Accuracy of ^{99m}Tc-sestamibi scintimammography for breast cancer diagnosis

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Received August 26, 2009; Accepted October 19, 2009

DOI: 10.3892/etm_00000033

Abstract. Scintimammography using ^{99m}Tc-sestamibi is a noninvasive and painless diagnostic imaging method that is used to detect breast cancer when mammography is inconclusive. Because of the advantages of labeling with ^{99m}Tc-sestamibi and its high efficiency in detecting carcinomas, it is the most widespread agent for this purpose. Its accumulation in the tumor has multifactorial causes and does not depend on the presence of architectural distortion or local or diffuse density variation in the breast. The objective of this study was to evaluate the accuracy of scintimammography for detecting breast cancer. One hundred and fifty-seven patients presenting 158 palpable and non-palpable breast nodules were evaluated. Three patients were male and 154 were female, aged between 14 and 81 years. All patients underwent scintimammography, and the nodule was subjected to cytological or histological study, i.e., the gold standard for diagnosing cancer. One hundred and eleven malignant and 47 benign nodules were detected, with predominance of ductal carcinomas (n=94) and fibroadenoma/fibrocystic condition (n=11/n=11), respectively. The mean size was 3.11 cm (7-10 cm) among the malignant nodules and 2.07 cm among the benign nodules (0.5-10 cm). The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 89, 89, 95, 78 and 89%, respectively. Analysis on the histological types showed that the technique was more effective on tumors that were more aggressive, such as ductal carcinoma. In this study, ^{99m}Tc-sestamibi scintimammography was shown to be an important tool for diagnosing breast cancer when mammography was inconclusive.

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*In memoriam

Key words: scintimammography, breast cancer, ^{99m}Tc-sestamibi

Introduction

Mammography is the safest method for breast cancer screening (1-3). It presents good sensitivity for detecting palpable and non-palpable lesions and low specificity for distinguishing between benign and malignant processes (4). Hence, a biopsy is often required for diagnostic confirmation (5). It also presents limitations in relation to detection of lesions in dense breasts (6-8). Mann *et al* demonstrated that false negative mammograms cause delays in undertaking biopsies among patients with cancer (9).

The high rates of unnecessary biopsies in cases of benign lesions (10) have encouraged research on non-invasive techniques with greater precision. Ultrasound, magnetic resonance imaging, positron emission tomography and scintigraphy are important aids for detecting cancer when mammography is indeterminate (11). High-risk patients (e.g., family antecedents, atypical proliferative lesions and previous cancer subjected to tumorectomy or radiotherapy) have benefited from combined use of these methods (11). Scintigraphy is a noninvasive imaging examination that uses small doses of radiation (12). It is painless, its cost and availability are reasonable and it enables functional or metabolic evaluation of various organs or structures. Its advantage is unequivocal, especially when analysis using other methods is limited, and it stands out as a diagnostic evaluation method for breast cancer. Sestamibi became commercially viable at the start of the 1990s and was proposed as an alternative to thallium 201 for investigating myocardial perfusion. Because of the advantages of the physical characteristics of labeling with ^{99m}Tc, the transition from thallium 201 to ^{99m}Tc-sestamibi for applications within nuclear oncology occurred naturally (13).

The exact mechanism for the way in which ^{99m}Tc-sestamibi becomes concentrated in tumors is not completely clear, and there are probably multiple causes. It is distributed inside tissues in proportion to the blood flow and penetrates cells by passive diffusion. By means of the difference in transmembrane potential, it attaches to mitochondria, especially in malignant cells with higher negative potential (14,15). Approximately 90% of this radiopharmaceutical is concentrated in mitochondria (16). Greater accumulation in lesions depends on the mitochondrial activity and density, cellularity, angiogenesis and presence of malformed vessels (17). Cell proliferation and desmoplastic activity factors also seem to be involved (18). The presence of architectural distortion and diffuse or localized increase in breast density do not change the ^{99m}Tc-sestamibi uptake in the lesion (19-24).

Materials and methods

One hundred and fifty-seven patients of both genders who underwent scintimammography were included. These patients presented palpable and non-palpable nodules, with cytological or histological confirmation of the lesions by means of fine-needle aspiration puncture, biopsy or excision of the lesion. Patients with bilateral carcinomas, acute inflammatory or infectious processes associated with the nodule, or inadequate scintimammograms were excluded from this study.

Scintimammography. The images were acquired using a Siemens-Orbiter scintillation camera, connected to an Icon computer, with software version 7.5. A low-energy, high-resolution collimator was used, with a matrix of 128x128 pixels and 15% windows centered on a 140 keV photopeak. A magnification factor of two was used for the lateral and oblique images of the breasts, while no magnification was used for the anterior projection of the chest and axillae. Images started 10 min after injection and lasted for 10 min.

For all of the scintigraphy examinations, sestamibi (Cardiolite®) was used. The preparation, labeling with ^{99m}Tc and quality control followed the manufacturer's recommendations. The dose administered ranged from 370 to 740 MBq (10-20 mCi) and was injected intravenously, preferably into a vein in the foot or in the arm contralateral to the compromised breast.

The images were captured in accordance with the protocol proposed by Diggles *et al* (25) and Khalkhali *et al* (26), using a special foam mattress of 30 cm in height, with lateral openings corresponding to the projected locations of the breasts. Lateral and posterior oblique images were obtained with the patient in a prone position, with one of the breasts hanging and fitted into the opening, while maintaining the edges completely free. Filling foam was placed in the contralateral opening, so that the contralateral breast was pressed against the mattress, thereby not allowing radiation to be transmitted to the breast under examination.

Two images of each breast were obtained 10 min after administration of ^{99m}Tc-sestamibi, beginning with the lateral projection of the breast with the suspected lesion. The axillary region and muscle wall were included in the field of view, and the breast was centralized from the neck to the abdomen, following the posterior oblique ipsilateral projection at 40°. After obtaining these images, the breast positioning was changed. Then, with the patient in a supine position with raised arms, an image of the anterior thoracic region was acquired, also covering the axillary region bilaterally.

The scintimammograms were evaluated on the computer screen, with manipulation of color, brightness and intensity, and the appearance and intensity of the ^{99m}Tc-sestamibi concentration in the breast were also analyzed. The images were interpreted by two experts in nuclear medicine independently. If their diagnoses did not coincide, agreement was reached by consensus. The scintimammograms were classified respectively as positive or negative for the malignant process, according to the presence or absence of focal uptake ^{99m}Tc-sestamibi uptake, at low, medium or high intensity. Scintimammograms without focal accumulations were classified as normal when they presented diffuse and homogeneous uptake and as benign alterations when they presented diffuse and heterogenous uptake.

Histopathological diagnosis. All of the nodules were subjected to cytological and/or histological study. Fine-needle aspiration puncture was performed using a Cameco puncture lever connected to a 10-ml syringe and 25x6-mm needle (27). The smears that were fixed in 95% alcohol were stained using the Shorr method and the smears that were air-dried were stained using the Giemsa method. Histological sections (4 μm) were obtained from specimens embedded in paraffin and were stained using H&E.

Statistical analysis. The positive and negative scintimammogram results were compared with the cytological or histological evaluation, which was considered to be the gold standard for diagnosing breast cancer. Sensitivity (S), specificity (SP), positive predictive value (PPV), negative predictive value (NPV) and accuracy were investigated, and false positive (FP) and false negative (FN) rates were established for the qualitative evaluation. These parameters were calculated in accordance with Faraj *et al* (28) as follows: S = TP/(TP + FN); SP = TN/(TN + FP); PPV = TP/(TP + FP); NPV = TN/(TN + FN); accuracy = TP + TN/(TP + TN + FP + FN). The prevalence rate expressed the number of malignant tumors in the study population.

Comparisons between the means of pairs of independent data sets were carried out using the two-tailed Student's t-test, with calculation of t and p statistics (29-32).

Comparisons between pairs of independent classificatory samples were made using the Chi-square test, with calculation of χ^2 and p statistics (29-32).

Results

Among the 157 selected patients with breast nodules who underwent scintimammography, one presented two nodules in the same breast and therefore 158 nodules were detected. The majority of the patients were female (154, 98.1%), while three were male (1.9%). The age group ranged from 14 to 81 years, with a mean of 53.7±14 years and median of 54 years. The mean age was significantly greater among the patients with malignant nodules (57.2±11.9) than among those with benign nodules (44.4±13.4); t=5.94; p<0.001.

In total, 111 malignant nodules and 47 benign nodules were detected, with sizes ranging from 0.5 to 10 cm (x=2.80±1.53 cm). Among the malignant nodules, ductal carcinomas prevailed (Table I) and among the benign

Table I. Results of scintimammography for malignant nodules (n=111).

Malignant nodules	Scintimammography		
	Positive	Negative	Total
Ductal carcinoma	88	6	94
Ductal *in situ* carcinoma	2	1	3
Ductal-lobular carcinoma[a]	0	3	3
Lobular carcinoma	3	0	3
Mucinous carcinoma	2	1	3
Medullary carcinoma	2	0	2
OBCAM	1	0	1
Papilliferous carcinoma	1	0	1
Tubular carcinoma	0	1	1
Total	99	12	111

[a]Ductal carcinoma with lobular invasion. OBCAM, occult breast carcinoma with axillary metastasis.

Table II. Results of scintimammography for benign nodules (n=47).

Benign nodules	Scintimammography		
	Positive	Negative	Total
Fibroadenoma	3	8	11
Fibrocystic condition	1	10	11
Lipoma	1	5	6
PEL without atypias	0	6	6
Negative for neoplasia	0	5	5
Interductal fibrosis	0	1	1
Adipose and fibrous tissue	0	1	1
Cystic lesion	0	1	1
Abscess	0	1	1
Adipose cells	0	1	1
Fibrolipoma	0	1	1
Intraductal papilloma	0	1	1
Chronic mastitis	0	1	1
Total	5	42	47

PEL, proliferative epithelial lesion.

nodules, fibroadenomas and fibrocystic conditions prevailed (Table II). The scintimammograms were positive for 99 malignant and 5 benign nodules. The false positive results included fibroadenomas (n=3), fibrocystic conditions (n=1) and lipoma (n=1). Malignant lesions with medium intensity of ^{99m}Tc-sestamibi occurred most frequently (64.6%), followed by high intensity (20.2%) and then low intensity (15.2%). Among the benign nodules, no high intensity was observed; 80% (n=4) were low intensity and 20% (n=1) were medium intensity.

Negative scintimammograms were observed for 54 breasts; 42 benign nodules and 12 malignant. The false negative results were observed in ductal carcinoma (n=6), *in situ* carcinoma (n=1), ductal carcinoma with lobular invasion (n=3), mucinous carcinoma (n=1) and lobular carcinoma (n=1).

The statistical analysis was carried out by comparing the positive and negative scintimammogram results for all nodules (n=157), thus resulting in S, 89%, SP, 89%, PPV, 95%, NPV, 78% and accuracy, 89%.

Discussion

Breast carcinomas are more frequent among older patients, whereas benign disease occurs more among younger groups, especially during the premenopausal phase (33). Our results are in agreement with these epidemiological data.

In our sample, the vast majority were women. Three men were evaluated, one with a malignant tumor and two with benign tumors. Case reports using ^{99m}Tc-MDP (34), ^{99m}Tc-sestamibi (35) and ^{99m}Tc-tetrofosmin (36) have shown the diagnostic usefulness of scintigraphy for detecting breast cancer. We did not find any other studies that included breast tumors among men. Our investigation seems to demonstrate that scintimammography is effective for differentiating malignant and benign tumors among men.

Among the proposed radiotracers for detecting breast tumors, ^{99m}Tc-sestamibi is the one that has been studied most (37-50). We chose this tracer since it was available on a day-to-day basis for cardiological evaluations, thus allowing a combined routine for scintimammography. The facts that its results have been more effective and that it had FDA approval (51) before other tracers were also important in this choice.

The diagnostic value of scintimammography was reevaluated in extensive meta-analyses carried out by Waxman (52), Taillefer (13) and Liberman *et al* (53). Waxman found that the sensitivity was between 84 and 94% (61). Higher results have been observed for palpable lesions (84-100%), in comparison with non-palpable lesions (25-75%). The overall specificity ranges between 72 and 94%, with values between 74 and 87% for palpable lesions and between 86 and 90% for non-palpable lesions. The prevalence of cancer ranged from 39 to 84% in the populations studied. Taillefer evaluated 2009 patients and found the means and intervals for sensitivity (85%; 67-95%), specificity (89%; 58-100%), accuracy (86%; 73-92%), PPV (89%; 67-100%) and NPV (84%; 55-97%) (13). In a recent study, Liberman *et al* found a sensitivity of 85.2% and specificity of 86.6% (53). The sensitivity was greater for palpable masses (87.8%) than for non-palpable masses (66.8%). Specificity did not vary. Our results are in agreement with the meta-analyses of Waxman (52) and Liberman *et al* (53). Hussain and Buscombe in the meta-analysis study conclude that there is evidence that scintimammography is a robust imaging techinique delivering high sensitivities and specificities too (54).

In Brazil, the first experience with scintimammography using ^{99m}Tc-sestamibi was reported by Barros *et al* (55), in 1995, in an analysis of 50 patients with nodules larger than 1 cm. These authors observed sensitivity, specificity, PPV, NPV and accuracy of 96.8, 77.7, 85.5, 93.3 and 90%, respectively. They studied 32 cases of carcinoma, 10 of fibrocystic abnormality, 6 of fibroadenoma, 1 of phyllodes tumor and 1 of papilloma. Five years later, Lima *et al* (56) studied 50 patients with palpable nodules or mammographic abnormalities and found a sensitivity of 100%, specificity of 80%, PPV of 85.3%, NPV of 100% and accuracy of 90.7%. Our sample was three times larger than these two Brazilian studies, with the additional inclusion of lesions smaller than 1 cm and different histological types of carcinomas, including those with good prognosis. Neither of the above-mentioned studies provided descriptions of the size and histological type of the carcinomas. These factors may have caused a difference in the observed sensitivity for detecting breast cancer.

Factors that cause greater tumor aggressiveness increase the ^{99m}Tc-sestamibi uptake, and it is also influenced by the histological type and grade (57,58). Tumors that are more aggressive concentrate more than those with a better prognosis. Buscombe *et al* demonstrated that ductal carcinoma causes accumulation of ^{99m}Tc-sestamibi (57). Papilliferous and mucinous carcinomas, with lesser cellularity and slow growth, frequently do not show significant concentrations of the radiotracer. Ductal carcinomas predominated in our sample (84.7%) and their prevalence was even greater than that reported by Tavassoli (47 to 75%) (59). These are aggressive tumors and their prognosis depends on the time of the diagnosis, volume, axillary involvement and histological grade (59). Occult breast carcinomas with axillary metastasis are rare, with an incidence of 0.3 to 0.8% (60-63). We found one case in our study, representing 0.9% of the patient sample.

The positive scintimammograms also showed subclavicular dissemination of occult breast carcinoma. Scoggins *et al* (64) reported the case of a patient with a palpable nodule in the right axilla, using ^{18}F-FDG. We noted the usefulness of scintimammography in this type of disease too. Among the *in situ* carcinomas, the only tumor with necrosis (which is an indicator of poor prognosis) (59) was not detected by scintimammography, possibly due to its small size and more central location. For the other two, which had greater volume, the scintimammogram was positive. Due to epithelial proliferation, fibroadenomas and fibrocystic disease can concentrate the radiotracers, thereby resulting in false positive images (20,38,39,59,68,69). We observed that three cases of fibroadenoma and one of fibrocystic condition were positive on scintimammograms. Lipoma was another benign lesion that was positive on scintimammograms, but no histological factors were correlated with this finding.

Scintimammography is a method with excellent reproducibility for detecting breast cancer. Since early diagnosis of breast cancer determines the evolution of the disease, all the lesions detected by scintimammography require microscopic study, even after taking into account the possibility of finding false positives. Considering that some researchers have correlated the presence of proliferative conditions with greater relative risk of developing breast cancer (64,65), and that *in situ* carcinomas may be associated with fibroadenomas (66), patients who undergo a scintimammography may benefit from this diagnostic approach. On the other hand, scintimammography supplies additional information for this disease, after it has been suggested by mammography. In cases of negative scintimammograms, it is highly likely that the tumors are benign.

Neoplasia with a poor prognosis is aggressive and grows rapidly (56). Such tumors present high expression of cellular proliferation factors, high mitotic rates, intense angiogenesis and high mitochondrial activity and density. These factors are the main determinants for the concentration of ^{99m}Tc-sestamibi in the lesion (13-17,54,55).

In conclusion, scintimammography showed excellent reproducibility for detecting breast carcinomas, especially ductal carcinomas. Although it is not a method indicated for screening, it allows diagnostic confirmation by means of biopsies because of its high specificity.

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