal uptake (arrows) in left axilla: left and right anterior view (A) and left and right lateral view (B). MIVE scintigrams taken 15 min (C) and 2 h (D) after injection show focal uptake in left axilla (arrows) and normal distribution in right breast and axilla (D).

in breast tumors compared with normal breast tissue. Altered cellular membrane potentials and altered metabolism (*8,26*) also contribute to MIBI tumor uptake and retention. Once in the cell, MIBI is believed to be trapped by electronegative cellular and especially mitochondrial membrane potentials (*27–29*). The localization mechanism may also involve the multidrug-resistant P-glycoprotein system, which uses MIBI as a substrate and effectively transports the ligand out of the tumor (*9*).

Knowledge of the ER concentration in the tumor is another important aspect of prognosis because ER-positive breast cancer is less aggressive than ER-negative cancer and is characterized by longer disease-free intervals and improved survival (*12*). In vitro ligand-binding and immunochemical ER assays of biopsy samples are routinely used to predict tumor response to therapy and patient prognosis. However, neither of the receptor assays accurately predicts the response of breast cancer patients to hormone therapy. These assays require a sample of fresh or fresh-frozen tissue of adequate size and tumor cell density, free of hemorrhage or necrosis. The sampling is often inadequate because of the extent of epithelial cellularity, resulting in heterogeneity of receptor expression within the tumor. The possible alteration of the ER functionality associated with tissue manipulation

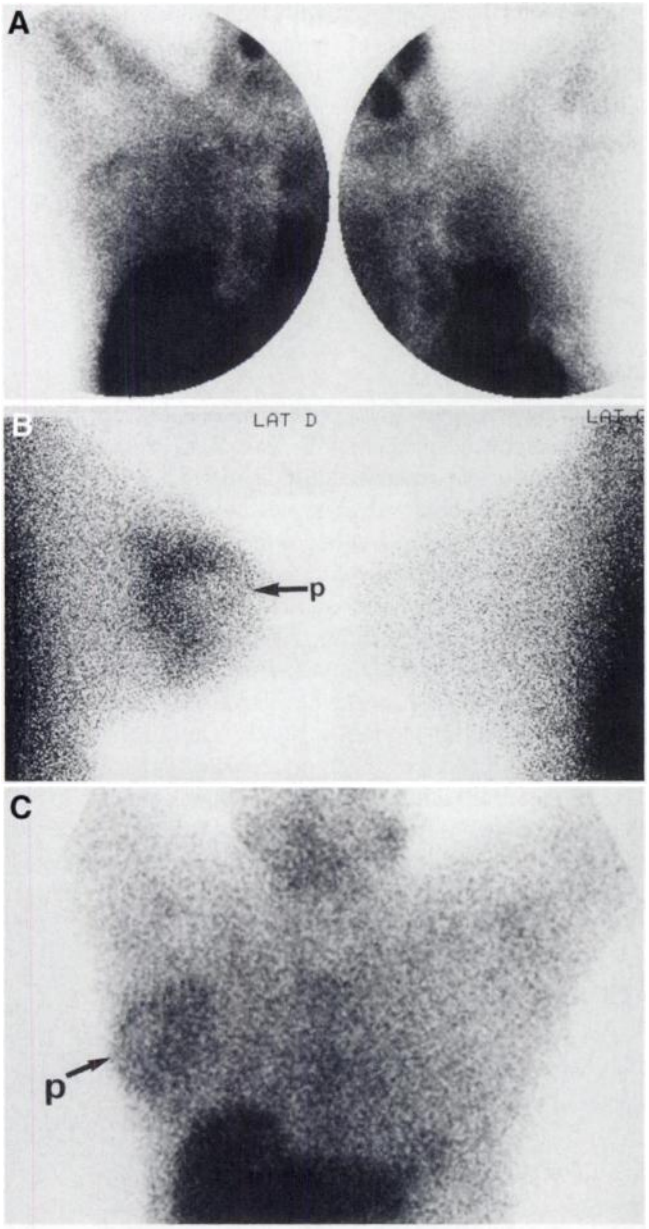

FIGURE 5. Planar anterior (A) and lateral (B) views of abnormal and heterogeneous MIBI uptake in right breast of patient 11 with photopenic area (arrow) (p) corresponding to necrotic center. (C) Corresponding MIVE uptake in right breast with same necrotic center (arrow).

is also a concern. These in vitro assays are not well suited for biopsies of osseous metastatic lesions, samples of bone marrow, ascitic fluid, or pleural fluid. High estrogen concentrations in the blood stream of premenopausal women or women on estrogen replacement therapy may also lead to false-negative results. Both types of assays also suffer from interlaboratory variability associated with differences in methodology and the lack of uniformity of accepted cutoff values to discriminate between ER-positive and ER-negative tumors. The interlaboratory agreement rate is 80% (*30–33*).

This study was designed to compare the tumor uptake of the new ER-based, ^{123}I-radiopharmaceutical MIVE with that of MIBI to search for possible relationships between ER status and MIBI uptake in breast cancer patients. Patients were referred for MIVE scintimammography after an abnormal mammogram or finding of a suspect mass on physical examination; patients with malignant and benign lesions were both included. Our MIVE tumor uptake data in breast cancer patients indicate a good correlation with the ER-positive or ER-negative status, as measured by the in vitro assays; however, there was no quantitative correlation between the intensity of MIVE uptake and the ER concentration. The scans of 2 patients (patients 1 and 11) showed MIVE uptake in spite of a negative in vitro ER assay. These 2 patients present circumstances that could compromise the results of the in vitro receptor determination. The MIVE-positive/ER-negative results of patient 1 pertain to a lymph node removed from the left axilla with evidence of recurrent ER-positive tumors of the left breast. Patient 11 had a large tumor with a necrotic center evident on pathologic examina-

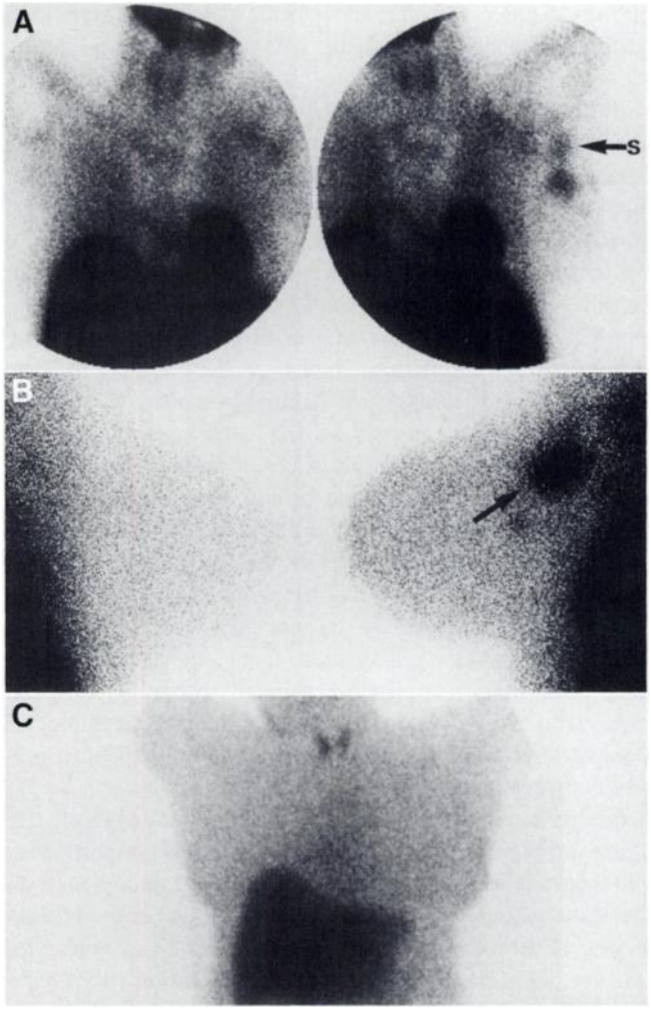

FIGURE 6. Anterior (A) and lateral (B) views of patient 12's breasts show intense focal uptake of MIBI in upper external left quadrant (arrows; s = satellite lesion) and normal distribution in right breast. (C) MIVE distribution is normal for both breasts.

tion and also visible on the MIBI and MIVE scans (Fig. 5). Again, this may have contributed to the false-negative in vitro result. Furthermore, the tumor was PR positive, and it has been documented that ER-negative/PR-positive tumors occur in <5% of all breast cancer cases (*34,35*) and that the presence of PR is indicative of ER function (*12,14*). Thus, MIVE uptake in both of these patients likely represents a true receptor-mediated uptake process. False-negative in vitro data may explain why some patients respond to tamoxifen treatment in spite of a negative ER assay (*36*). Furthermore, false-positive assays associated with in vitro receptor interaction with ER, which have lost their in vivo functionality, may lead to a recommendation of hormone therapy in a situation in which such a treatment would be ineffective.

No statistically significant correlation was found between MIVE and MIBI tumor-to-normal tissue ratios. This suggests that the known relationship between MIBI uptake and the aggressiveness or lack of differentiation of the tumor (*10*) does not translate in diminished ER expression. Alternatively, one may argue that the limited number of patients in our study did not suffice to detect a potential correlation, particularly because the mean MIBI tumor-to-normal tissue ratio is somewhat inferior for MIVE-negative compared with MIVE-positive tumors. Dehdashti et al. (*16*) conducted a similar investigation to search for a relationship between breast tumor aggressiveness and ER status using tumor uptake of the metabolic tracer FDG and the ER ligand 16α-[^{18}F]fluoroestradiol as probes. No relationship between the metabolic activity of the tumor and ER status could be established. However, both this study and our current study emphasize the uniqueness of the information provided by radioestrogen scintimammography.

Previous studies with other radiolabeled estrogen analogs indicate that some tracer uptake does occur in certain benign lesions (*20*). This could result in false-positive MIVE scans, and, accordingly, we included benign lesions in our study. We found a marked difference between MIVE and MIBI uptake when comparing fibrocystic disease versus malignant lesions. The normal amount of ER will usually be increased severalfold in ER-positive tumors and will appear on a MIVE scan as a well-defined focal uptake. However, high-grade tumors are undifferentiated with very poor ER expression and will fail to accumulate the labeled estrogen. Benign tumors, on the other hand, show a mild, diffuse, and relatively symmetric breast uptake.

Our data suggest a role of MIVE scintimammography in the assessment of the ER status of the tumor, lymph nodes, and metastases rather than in establishing the malignancy of the lesion. Therefore, in theory, all breast cancer patients would benefit from an MIVE scan before surgery. In practice, especially in early-detected cancers in which lymph node involvement is less likely, in vitro ER determination should be sufficient to establish the receptor status of the tumor. The fact remains, however, that the in vitro ER assay does not provide full proof. Scintimammography, using a radiolabeled estrogen with high affinity for the ER, could eliminate many of the limitations associated with the in vitro procedure. Thus, this technique could contribute to selecting the preferred mode of therapy on an individual basis. Direct in vivo imaging also provides the opportunity to verify ER status during the course of therapy. The latter is of importance to guide appropriate follow-up procedures. Finally, the scintigraphic procedure also is well adapted for the determination of the ER status of metastases that may differ from that of the primary tumor (*30*).

CONCLUSION

We compared the tumor uptake of the new ER-based, ^{123}I-radiopharmaceutical MIVE with that of MIBI and sought relationships between ER status and scintigraphic uptake ratios in breast cancer patients. MIBI uptake increases with the aggressiveness of the tumor. More aggressive tumors are usually less differentiated, which may result in a diminished likelihood of ER expression and MIVE uptake. There is an indication that MIBI uptake is more intense in MIVE-negative tumors. However, no statistically significant correlation could be established between the MIBI and MIVE uptake ratios. MIVE scintimammography provides a direct assessment of the ER status of breast tumors in cancer patients, adding a unique parameter to the characterization of the disease. Evidently, a larger number of patients need to be tested to validate the usefulness of this procedure in the routine management of breast cancer patients.

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