

Breast Cancer Detection With ^{99m}Tc-Sestamibi Scintigraphy, Mammography, and Fine-Needle Aspiration Cytology: Comparative Study in 64 Surgically Treated Patients

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Background: In breast cancer, mammography (MG) fails to reveal malignancy in 10% to 15% of patients, and its sensitivity is limited by dense breast tissue. The aim of this study was to evaluate the usefulness of ^{99m}Tc-sestamibi scintimammography (SMM) in conjunction with MG and fine needle aspiration (FNA) cytology in the detection of low-stage breast cancer.

Methods: A total of 64 women (median age 58 years, range 32–86 years), 53 (82.8%) with palpable and 11 (17.2%) with nonpalpable breast mass, underwent SMM; 61 patients had MG and 62 underwent FNA cytology. At histological examination, breast cancer was found in 59 (92.2%) of the women (pTis = 2, pT1a = 2, pT1b = 13, pT1c = 20, pT2 = 22).

Results: Of the 61 patients who had MG, 45 (73.8%) showed signs of cancer or abnormalities. Of the 62 patients who had FNA cytology, 55 (88.7%) showed malignancy. In 5 (8.1%) patients, atypical ductal hyperplasia or complex sclerosing lesions were found. MG, SMM, and FNA cytology were 80.4%, 78.0%, and 96.5% sensitive, respectively, and their positive predictive value was 97.8%, 100%, and 100%, respectively. In all patients, cancer was at least detected by one of these three techniques.

Conclusions: In women with suspicious MG or abnormal FNA cytology that required further investigations, SMM may be helpful in surgical planning and should be considered in most patients before biopsy as an additional noninvasive procedure.

Key Words: Breast cancer, Scintimammography, Mammography, ^{99m}Tc-sestamibi, FNAB.

Breast carcinoma is the most common cancer in women and the main cause of death in women aged 35–54 years in the United States.^{1,2} Screening for breast cancer, including breast self-examination, physical examination by a physician, and mammographic surveillance, is the most extensively studied cancer screening program next to cervical cancer. Detecting clinically

unrecognized cancer in asymptomatic women represents the most important factor that contributes to improved survival, when used with presurgical adjuvant chemotherapy.^{1,3} Unfortunately, because the usefulness of mammography (MG) is limited by the individual anatomy (breast density) of breast tissues and the age of patients, its sensitivity is 85% and specificity 80%, with a low (15% to 25%) positive predictive value (PPV).^{4–6} Therefore, most mammographic abnormalities require a biopsy, which results in a large number of non-malignant specimens. In some studies, < 50% sensitivity for MG in detection of malignancy have also been reported.^{4,7,8} Fine-needle aspiration (FNA) cytology and core needle biopsy are also available, but these techniques cannot be used in all patients; the biopsies may be associated with sampling errors, and, in any case, they are not useful in screening populations.⁹ Several reports have found that technetium-^{99m}-methoxy-isobutylisonitrile (sestamibi)

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scintigraphy may be useful in identifying brain, thyroid, and parathyroid tumors, and ^{99m}Tc-sestamibi scintimammography (SMM) seems to be an accurate, noninvasive technique in the detection of breast cancer.^{10,11} The aim of this preliminary retrospective study was to evaluate the usefulness of SMM in conjunction with MG and FNA cytology to detect malignancy in patients undergoing surgery for suspected breast cancer.

MATERIALS AND METHODS

Sixty-four consecutive women (median age 58 years, range 32–87 years) with suspicious breast cancer underwent SMM 1–3 days before surgery. Seven (10.9%) patients required a wire needle localization under stereotactic guidance before biopsy. There were 29 premenopausal and 35 postmenopausal patients; 53 (82.8%) patients had clinically palpable breast mass and 11 (17.2%) patients had nonpalpable lesions. Lateral, anterior, and oblique posterior projections were acquired 10' after 750 MBq ^{99m}Tc-sestamibi injection. Labeling efficiency was higher than 97%. A single detector gamma camera with a parallel-hole high-resolution collimator interfaced to a computer was used and counts of 600 seconds per view were acquired. A tumor-to-background ratio was obtained that compared the ^{99m}Tc-sestamibi uptake in the suspected breast with the uptake in the contralateral side. A ratio of > 1.4 was considered a positive result, while a lower value was considered non significant and SMM was classified as negative. Moreover, 61 (95.3%) women underwent MG and in 62 (96.9%) patients, a FNA cytology, obtained 7–10 days before SMM by ultrasound (US) or stereotactic guidance in the nonpalpable mass, was performed. Final diagnosis was confirmed histologically after excisional biopsy and frozen section examination, followed by lumpectomy or mastectomy and axillary dissection, when requested by tumor staging. In the confirmed breast cancer cases, estrogen (ER) and progesterone (PgR) receptor content, by use of monoclonal antibodies and Ki-67 antigen (using MIB-1 antibody), were also assayed.

RESULTS

Histopathologic diagnosis of breast cancer was obtained in 59 (92.2%) patients, whereas 5 (7.8%) patients had benign lesions (atypical adenosis or fibroadenoma and atypical ductal hyperplasia). The TNM distribution and the average of maximum diameter measured by the pathologist are shown in Table 1. Forty-five (76.3%) of the breast cancers were of the invasive ductal type, and the next most common variety, infiltrating lobular carcinoma, was found in 6 (10.2%) of the breast cancers. In 7 out of the 11 patients with nonpalpable lesions, the tumor was excised under stereotactic guidance that required a wire needle localization. Definitive surgical procedures in patients with histologically confirmed breast cancer were modified radical mastectomy¹ in the 30 (50.8%) patients with a tumor sized over 15 mm in maximum diameter, and lumpectomy² in the other 29 (49.1%) patients. The results obtained using MG, SMM, and FNA cytology are shown in Table 2. Nine (69.2%) out of the 13 tumors undetected by SMM were nonpalpable and in only 6 (46.2%) cases there were mammographic signs of malignancy. In 4 (6.2%) patients (pT1b), both MG and SMM had false-negative results, and their overall sensitivity was 93.2%, while FNA cytology showed breast cancer in all of them. In all patients, cancer was at least suspected by one of these three techniques. No differences ($P = NS$) in age and in percentage of ER, PgR, and MIB-1 positivity were found between patients with true-positive and false-negative results using SMM (Table 3).

DISCUSSION

MG represents the chosen technique in the screening of breast cancer but unfortunately, because 20–30% of breast cancers occur in patients aged < 50, MG has a poor PPV, which results in a large number of biopsies revealing benign lesions.^{2,4–6} In some patients, MG is not diagnostic in differentiating between benign and malignant lesions and usually shows only a “suspicious” finding.⁹

TABLE 1. Pathological TNM staging and maximum diameter (mean \pm standard deviation) of the tumor (mm) for each group. The two patients with Paget disease were considered pTis

Size	pTis In situ	pT1a <6 mm	pT1b 6–10 mm	pT1c 11–20 mm	pT2 21–50 mm	Overall
N	2	2	13	20	22	59
%	3.4	3.4	22.0	32.2	39.0	100
mm	3.0	5.0	8.61 \pm 1.04	16.1 \pm 2.83	30.45 \pm 4.99	18.69 \pm 9.73

N = number of patients.

TABLE 2. Results of preoperative procedures

Procedure	N	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
SMM	64	46	13	0	5	78.0%	100%	100%	27.8%
MG	61	45	11	1	4	80.4%	80.0%	97.8%	26.7%
FNAC	62	55	2	0	5	96.5%	100%	100%	71.4%

N, number of patients; TP, true-positive; FN, false-negative; FP, false-positive; TN, true-negative; PPV, positive-predictive value; NPV, negative-predictive value; SMM, scintimammography; MG, mammography; FNAC, fine-needle aspiration cytology.

Several radionuclide imaging techniques have been used in human breast cancer detection, but presently these radiopharmaceutical techniques are more extensively applied: (1) fluorine-18-deoxyglucose (^{18}F FDG) with PET, (2) 201-Tl, and (3) 99m-Tc-sestamibi. Clinical experience with ^{18}F FDG is limited by the cost (about US \$1,200 at our University Hospital) and availability of PET, while 201-Tl, notwithstanding a reported >95% sensitivity in detection of malignancy because of its physical characteristics (washout and redistribution in tumors), is not ideal for modern gamma cameras.^{11,12} Technetium-99m-tc-furifosmin, although used in *in vitro* studies may have tumor-seeking properties, is of no value in the imaging of breast cancer, whereas 99m-Tc(V) DMSA scintimammography appears superior to 99m-Tc-sestamibi only in the detection of axillary lymph node metastases.^{13,14}

Several studies reported the usefulness of SMM with 99m-Tc-sestamibi in breast cancer detection and its role in improving sensitivity and specificity of breast imaging. Taillefer et al.¹¹ studied a group of 65 patients with breast lesions (44 palpable and 21 nonpalpable) of which 47 (72.3%) were breast cancers (ranging between 3–30 mm in size) and found that SMM was 92.5% sensitive with a specificity of 94.4%. Villanueva-Meyer et al.⁸ studied 66 patients with a prevalence of cancer in 54% reporting an overall sensitivity of 83% and specificity of 93% (94% and 91% in palpable lesions, respectively). In a multicentric study performed in a group of 420 patients, Scopinaro et al.¹⁵ found that SMM sensitivity in palpable masses was 98% and specificity 89%, whereas in nonpalpable masses it was 62% and 91%, respectively.

Uriarte et al.¹⁶ evaluated the contribution of SMM in 78 patients with nonpalpable [37 (47.4%) benign and 41 (52.6%) malignant] lesions, showed that sensitivity, specificity, and PPV were 92%, 100% and 100% respectively, for a prevalence of malignancy of 86%. It has also been established by the same authors that the addition of SMM to MG may reduce the number of unnecessary biopsies in nonpalpable breast lesions by up to 55%.¹⁷ Nevertheless, different results and suggestions have been reported recently by Flanagan et al., who enrolled 79 women with palpable breast mass and abnormal MG. They found a SMM sensitivity, specificity, and PPV of 81%, 81%, and 61% respectively, but their conclusion was that SMM does not increase the specificity of conventional MG and physical examination in diagnosing or excluding breast cancer.³

In our experience, MG and SMM sensitivity was quite similar (78.0% vs. 80.4%) and we did not find false-positive results using SMM (PPV = 100%). Moreover, using both MG and SMM in conjunction with US- or stereotactic-guided FNA cytology, sensitivity in detection of malignancy reached 100%. In experienced hands, US-guided aspiration and/or core-biopsy performed by surgeons can accurately diagnose nonpalpable breast masses detected by MG, with a low (<6%) insufficient specimen rate and no false-positive results.¹⁸ It has also been established that stereotactic breast biopsy can be a less expensive alternative to open excisional biopsy for the diagnosis of nonpalpable mammographic findings and should be preferred in most patients; but with this technique, only a minority of patients with suspected malignancy had breast cancer and the cancer/biopsies

TABLE 3. Differences between patients with cancer correctly detected and undetected by scintimammography

Results	Patients (N)	Age (y)	Size (mm)	ER (%)	PgR (%)	MIB-1 (%)
TP	46	61.52 ± 14.38	22.04 ± 9.27	56.35 ± 33.32	44.70 ± 28.74	17.44 ± 13.73
p		.020	.000	.188	.015	.558
FN	13	51.38 ± 9.46	9.38 ± 3.64	70.0 ± 29.81	67.50 ± 30.2	20.08 ± 16.15
TP + FN	59	59.29 ± 14.03	19.25 ± 9.87	56.60 ± 32.33	47.10 ± 29.10	18.02 ± 14.18

N, number of patients; Size, maximum diameter of the tumor; ER, estrogen receptors rate; PgR, progesterone receptors rate; MIB-1, Ki-67 positivity rate (using MIB-1 antibody); TP, true-positive; FN, false-negative.

ratio was 20.9%.¹⁹ Only FNA cytology does not change breast anatomy, whereas in patients who underwent open breast biopsy, false-positive mammographic postsurgical imaging may occur. Unfortunately, FNA cytology cannot be used in some mammographically suspected breast lesions and in such patients, SMM may offer interesting results that play a significant role in complementing MG for breast cancer detection.¹¹

A recent study did not show any correlation ($r = 0.08$, $P > 0.05$) between 99m-Tc-sestamibi uptake and the degrees of neovascularity and intracellular mitochondrial density, showing only a moderate correlation with cellular proliferation.²⁰ We also did not find any correlation in the percentage rate of ER, PgR, and MIB-1 between cancer that was correctly or incorrectly detected by SMM.

In conclusion, in women with suspected MG or abnormal FNA cytology that requires further investigations, SMM may be helpful in surgical planning and should be considered in most patients before biopsy as an additional noninvasive procedure.

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