sensitivity of lymphoma lesion detection as opposed to the constantly good results in GEP tumors. Also, SRI may not be sensitive enough to characterize the presence of somatostatin receptors in known lymphoma, in view of adjunctive therapy with octreotide. Finally, although metabolic therapy using radiolabeled somatostatin analogs can be reasonably envisioned for GEP tumors (*16*), it is doubtful that success can be anticipated in lymphoma.


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# Technetium-99m-Sestamibi Uptake in Breast Tumor and Associated Lymph Nodes


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The aim of this study was to measure the accumulation of $^{99m}$Tc-sestamibi in breast tumors and their axillary lymph nodes in patients undergoing scintimammography. **Methods:** Eighteen patients who were scheduled for breast surgery underwent scintimammography with 740 MBq of $^{99m}$Tc-sestamibi on the day before the operation. The next morning, reinjection with 370 MBq was performed. Immediately after the surgical procedure, the $^{99m}$Tc activity of the tumor samples and, when available, the related lymph nodes was measured in a gamma counter. The samples were weighed and prepared for histological analysis. The activity of each sample was normalized to the mean activity of normal tissue samples obtained from the same patient. **Results:** Among the 198 samples analyzed, the relative uptake of sestamibi was increased in 111 containing normal lymph nodes (1.80 ± 0.79 vs 1.00 ± 0.22, $p < 0.05$), as well as in the seven containing invaded lymph nodes (2.01 ± 0.83, $p < 0.01$) and, more dramatically, in the 22 with a carcinoma (5.64 ± 3.06, $p < 0.001$). In two patients with a benign lesion, both scintigraphy and counting demonstrated increased activity in the tumor. Four patients had negative scan results despite the presence of a malignant tumor and a more than fourfold increase of sestamibi concentration in two of them. **Conclusion:** Technetium-99m-sestamibi concentrates strongly in breast carcinoma, sometimes even when the scan results appear normal, and mildly in lymph nodes, especially when invaded; it also concentrates in some benign tumors, possibly in relation to the presence of epithelial hyperplasia.



**Key Words:** technetium-99m-sestamibi; breast tumors; lymph nodes

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Technetium-99m-sestamibi is a lipophilic cation that concentrates in cardiac mitochondria (*1,2*) and is widely utilized for the scintigraphic assessment of coronary blood flow. However, it also concentrates in tumor cells in vitro (*3,4*) and can help detect several types of malignant tumors by scintigraphy (*5–12*). This imaging procedure could be of great use in the evaluation of breast tumors (*13*), but the actual concentration of this agent in the tumorous tissue remains unknown. In particular, whether the false-negative results at imaging are due to a lack of sestamibi uptake by the malignant tumor (e.g., an effect of the Pgp-170 membrane protein (*14*)), or to the physical limitations of the scintillation cameras used is not understood. We attempted to address this issue by measuring the concentration of $^{99m}$Tc-sestamibi in tissue samples of patients who received this agent several hours before undergoing surgery.

## MATERIALS AND METHODS

A series of 18 patients who were scheduled for breast surgery were included in the study after having provided written informed consent. All had undergone mammography. All fine-needle biopsy procedures had been performed at least 1 wk before scintigraphy. On the day before surgery, 740 MBq of $^{99m}$Tc-sestamibi was injected into the arm opposite the lesion. A few minutes later, three 10-min scintigraphic views were collected using a scintillation camera equipped with a very high resolution collimator (DSX, Sopha, Atlanta, GA) under the lateral and anterior projections. For the lateral views, the patients were in a prone position with their arms above their head and the imaged breast hanging along the side of the bed as close as possible to the collimator. The black-and-white scale used for display was set such that the abdominal and intrathoracic areas were saturated, and the entire gray scale could cover the breast area. The images were printed without additional processing on a transparent x-ray film and read independently by two observers. If necessary, a consensus was reached. The scans were scored using the following system: 0 = normal; 1 = doubtful; 2 = focal increased uptake with low intensity; 3 = focal increased uptake with medium intensity; 4 = focal increased uptake with high intensity.

The next morning the patients received another injection in the same arm of 370 MBq of $^{99m}$Tc-sestamibi, except for two patients who were sent directly to surgery. After surgical removal of the tumor and, if indicated, of the axillary lymph nodes, small pieces of the tumor, lymph nodes and normal tissue were prepared by the pathologist. The $^{99m}$Tc activity of these samples was rapidly counted in a well-counter (1 min/sample). They were then weighed and processed for histological analysis.

For each sample, the value of the counted activity was divided by the weight of the sample, thus providing a mass activity in counts per minute per milligram. To compare the results between patients, the mass activity of all the samples from an individual patient that were normal at histological analysis was averaged, resulting in a reference mass activity for each patient. The mass activity of all the other samples was divided by the corresponding reference mass activity. The results are therefore expressed as a dimensionless parameter called the relative uptake.

Statistical analysis was performed using the Student's t-test for unpaired data and linear regression analysis.

## RESULTS

A series of 18 patients (mean age 57 ± 11 yr, range 41–71 yr) were included in the study. One patient was a 67-yr-old man. Two patients had known breast cancer, one of whom had been treated medically; 10 had a palpable nodule; and 7 had a lesion revealed by routine mammography. Mammographic results were abnormal in all patients but one who had been treated by radiotherapy and in whom the retracted breast could not be imaged properly. Mammoscintigraphic results were clearly positive in 14 patients, including the patient treated by radiotherapy, and normal in the other 4. At histological analysis, the mean size of the tumors was 1.62 ± 1.31 cm (range 0.4–3.5). An infiltrating ductal carcinoma was found in 14 patients and an infiltrating lobular carcinoma in 2. Their modified Scarff-Bloom-Richardson (MSBR) histologic grade ranged from 2 to 5. Two patients had a benign fibroadenoma with some degree of epithelial hyperplasia, and both had positive findings on scintimammography. Axillary lymph node dissection was performed in 15 patients, and malignancy was found in 5.

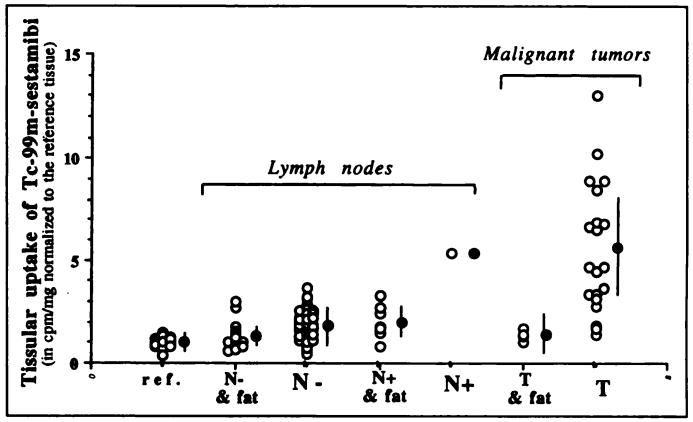


**FIGURE 1.** Relative tissular uptake of $^{99m}$Tc-sestamibi in samples from 18 patients with a breast tumor. The 194 samples are reclassified on the basis of histological analysis into normal breast and fat tissue (ref., n = 34); noninvaded lymph nodes mixed with fat tissue (N−&fat, n = 14); noninvaded lymph nodes only (N−, n = 111); invaded lymph nodes with fat tissue (N+&fat, n = 7); invaded lymph nodes only (N+, n = 1); carcinoma mixed with fat or breast tissue (T&fat, n = 5); and carcinoma only (T, n = 22).

A total of 198 postoperative tissue samples were prepared for counting (mean mass 562 mg, mean activity 89 cpm/mg). At histological analysis, 34 of the 198 samples corresponded to normal breast and fat tissue, 111 to normal lymph nodes, 7 to partially invaded lymph nodes, 1 to a completely invaded lymph node, 4 to a fibroadenoma and 22 to either ductal or lobular carcinoma. The other samples were not histologically pure and contained a mixture of normal breast or fat tissue with either lymphoid tissue in 14 or clusters of tumoral cells in 5.

In two patients, including the one who had been treated medically for known breast carcinoma, the reference normal tissue samples that had been visually selected before histological analysis were found to contain minute clusters of lymphoid cells in one patient and carcinoma cells in the other. In these two patients no other sample could be used as the reference for normal tissue; therefore their samples were used as the reference for calculating the relative tumor and lymph node sestamibi uptake. Further analysis demonstrated that these types of samples do not differ greatly from normal tissue. Consequently, the total number of samples representing the highest tumor contrast value per patient was 16.

Figure 1 shows the distribution of the relative sestamibi uptake in 194 samples reclassified into seven subgroups according to histological analysis: normal breast and fat tissue (1.00 ± 0.22, n = 34), noninvaded lymph nodes with fat tissue (1.31 ± 0.73, n = 14), noninvaded lymph nodes only (1.80 ± 0.79, n = 111), invaded lymph nodes with fat tissue (2.01 ± 0.83, n = 7), invaded lymph nodes only (5.35, n = 1), carcinoma with fat or breast tissue (1.40 ± 0.26, n = 5), carcinoma only (5.64 ± 3.06, n = 22). Uptake was significantly higher in the samples containing carcinoma ($p < 0.01$) and significantly lower in the

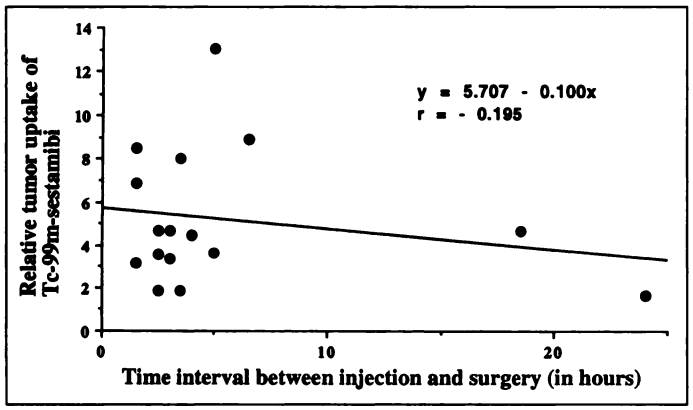


**FIGURE 2.** Tumor contrast uptake (highest value per patient) in relation to the time interval from injection to surgical ablation of the breast tumor. Only a weak negative correlation is seen between these two variables.

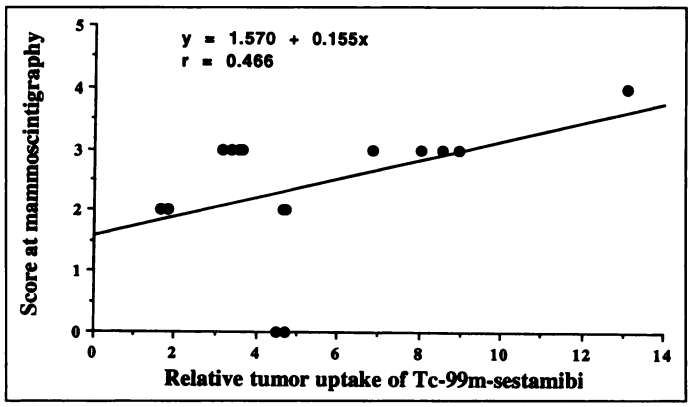


**FIGURE 4.** Tumor contrast uptake (highest value per patient for 16 patients) correlated with scintimammographic score, although two patients with increased uptake at counting had normal findings at scintimammography.

normal samples than in all other series of samples ($p < 0.05$). Mean uptake was 2.83 ± 0.81 in the four samples corresponding to fibroadenoma. Activity in the invaded lymph nodes was generally higher than that in normal lymph nodes, but with considerable overlap between the distributions.

Because the distribution of relative uptake was much more widespread in the carcinoma group than in any of the other series of samples, we attempted to isolate the factor that could account for this dispersion. The normal tissue samples that were used as a reference in each patient to calculate the relative sestamibi uptake were composed of either fat (12 patients) or a mixture of fat and breast tissue (10 patients). A difference between these two subgroups could have biased the calculation of the tumor/normal uptake ratio. For instance, a lower absolute sestamibi uptake in fat tissue than in breast tissue would have led to an overestimation of the relative tumor uptake in patients with fat as a tissue reference. However, there was no significant difference between tumor uptake relative to fat tissue only (6.13 ± 2.37) and that relative to a mixture of breast and fat tissue (5.09 ± 3.88). Another factor that could have influenced the tumor relative uptake is the time interval that elapsed between the sestamibi injection and the surgical removal of the tissue samples, during which "redistribution" of sestamibi could have occurred. Although this time interval varied widely, namely, between 1.5 and 24 hr, Figure 2 shows that there was no correlation with tumor contrast. When a correlation was sought between the contrast uptake of the tumor and the clinical or biologic characteristics of the patients, the only significant variable was body weight ($r = -0.628$), as shown in Figure 3.

Tumor contrast uptake was significantly correlated with scintimammographic score (Fig. 4) but not with MSBR histological grading of the tumor ($r = 0.134$). Among the four patients with normal scan results, one had a 4-mm infiltrating lobular carcinoma but was the only patient in the study with counted samples that did not contain tumor cells. Another patient had clusters of carcinoma cells in fat tissue with a contrast of 1.40. In the two other patients, the tumor/normal ratio at counting ranged between 3.15 and 4.69. The sample with the highest relative uptake had been obtained 18 hr after injection from a patient with a 7-mm MSBR grade 5 lesion. The other sample was from a 25-mm MSBR grade 2 tumor with 3.15 contrast. The two false-positive scans were from patients with large benign lesions, respectively, 1.5 and 3.5 cm (Fig. 5) and tumor/normal ratios of 4.71 and 3.55, respectively.

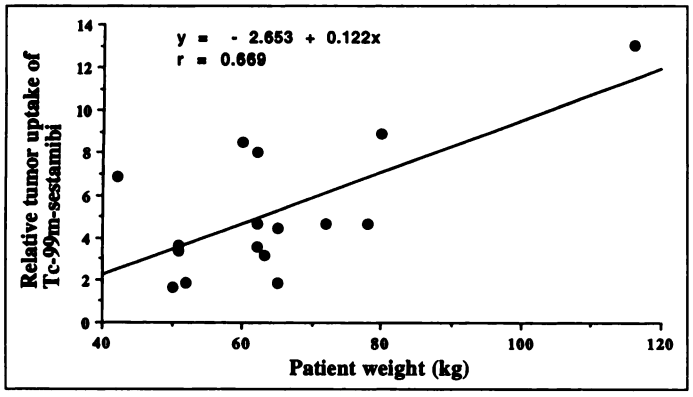


**FIGURE 3.** Patient body weight in relation to tumor contrast uptake (highest value per patient) shows statistical significance.

## DISCUSSION

The results of the present study demonstrate that $^{99m}$Tc-sestamibi strongly concentrates in malignant breast tumors, with a mean contrast ratio of nearly 6:1 compared with that of the surrounding normal breast or fat tissue. However, in some patients with proved breast carcinoma, scintimammographic results are normal, whereas the tumor actually does concentrate $^{99m}$Tc-sestamibi. In contrast, benign tumors can show increased sestamibi uptake and positive results on scintimammography, which was the case in two patients in the present study. Uptake also occurs in axillary lymph nodes, but at a lesser degree and

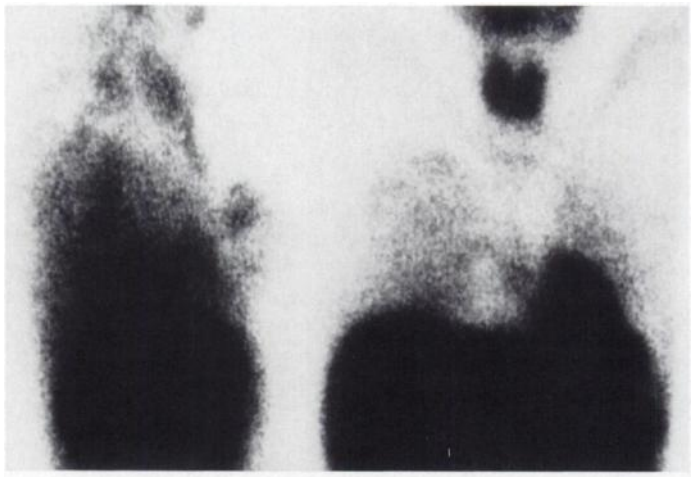

**FIGURE 5.** Right lateral (prone) and anterior (supine) views in a patient with a history of right breast palpable tumor and false-positive findings on scintimammography. Histological analysis revealed a 3.5-cm fibroadenoma with atypical epithelial hyperplasia. The four tissue samples obtained from the tumor showed a relative sestamibi uptake ranging between 2.50 and 3.55.

with a less discriminant difference between normal and invaded lymph nodes, it usually does not appear on the scintigrams.

The presence of an overconcentration of sestamibi in breast carcinoma is not surprising because several types of malignant tumors are detected by scintigraphy (*5–12*). The cellular localization of this agent has been demonstrated by Delmon-Moigeon et al. (*3*) in cultured cells. We have shown, also in vitro, that sestamibi is more favorable in this respect than $^{201}$Tl and $^{99m}$Tc-teboroxime (*4*). However, even if the mechanism of cellular accumulation is now well known in cardiac cells (*1,2*), there is no proof that the same mechanism is present in tumor cells. Our observation that the overconcentration of sestamibi in carcinoma occurs over a large range of values could have several explanations. Vascularization, as well as the proportion of cells accumulating sestamibi, could vary from one tumor to another. Also, because the time interval between injection of sestamibi and surgical ablation of the tumor was not identical for all patients, the contrast could have changed as a function of time. However, the plot of Figure 2 argues against this hypothesis. With the present data, the only variable that correlated significantly with tumor contrast was patient weight: The contrast count was greater in fat than in thin patients. However, this effect is difficult to explain biologically. Most of the correlation resulted from the very high contrast observed in the heaviest patient (also the only male patient). In fact, if this data point is removed from the calculation, the r value decreases to 0.293, but another factor is the expression of the membrane glycoprotein Pgp-170, the product of the multidrug resistance (MDR) gene. Sestamibi has been demonstrated to have a lower accumulation in Pgp-170-enriched cell lines than the parental cell lines (*14*), suggesting that it is a transport substrate recognized by this structure. Because Pgp-170 can be elevated at varying degrees in breast carcinoma (*15*), it could decrease the scintigraphic score and tumor uptake in patients with a high expression. Unfortunately, this factor could not be measured in our patients.

One principal finding of the present study is that of the four patients with false-negative results on scintimammography, two patients had tissue samples containing carcinoma that actually showed an increased uptake of sestamibi. The contrast levels attained were theoretically sufficient to visualize these tumors on the scintigrams because several other patients who presented with a clearly visible tumor on the scans had lower contrast levels. Tumor size was probably one of the limiting factors. In one of these four patients, two foci 4 mm in diameter were found at histological analysis in samples that unfortunately were not counted because they macroscopically looked normal. Another patient had two nonpalpable lesions, a 7-mm lesion on one side, and a 1.2-cm lesion on the other. Lesion location in the breast could also be a limiting factor. The two other false-negative results corresponded to the only two patients with a palpable tumor located in the lower internal quadrant of the left breast. An internal location increases the tissue thickness interposed between the tumor and the detector, whereas a left side location can produce an overlap between the tumor and the myocardial images.

Two patients in this study had false-positive results, which could be explained by the presence of epithelial hyperplasia associated with the fibroadenoma because it was present in the samples from both patients; in one patient, however, only a few cells were involved. This finding suggests that the specificity of scintimammography remains somewhat limited, even if epithelial hyperplasia with fibroadenoma is not very frequent.

The reasons for the increased uptake of sestamibi in normal lymph nodes remain unclear. Although there is some degree of overlap between the distribution of relative activity in our normal tissue samples and the group of the normal lymph nodes, the difference is clearly significant. However, it is obviously not high enough to ensure detection on scintigraphy. The same overlap can be seen when the invaded lymph nodes are compared with the normal ones. Therefore, even if some important information is present in situ, scintigraphic imaging with sestamibi does not seem to be presently sensitive enough to allow the noninvasive detection of invaded lymph nodes.

## CONCLUSION

The ex vivo measurement of $^{99m}$Tc activity in samples obtained from patients undergoing operation for breast carcinoma who received an injection of $^{99m}$Tc-sestamibi several hours before the surgical procedure demonstrated that this agent does concentrate in carcinoma. False-negative results at imaging could be explained by the small size of the lesion, tissue attenuation or superimposition with the myocardial image. False-positive results were observed, possibly in relation to the presence of epithelial hyperplasia. Accumulation in the lymph nodes was not highly specific and was generally too faint for imaging.

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