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# Dynamic Indium-111-Pentetreotide Scintigraphy in Breast Cancer

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The efficacy of imaging breast cancer with $^{111}$In-pentetreotide (somatostatin receptor scintigraphy) was evaluated before surgery. **Methods:** Seventy-one whole-body scintigrams in 24 patients with known breast cancer and 24 whole-body scintigrams in 8 controls were obtained at 0.5, 5 and 24 hr after intravenous injection of 110 MBq $^{111}$In-pentetreotide. Anterior and posterior projection images were acquired simultaneously. SPECT of the thorax was performed at 5 or 24 hr after injection in all breast cancer patients. The specimens were imaged immediately after surgery and the distribution of pentetreotide was assessed qualitatively and quantitatively. **Results:** Somatostatin receptor-positive tumors were found in 18/24 patients with breast cancer. Pentetreotide uptake was significantly greater in breast cancer patients compared to control patients. In all patients with positive images, the early scintigram (0.5 hr) showed abnormal uptake. It was possible to delineate three different dynamic patterns. Increased uptake was visually most distinct either at 0.5 hr (4 patients) or at 5 hr (5 patients), or equally distinct at each time (9 patients). Moreover, bilaterally increased pentetreotide uptake was observed in 10/18 true-positive patients (in 8 at each time and in 2 patients only at 5 hr), but only one patient had a known bilateral tumor. **Conclusion:** We found higher incidence of somatostatin receptors in patients with breast cancer than in the control group. Moreover, bilaterally increased pentetreotide uptake in clinically unilateral disease was an unexpected finding.

**Key Words:** breast cancer; indium-111-pentetreotide; dynamic imaging

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Indium-111-pentetreotide scintigraphy has made it possible to visualize tumors expressing somatostatin receptors in vivo. The method has been established for diagnosis of gastrointestinal endocrine tumors (GEP) and has high sensitivity (*1*). In addition to neuroendocrine tumors, there are a variety of tumors in the lungs, lymphopoetic system, central nervous system and breasts which also express somatostatin receptors (*2–6*).

Nesland et al. (*7*) have argued that some breast tumors have neuroendocrine features. Moreover, Papotti et al. (*8*) have defined a group of breast carcinomas expressing neuroendocrine features and the presence of somatostatin receptors. Reubi et al. (*4*) measured in vitro somatostatin receptors and showed that approximately half of the breast cancer tumors possess specific receptors. Krenning et al. (*1*) and van Eijck et al. (*9*) used in vivo scintigraphy and observed an even higher incidence of somatostatin receptors (74%). The detection of breast tumors with somatostatin receptor imaging is of biological and potentially of therapeutic interest. Presence of somatostatin receptors may be a useful prognostic factor and may play an active role in regulating tumor development (*10*).

The aim of this study was to investigate whether breast cancer expresses somatostatin receptors. The relation of the somatostatin receptor to the histopathology and to estrogen (ER) or progesterone receptor (PgR) also was studied.

## MATERIALS AND METHODS

### Patients

Patients with invasive breast cancer detected by physical examination, mammography and cytology who were scheduled for surgery were studied. The study was approved by the Ethics and Isotope Committees at Lund University. The study group consisted of 22 women and 2 men; aged 36–83 yr (mean age 61 yr). One woman had a bilateral tumor. There was a total of 25 known breast tumors used in the study. Pentetreotide scintigraphy was started 48 hr before surgery. Eight patients with GEP tumors in the same age group undergoing pentetreotide scintigraphy served as controls.

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Whole-body scintigrams were obtained 0.5, 5 and 24 hr after intravenous injection of 110 MBq $^{111}$In-pentetreotide. Scintigraphy was performed simultaneously in anterior and posterior projections as described previously (*11–12*). The 24 hr scintigram was not performed in one patient for technical reasons. SPECT of the thorax was performed at 5 or at 24 hr after injection. Data were collected in continuous rotation with 4° divisions over 360° for 28 min using a 128 × 128 matrix and energy windows of 20% over the 171 and 245 keV peaks. Projections were pre-processed using a Buttherworth filter from available software and transversal, frontal and sagittal sections were reconstructed. Attenuation correction was not performed. Slice thickness was 12 mm. Surgical tissue was imaged immediately after removal (48 hr after injection). Preset time for specimen imaging was 5 min.

Focally or diffusely increased uptake of pentetreotide in either breast was considered abnormal if it was present on at least two scintigrams. Pathological uptake was assessed qualitatively by visual estimation, and quantitatively by measuring the breast index, defined as the ratio of count densities between a region of interest (ROI) corresponding to the breast uptake and an ROI corresponding to the background (thigh). The ROIs were of a standardized size and shape. The scintigraphic ROI data were analyzed with Student's t-test. The scintigrams were examined and interpreted blindly by two independent observers who had no prior knowledge of the localization of tumor, medical history or surgical outcome. An interpretation was assigned by consensus in cases in which the observers initially differed. Comparisons were made to the control group of patients. After surgery, the scintigraphic results were related to the histopathological diagnosis according to WHO.

The presence of ER and PgR was determined with an enzyme immunoassay kit. A cutoff level of 25 fmole/mg protein was used to classify tumors as receptor-positive or receptor-negative.

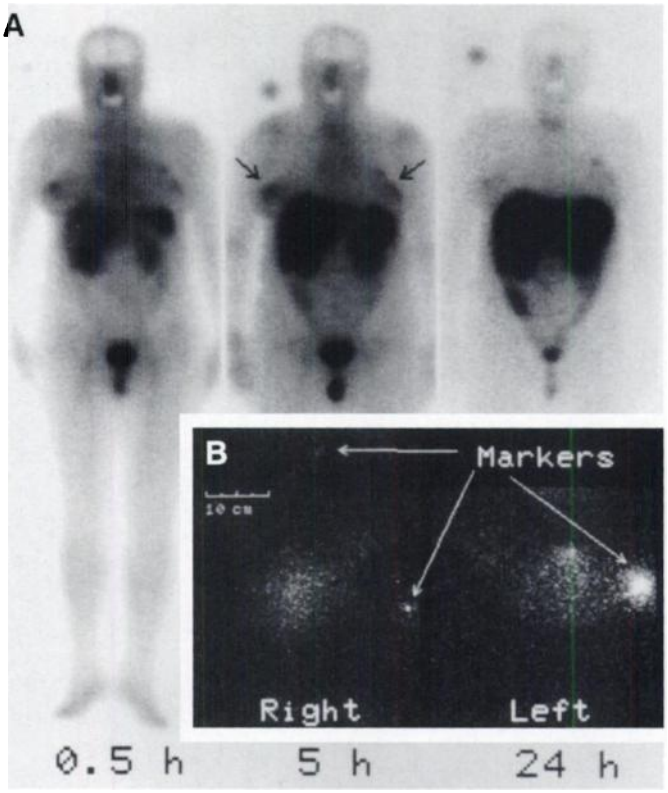


**FIGURE 1.** Patient 4, with histopathologically confirmed bilateral infiltrating ductal carcinoma. Anterior projection of whole body at 0.5, 5 and 24 hr. Note that the uptake was most distinct in the early scintigram (A). Surgically removed breast tissue specimens at 48 hr show diffuse, low-density nonhomogenous distribution of somatostatin receptors in tumors (B). The images at 5 and 24 hr were scaled up by factors 1.5 and 3.0, respectively.

## RESULTS

Postoperative histopathological examinations showed that twenty patients had an infiltrative ductal carcinoma (Patient 4 had bilateral tumor, Fig. 1). Four patients had an infiltrative lobular carcinoma. The tumor size in specimens ranged from 7 to 90 mm. Some patients had more than one site of primary tumor identified. The results obtained for each patient are listed in Table 1. All 19 specimens (18 patients) studied after surgery (specimen imaging was not done in 6 patients) showed focally (single/multiple) or diffusely increased uptake on pentetreotide scintigraphy. Each site of primary tumor obtained by histopathological examination corresponded to increased uptake on specimen scintigraphy. The distribution of somatostatin receptors varied in intensity and appeared nonhomogeneous on all specimen images (Figs. 1B, 2B and 3B). There was no obvious relationship between the histopathological type of tumor and intensity of somatostatin receptors (Table 1).

Sixteen of twenty-one infiltrative ductal carcinomas, and three of four lobular carcinomas were visualised on pentetreotide whole-body scintigraphy. All false-negative ductal carcinoma were less than 20 mm (Table 2). Increased uptake was visually most distinct either at 0.5 (4 patients) or at 5 hr (5 patients), or was equally distinct at each time (9 patients) (Table 2). Thus, three patterns could be discerned. All true-positive studies, however, showed increased uptake already on the early scintigram (0.5 hr). SPECT gave further information in only one case delineating liver tissue activity from superimposed tumor activity. Moreover, 10/18 patients with true-positive scans had increased pentetreotide uptake in the contralateral breast, eight at each scintigraphy time (Fig. 2A) and two only at 5 hr (Fig. 3A). Only Patient 4 had known bilateral cancer (Fig. 1). In all patients with positive pentetreotide scintigraphy, it was possible to determine the specific quadrant where the tumor was localized.

Fourteen patients had lymph node involvement based on histopathology. In 7 of the 14, pentetreotide scintigraphy showed increased uptake in the axilla. Eight patients had histopathologically-negative nodes. Pathological uptake in the axilla was found bilaterally in one of them. Pentetreotide scintigraphy was normal in two patients who did not undergo axillary operation.

In the control group, four of eight patients showed increased uptake in both breasts on 5-hr whole-body images.

Quantitative analysis showed a significantly increased breast index in the group of patients with breast cancer at 0.5, 5 and 24 hr compared to the control group (Table 3).

Estrogen and progesterone receptors were positive in 12 and 11 patients, respectively. No obvious relationship existed between either ER or PgR and somatostatin receptors (Table 1).

## DISCUSSION

Pentetreotide scintigraphy showed a high incidence of somatostatin receptors in patients with known breast cancer. Of course, the scintigraphic results cannot differentiate between increased pentetreotide uptake due to the specific somatostatin receptor binding or nonspecific uptake. The uptake pattern, however, was generally too focal and corresponded too well to sites of tumor foci to postulate that increased uptake was due to binding to other structures that may have led to the positive finding. Compared to the results that others (*9*) have achieved in patients with breast tumor comparing pentetreotide scintigraphy results with autoradiography, it is obvious that the positive pentetreotide scintigraphy in these tumors reflects specific receptor binding, and that the degree of intensity on

**TABLE 1**
Results of Histopathology, Specimen Scintigraphy, Estrogen and Progesteron Receptor Immunoassay in Primary Breast Cancer

| Patient no. | Age (yr) | Sex | Side | Tumor size (mm) | Histology | Uptake in tumor | ER | PgR |
|---|---|---|---|---|---|---|---|---|
| 1 | 63 | F | R | 48 | Ductal | Focal | + | − |
| 2 | 43 | F | L | 19 | Ductal | Not done | + | + |
| 3 | 59 | F | L | 20+13 | Ductal mf | Focal | Not done | Not done |
| 4a | 60 | F | L | 30 | Ductal | Low diffuse | + | + |
| 4b | 60 | F | R | 29 | Ductal | Low diffuse | + | + |
| 5 | 46 | F | R | 13 | Ductal | Low diffuse | − | + |
| 6 | 52 | F | L | 90 | Ductal | Not done | − | − |
| 7 | 44 | F | R | 40+22+ 10 | Ductal mf | Multifocal | − | − |
| 8 | 72 | M | L | 35 | Ductal | Focal | Not done | Not done |
| 9 | 69 | M | L | 30 | Ductal | Low diffuse | − | + |
| 10 | 56 | F | L | 55 | Ductal | Focal | − | − |
| 11 | 36 | F | L | Inflammatory | Ductal mf | Not done | Not done | Not done |
| 12 | 65 | F | L | 15 | Ductal | Not done | − | + |
| 13 | 43 | F | L | 19 | Ductal | Low diffuse | − | − |
| 14 | 83 | F | R | 50 | Ductal | Focal | + | + |
| 15 | 44 | F | L | 21 | Ductal | Not done | + | + |
| 16 | 74 | F | L | 25 | Ductal | Focal | + | − |
| 17 | 74 | F | L | 21 | Ductal | Diffuse | + | − |
| 18 | 81 | F | R | 10+7 | Ductal mf | Multifocal | + | − |
| 19 | 79 | F | R | 17 | Ductal | Focal | + | + |
| 20 | 66 | F | L | 20 | Ductal | Low diffuse | Not done | Not done |
| 21 | 51 | F | L | 21 | Lobular | Focal | + | + |
| 22 | 65 | F | R | 40+20 | Lobular mf | Multifocal | Not done | Not done |
| 23 | 83 | F | L | 25 | Lobular mf | Multifocal | + | + |
| 24 | 63 | F | L | 32+5 | Lobular mf | Low mf | + | + |

ductal = infiltrative ductal carcinoma; lobular = infiltrative lobular carcinoma; mf = multifocal; ER = estrogen receptor; PgR = progesterone receptor.

scintigraphy reflects the density of somatostatin receptors in the tumors.

All ductal carcinomas ≥20 mm were visualized, but some smaller tumors were also seen. Tumor size is probably not the limiting factor, but rather, the density of somatostatin receptors. Scintigraphy of surgically removed breast tissue showed a nonhomogenous distribution of somatostatin receptors in each patient (high or low density of radioactivity over the cancer area Figs. 1, 2 and 3). Our results disagree with those of Eijck et al. (*9*), who found that high density of radioactivity in vivo pentetreotide scintigraphy correlated with homogeneous and dense distribution of receptors in autoradiography and that low density of radioactivity over the cancer area in vivo corresponded with a nonhomogeneous and sparse distribution of receptors in vitro. This discrepancy probably reflects technical rather than biological differences. Moreover, the hypothesis proposed by van Eijck et al. (*9*) that low density of receptors is due to a noninvasive cancer cannot be supported by our results, because we did not find any association between tumor type and density of somatostatin receptors, although patients with benign breast masses and other nonspecific breast findings were not studied.

All true-positive pentetreotide scintigrams (19/25 breast cancer) already showed increased breast uptake already immediately (0.5 hr) after injection. The dynamics of somatostatin receptor scintigraphy may help to differ pathological pentetreotide uptake in patients with breast cancer from normal pentetreotide uptake in patients without breast tumor. Early (0.5 hr) and late (24 hr) scintigrams seem the most important for differentiation, because we usually did not see increased pentetreotide uptake in the control group on these scintigrams. Some patients without breast tumors showed increased pentetreotide

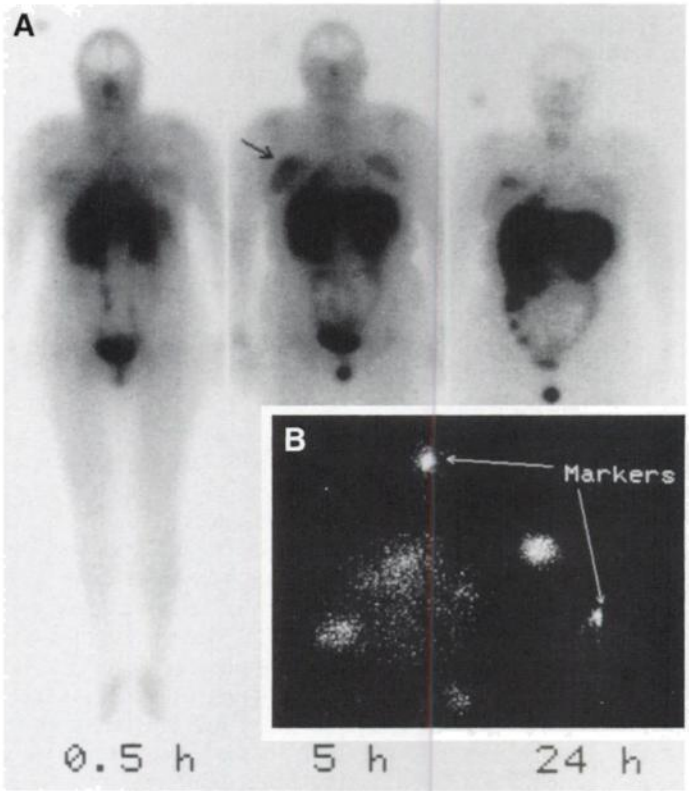


**FIGURE 2.** Patient 7, with histopathologically confirmed infiltrating ductal carcinoma of the right breast. Anterior projection of whole body at 0.5, 5 and 24 hr. On the right side, it is possible to delineate two sites with increased penteterotide uptake. Note the increased uptake also on the left side (A). Surgically removed breast tissue at 48 hr shows multifocally increased pentetreotide uptake corresponding to tumor foci (B). The images at 5 and 24 hr were scaled up by factors 1.5 and 3.0, respectively.

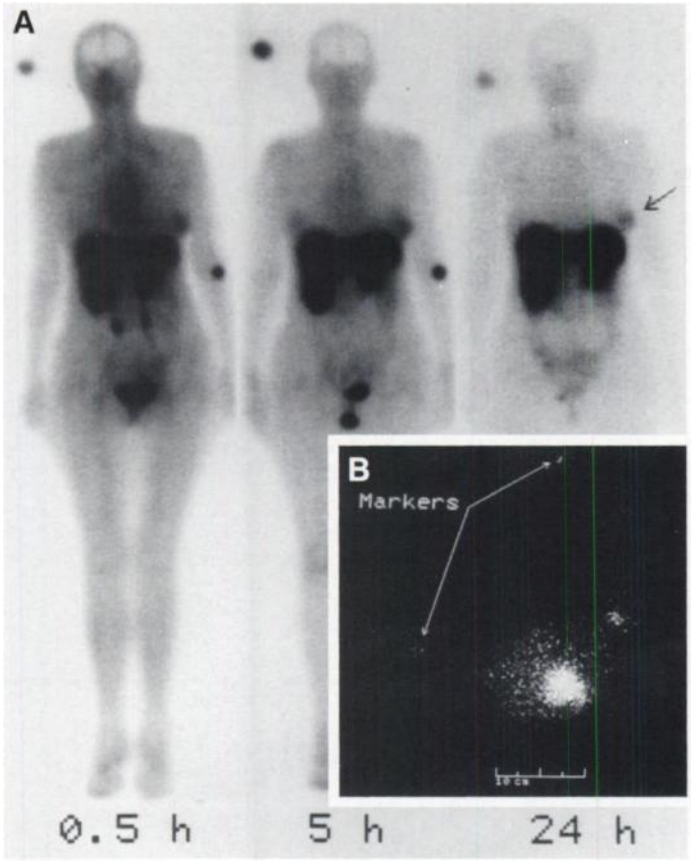


**FIGURE 3.** Patient 10, with histopathologically confirmed infiltrating ductal carcinoma of the left breast. Anterior projection of whole body at 0.5, 5 and 24 hr. Note the increased uptake also on the right side at 5 hr. (A). Surgically removed breast tissue at 48 hr shows dense, nonhomogenous, focal uptake corresponding to the tumor (B). The images at 5 and 24 hr were scaled up by factors 1.5 and 3.0, respectively.

uptake only at 5 hr after injection. That may represent biological pentetreotide behavior.

The striking finding is the bilaterally increased uptake observed in 8 of 18 true-positive findings at each imaging time. Only one patient had clinically and histologically known bilateral cancer. Two of 18 patients showed increased uptake on the contralateral breast only on the 5-hr scintigram. This uptake pattern is similar to that in the control group, which may be interpreted as normal pentetreotide distribution. The finding of bilaterally increased uptake at each time in 7 additional patients with known unilateral breast cancer, however, may also be false-positive and represent nonspecific accumulation of activity due to changed breast tissue permeability. Alternatively, it may represent a binding to pre malignant cells in the breast. Somatostatin receptors may have a role in the proliferation of breast cancer (*13–14*). We do not know whether bilateral expression of somatostatin receptors is a prognostic sign or a general mechanism to inhibit tumor growth (*2–3*). So far, we have no evidence indicating that a bilaterally increased uptake is a sign of tumor development in the contralateral breast. This finding warrants follow-up of these patients and requires investigation of larger groups to determine the significance of these findings.

It is to be expected that pentetreotide blockade will influence the distribution and results of pentetreotide scintigraphy in patients with breast cancer, in the same manner as we have experienced in patients with other neuroendocrine tumors before and during treatment with pentetreotide (diminished uptake in the tumor, increased uptake in the liver and decreased

**TABLE 2**
Results of Dynamic Indium-111-Pentetreotide Whole-body Scintigraphy: Tumor Size in Relation to Breast Uptake

| Patient no. | Tumor size (mm) | Time postinjection | | |
|---|---|---|---|---|
| | | 0.5 hr | 5 hr | 24 hr |
| 1 | 48 | ++ | ++ | ++ |
| 2 | 19 | ++ | ++ | + |
| 3 | 20+13 | bil++* | bil++ | bil+ |
| 4a | 30 | ++ | ++* | + |
| 4b | 29 | ++ | ++* | + |
| 5 | 13 | bil+ | bil++* | bil+ |
| 6 | 90 | bil++ | bil++* | ++ |
| 7 | 40+22 + 10 | bil+ | bil++ | bil++ |
| 8 | 35 | ++ | ++ | ++ |
| 9 | 30 | + | +* | + |
| 10 | 55 | ++ | ++ | ++ |
| 11 | Inflammatory | bil+ | bil+ | bil+ |
| 12 | 15 | Negative | Negative | Negative |
| 13 | 19 | Negative | Negative | Negative |
| 14 | 50 | ++* | + | + |
| 15 | 21 | +* | + | + |
| 16 | 25 | bil+ | bil++* | bil+ |
| 17 | 21 | ++ | ++ | ++ |
| 18 | 10+7 | Negative | Negative | Negative |
| 19 | 17 | Negative | Negative | Negative |
| 20 | 20 | Negative | Negative | Negative |
| 21 | 21 | bil++* | bil++ | bil+ |
| 22 | 40+20 | ++ | ++ | Not done |
| 23 | 25 | + | + | + |
| 24 | 32+5 | Negative | Negative | Negative |

Qualitative uptake assessment: *visually most distinct; ++ = high intensity; + = low intensity; bil = bilaterally increased activity.

uptake in the spleen, *unpublished data*). It would be of interest to study breast cancer patients under pentetreotide blockade.

The sensitivity of pentetreotide scintigraphy is rather low for the detection of metastases in lymph nodes as seen by our results. Seven of fourteen patients were false-negative, which makes this technique of minor value to evaluate axillary lymph node metastases. One of eight patients (Patient 2) showed bilateral uptake on early scintigraphy which was false-positive. That may be due to hyperemia and not to specific binding of somatostatin receptors. SPECT did not improve the sensitivity of detection.

No obvious relation existed between somatostatin receptors expression and ER and PgR hormonal status (Table 1), but there are some patients who still express both ER and somatostatin receptors. Somatostatin analogs may be used more effectively as a combination therapy, with luteinizing hormone-releasing hormone agonists or antagonists, as proposed by Sepeshazy et al. (*14*).

## CONCLUSION

Breast cancer has a high incidence of somatostatin receptor expression. Pentetreotide scintigraphy selects patients with high

**TABLE 3**
Ratio of Count Densities between Breast and Reference ROIs over the Thigh

| Time | Controls | Patients | Probability |
|---|---|---|---|
| 0.5 hr | 1.77 | 2.31 | <0.05 |
| 5 hr | 1.76 | 2.91 | <0.01 |
| 24 hr | 1.94 | 3.31 | <0.01 |

somatostatin receptor densities who might benefit from treatment with a somatostatin analog. It is necessary to obtain early (0.5-hr) as well as late (24-hr) scintigrams. Early scintigraphy is important because, at that time, no increased uptake is seen in patients without breast tumors, but it is always seen in the breast tumor patients. Late scintigraphy is most important for selecting patients who might benefit from treatment with somatostatin analogs. Because bilaterally increased uptake is seen in some patients with unilateral disease, scintigraphy is probably of limited value to stage uni/bilateral disease.

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# Technetium-99m-MIBI Scintimammography for Suspicious Breast Lesions


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The aim of this study was to evaluate the diagnostic accuracy of scintimammography with $^{99m}$Tc-MIBI in patients with suspected primary breast cancer as monitored by SPECT or planar imaging. **Methods:** Patients with a suspect lesion detected by palpation or mammography were entered in the study. Excisional biopsy was performed on all patients and a mammography was performed within three weeks prior to scintigraphy. All patients received intravenously 740 MBq $^{99m}$Tc-MIBI in the arm, contralateral to the suspicious breast, and were subsequently examined in a prone position. At 5–10 min postinjection, planar images were obtained in both the lateral and anterior views with an acquisition time of 10 min. After planar imaging, SPECT imaging was performed using a two-head high-resolution gamma camera. **Results:** In the total patient group of 54 patients, 40 lesions were palpable and 14 were nonpalpable but were detected by mammography. Breast cancer was confirmed in 24 of the patients and 20 of the palpable masses were found to be carcinomas. The tumor size ranged from 6 to 90 mm in diameter. In scintigraphic studies, the overall sensitivity was 88% for planar imaging and 83% for SPECT. Specificity was 83% and 80%, respectively. Sensitivity for palpable lesions was 100%. The smallest detectable tumor measured was 9 mm in diameter and could only be visualized in the planar scintigram. **Conclusion:** Scintigraphy with $^{99m}$Tc-MIBI is extremely sensitive for the detection of primary breast cancer in patients with a palpable mass. SPECT, however, did not improve the diagnostic accuracy over planar scintimammography.



**Key Words:** breast cancer; scintimammography; technetium-99m-MIBI

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Breast cancer is the leading cause of cancer-related death in women throughout developed countries (*1*). Statistically, one of nine women will suffer from breast cancer during her life. Patients who have cancer and have it detected at an early stage will have a better survival rate (*2*).

Besides the physical examination, the most widely tool for primary breast cancer is mammography, which has high diagnostic value in detecting breast lesions (*3*). In older women with an involution of the breast, small lesions, a few millimeters in size, can be detected. Additionally, occult carcinomas can be detected by monitoring microcalcifications in the tumor (*4*). Nevertheless, mammography has a low positive predictive value for breast cancer (*5,6*). Thus, breast cancer can be confirmed in only about one-third of the patients undergoing excisional biopsy. Sensitivity of mammography in patients with dense breasts can be low (*7–9*), and in patients with fibrocystic changes of the breast, mammographical diagnosis of cancer can be difficult. In some of these cases, it is not possible to diagnose breast cancer solely by the means of mammography (*7*).

Although $^{201}$Tl-chloride is useful to diagnose breast cancer in patients with a suspicious breast mass (*10,11*), in comparison to $^{99m}$Tc, the gamma emission characteristics of $^{201}$Tl are less favorable and patient's absorbed doses are higher. Therefore, a $^{99m}$Tc-labeled tracer would be advantageous. Recently, it has been observed that $^{99m}$Tc-MIBI accumulates in various kinds of tumors (*12–22*). For suspect tumors of the breast, some studies demonstrated that scintigraphy with $^{99m}$Tc-MIBI differentiated benign from malignant lesions (*23–25*). In current studies, the sensitivity of $^{99m}$Tc-MIBI to detect primary breast cancer in patients with a palpable breast mass ranged from 84% to 100%; the specificity ranged from 72% to 100% (*24–29*). For breast


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