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Clinical Applications of ^{99m}Tc-Sestamibi Scintimammography

Raymond Taillefer, MD, FRCP(C), ABNM

Mammography is the imaging modality of choice in detection of early, nonpalpable breast cancer. However, scintimammography may prove to be a very useful adjunct to a nondiagnostic or difficult mammography. Future prospective studies will have to be designed so that the specific clinical applications of scintimammography will be well defined. To be clinically relevant, each niche where scintimammography is potentially indicated should be clearly evaluated and incorporated into an algorithm of investigation of breast cancer, taking into consideration the relative advantages and limitations of scintimammography. Special care to obtain high-quality scintimammographic studies is mandatory. Because poor quality studies may be the major drawback, the nuclear medicine community should remind the lesson learned from radiologic mammography. Furthermore, it is also hoped that significant improvement in the scintigraphic equipment and data acquisition will be seen in a very near future to have more widespread clinical diagnostic applications of scintimammography.
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Breast carcinoma is a major health problem for women. It is the second most common cancer affecting women in the western hemisphere after lung cancer and its incidence is increasing with an age-adjusted incidence rates of 106 to 110 per 100,000 women.[1,2] In 1990, 150,000 new cases of breast cancer were reported in the United States, whereas this number increased to approximately 185 000 cases in 2002, representing a rising rate of at least 3% per year. Approximately 45,000 of these women would die of this disease. Current statistics show that approximately 1 in 9 women will develop invasive breast cancer during her lifetime. Despite increases in its incidence, age-adjusted breast cancer mortality rates have been quite stable for different reasons such as advances in treatment and earlier detection. To reduce the mortality associated with this disease, screening of asymptomatic women has been advocated to allow for diagnosis in an early stage with breast self-examination, regular breast physical examination performed by an experienced physician and radiological mammography on an annual basis after the age of 50. Many studies have demonstrated that mammography is the most effective method and is superior to physical examination alone for early breast cancer detection.[3-5] Technical improvements in film quality, processing and imaging techniques, better guidelines for the evaluation of breast cancer, dedicated mammography units, and greater availability of well-trained mammographers and technologists also contributed to enhance the clinical usefulness of mammography. Its wide availability and extensive use have resulted in earlier diagnosis and up a 25% to 30% reduction in the relative risk of dying from breast cancer in women older than the age of 50.[6]

Despite the major advantages associated with the use of mammography, this technique has some limitations in clinical practice.[7-9] Although mammography has a relatively high sensitivity in the range of 85% to 90%, especially in examination of fatty breasts of older women, it is less reliable for detecting lesions in patients with dense breasts, severe dysplastic disease, breast implants, or in patients evaluated after breast surgery or radiotherapy with a false-negative rate of 25% to 30%.[10,11] An important drawback of mammography is its low specificity and low positive predictive value of only 10% to 35% for nonpalpable cancers. Mammography cannot always accurately differentiate benign from malignant lesions. Consequently, many mammography-directed surgical breast biopsies are benign. In the event that a localized abnormality suggestive of malignant disease is suspected on mammography, most patients will have a short-interval follow-up mammography, fine-needle aspiration cytology, or surgical excision. Although fine-needle aspiration and stereotactic core biopsy are less invasive than excisional biopsies, they can be inadequate for early cancer detection and may have sampling errors. However, excisional biopsies expose patients to morbidity, risk and costs associated with surgical

Department of Nuclear Medicine, Hotel-Dieu du CHUM, Montréal, Canada.
Address reprint requests to Raymond Taillefer, MD, FRCP(C), ABNM, Department of Nuclear Medicine, Hotel-Dieu du CHUM, 3840 St-Urbain, Montréal H2W 1T8, Canada. E-mail: rtaillefer@hotmail.com

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procedures. Other complementary imaging techniques, such as breast ultrasonography, color Doppler ultrasound, computed tomography, magnetic resonance imaging, and digitization of mammograms with artificial neural network analysis have been developed to improve the sensitivity and, more specifically, the specificity of mammography in the diagnosis of breast cancer.[9] These techniques currently cannot replace mammography as a screening tool for the detection of breast cancer because of their relatively low sensitivity and their variable specificity. These complementary procedures usually are used in more specific clinical situations. Therefore, there is a need for the development of new and reliable diagnostic methods of breast cancer to complement the existing diagnostic modalities.

Nuclear medicine also has been actively involved in the detection of breast cancer as early as in 1946 with the use of ^{32}P-phosphorus.[12] Many radionuclide imaging techniques with different radiopharmaceuticals have been evaluated.[12-20] The most commonly used radiopharmaceuticals for detection of breast cancer are the "perfusion imaging" agents (^{201}thallium, ^{99m}Tc-sestamibi, and ^{99m}Tc-tetrofosmin, named from their use for myocardial perfusion imaging), ^{18}F-fluorodeoxyglucose (FDG), and ^{99m}Tc-MDP (^{99m}Tc-methylenediphosphonate).[21-29] Despite a high diagnostic accuracy in the detection of breast cancer, ^{201}thallium imaging still presents some limitations related to the poor physical characteristics of the radiopharmaceutical. The relatively long half-life of 73 h and the physical characteristics of the photons limit the injected dose to 3 to 5 mCi (110-185 Mbq). The low counting statistics result in a relatively poor resolution for both planar and single-photon emission computed tomography (SPECT) imaging. Furthermore, the normal uptake of ^{201}thallium in the myocardium, liver, and muscles may limit its use for breast cancer localization proximal to these structures. ^{99m}Tc-labeled imaging agents are more attractive for breast cancer detection. The main purpose of this article is to review some of the clinical results and applications of radionuclide breast imaging (or scintimammography) performed with ^{99m}Tc-sestamibi, the most commonly used radiopharmaceutical and currently the only approved radiotracer for scintimammography in clinical practice and to summarize the mostly known clinical applications.

Mechanisms of ^{99m}Tc-Sestamibi Tumoral Uptake

In the early 1990s, ^{99m}Tc-sestamibi (Cardiolite or Miraluma; Bristol-Myers Squibb Medical Imaging, Billerica, MA) became commercially available and was proposed as an alternative agent to ^{201}thallium for myocardial perfusion imaging studies. Taking advantage of the physical characteristics of the ^{99m}Technetium labeling, the transition from ^{201}thallium to ^{99m}Tc-sestamibi for tumor imaging seemed natural. Muller and coworkers[30] in 1987 were the first to report, in an abstract form, the use of ^{99m}Tc-sestamibi for tumor detection. Two years later, Hassan and coworkers[31] reported in a full paper the results of a study using ^{99m}Tc-sestamibi imaging in the detection of lung cancer. The first cases of breast cancer detection with ^{99m}Tc-sestamibi were described in1992 by Aktolun and coworkers.[32] Four of 34 patients with histologically proven cancers had breast carcinomas. These patients were imaged with both ^{99m}Tc-sestamibi and ^{201}thallium. Subsequently, several articles have been published on the use of both planar and SPECT ^{99m}Tc-sestamibi imaging in the detection of breast cancers. The clinical introduction of ^{99m}Tc-sestamibi, which was the first radiopharmaceutical to be approved by the Food and Drug Administration in USA in June 1997 for radionuclide breast imaging, undoubtedly contributed to stimulate research in the field of breast cancer detection with scintigraphic procedures, judged by the constantly growing number of articles and abstracts dealing with this issue.

The mechanisms of cellular uptake of ^{99m}Tc-sestamibi by cancer cells are the subject of continuous investigation. Chiu and coworkers[33] have demonstrated that ^{99m}Tc-sestamibi, a small lipophilic cation, is sequestered within the cytoplasm and mitochondria of cultured mouse fibroblasts and that its net cellular uptake and retention occurred in response to the electrical potentials generated across the membrane bilayers of both the cell and the mitochondria. ^{99m}Tc-sestamibi uptake is driven by a negative transmembrane potential and as much as 90% of the radiotracer activity is found in the mitochondria. This uptake is energy dependent because energy-consuming biochemical reactions control these transmembrane potentials. Delmon-Moingeon and coworkers[34] were the first to demonstrate the increased uptake of ^{99m}Tc-sestamibi by carcinoma cells. Piwnica-Worms and coworkers[35] observed that ^{99m}Tc-sestamibi is a substrate of the transmembrane P-glycoprotein (Pgp-170) which is present in the cells overexpressing the multidrug resistance gene (MDR1) and acts as a protective pump by extruding out of the tumor cells a wide range of molecules, including ^{99m}Tc-sestamibi. This observation is of clinical interest because ^{99m}Tc-sestamibi scintimammography may allow in vivo visualization of the MDR1 level of expression, which can represent an important factor in the evaluation of patients on chemotherapy.[36,37] Studies performed in humans demonstrated that in tumor with high levels of Pgp, ^{99m}Tc-sestamibi efflux was significantly faster than in the control group or in the group with no Pgp. The induction of multidrug resistance is a rapid process and enhanced resistance is associated with reduced intracellular ^{99m}Tc-sestamibi accumulation. Crane and coworkers[38] studied the intratumoral distribution patterns of ^{99m}Tc-sestamibi in the c-neu OncoMouse, a transgenic mouse that spontaneously develops breast tumors. The retention was related to tumor morphology and viability. The mean ^{99m}Tc-sestamibi tumor retention was 0.38% $\pm$ 0.2% of injected dose per gram with a peak tumoral uptake of 0.94% $\pm$ 0.85% of injected dose per gram. Tumor retention remained the same at 30 and 60 min after the injection. Experimental comparative culture cell studies[39] also suggested that tumoral uptake of ^{99m}Tc-sestamibi far exceeds that of ^{201}thallium. This characteristic and physical properties of ^{99m}Tc-sestamibi make it an interesting radiopharmaceutical for tumor imaging. Several factors are involved in the level of ^{99m}Tc-sestamibi uptake by breast cancer. Papantoniou and coworkers[40] performed a

study to evaluate the relationship between histological type and grade of the tumor with the uptake and washout of ^{99m}Tc-sestamibi. They showed that ^{99m}Tc-sestamibi uptake ratios were significantly higher in ductal than in lobular carcinomas on both early and delayed images. Grade II carcinomas also show a significantly faster washout (lower retention index values) than grade III carcinomas.

Technical Aspects of ^{99m}Tc-Sestamibi Scintimammography

The introduction of ^{99m}Tc-sestamibi in clinical research raised more technical questions than any other radionuclide breast imaging procedures did before.[41-43] Although ^{99m}Tc-sestamibi scintimammography does not necessitate any specific patients preparation, technologist performing the injection and image acquisition is usually asked to explain the most important technical details to the patients to decrease their level of anxiety. The patient should remove all clothing and jewelry above the waist and should wear a hospital gown open in front. Results of breast physical examination, prior mammograms, as well as ultrasound studies should be available at the time of the procedure and analysis. Because of the possibility of nonspecific ^{99m}Tc-sestamibi uptake, scintimammography should be performed before or at least 7 to 10 days after a fine-needle aspiration, 4 to 6 weeks after a breast biopsy, and at least 2 to 3 months after breast surgery or radiotherapy. Although there are no serial studies to confirm these time intervals, clinical practice showed that these intervals are satisfactory most of the time and do not influence the specificity of the procedure. It is not clear at the present time what is the best phase of the menstrual cycle to perform scintimammography. Until serial studies evaluating scintimammographies obtained in the same patients show a clinically relevant difference between phases of the cycle, no definite guidelines exist as to what is the best timing for the study. Different imaging modalities have been proposed to improve the diagnostic accuracy of the test.

In contrast to the standard supine position and multiple projection imaging performed at fixed time post intravenous injection, as published with several previous agents, ^{99m}Tc-sestamibi breast imaging has been the subject of different technical variations. The "standard" dose of ^{99m}Tc-sestamibi described in most articles is approximately 20 to 25 mCi (740-925 MBq). However, given the relatively low absolute uptake within the primary breast cancer and the possibility of simultaneously imaging the axilla, this dose can be weight adjusted and Taillefer and coworkers[44] have used doses up to 30 mCi (1100 MBq) of ^{99m}Tc-sestamibi, similar to the dose that is currently used in the detection of coronary artery disease with radionuclide myocardial perfusion imaging studies. The dosimetry to the gall bladder is 0.039 mGy/MBq (0.14 rads/mCi) and the effective dose is 0.0085 MSv/MBq (0.031 rem/mCi). The intravenous injection should be performed as a bolus into an antecubital vein (preferably through an indwelling catheter or butterfly to limit any extravasation of the radiotracer at the site of injection) in the arm on the opposite side of the known or suspected breast lesion to avoid any false-positive uptake in the ipsilateral axillary lymph nodes. If bilateral lesions are suspected, or if the patient has had a previous mastectomy, the injection can be performed in a dorsal pedal vein. The radiopharmaceutical injection should be followed by 10 mL of saline solution to flush the vein and avoid local residual activity.

Khalkhali and coworkers[41] were the first to propose the use of the prone position instead of supine imaging. Prone-dependent breast imaging can be performed with either a special table with lateral cutouts or foam cushion (with a lateral semicircular aperture) placed over the imaging table. Prone imaging has several advantages over the supine or upright position. It provides improved separation of the breast tissue from the myocardium and liver, 2 organs showing very high ^{99m}Tc-sestamibi uptake, which may mask overlying breast activity. The prone position will also allow evaluation of deep breast tissue adjacent to the thoracic wall. It will result in visualization of more breast tissue and will better delineate the natural breast contour, which is helpful in more precisely localizing a breast lesion. The distance between the detector and the breast is also minimized. Although the prone position is preferred for breast imaging, supine images can be useful mainly for better localization of the primary tumor, especially those in the inner quadrants, and also to visualize axillae and possible internal mammary lymph node involvement. Thus, a combination of prone and supine images is preferable. If necessary, additional views such as oblique anterior or posterior can be obtained. Images are usually acquired during a period of 10 minutes. Planar images are acquired using a $128 \times 128 \times 16$ or larger matrix to allow for pixel overload that may come from the liver or heart. This will improve the counting statistics of the images. Preset-count images are subject to a very large variation in quality due to several technical factors, such as the detector surface or activity within the organs. Several authors agree that direct reading from the computer screen with appropriate contrast adjustment is mandatory for optimal diagnostic accuracy, especially in the detection of small breast lesions or the detection of metastatic axillary lymph node involvement. A logarithmic scale to enhance low-count areas instead of a linear scale is preferable for image display and gray scale is always preferable to color for interpretation.

Although few anecdotal reports that delayed imaging beyond 60 to 90 min improved the target-to-background activity ratios,[42] it is currently recognized that high diagnostic accuracy can be achieved with images obtained as soon as 5 to 15 min after the injection of the radiotracer. Furthermore, delayed imaging may result in false-negative study if there is an increased washout of ^{99m}Tc-sestamibi from a primary breast cancer expressing the MDR1 gene. However, if chemoresistance is assessed, imaging acquisition at various time intervals should be acquired. Paz and coworkers[45] studied 322 women using early (5-10 min after injection) and delayed views (90-120 min post intravenous injection). They compared the early-phase to double-phase study (defined as a combination of both immediate and delayed phase images).

There were no data on the results of delayed phase analyzed separately. They showed that overall, early phase scintimammography had a sensitivity of 94.9% and a specificity of 80.2% in detecting breast cancer, whereas double phase scintimammography had a sensitivity of 89.8% and a specificity of 94.3%. Both methods had a sensitivity of 100% for tumor larger than 1 cm.

The use of routine SPECT imaging for breast cancer detection is still a subject of debate in the nuclear medicine literature. Although SPECT imaging can provide better contrast resolution, accurate localization and characterization of the lesion can be sometimes more difficult to obtain. Initial studies by Nagaraj and coworkers[46] comparing planar and SPECT ^{99m}Tc-sestamibi scintimammography in 34 patients showed that the sensitivity for detecting breast cancer or axillary abnormalities was similar for planar and SPECT imaging, but the specificity was decreased with SPECT compared with planar acquisition: 70% for planar versus 50% for SPECT in detecting breast cancer and 100% for planar versus 75% for SPECT for detecting axillary lymph node involvement. Palmedo and coworkers[47] demonstrated that planar imaging was slightly more sensitive and specific than SPECT imaging for breast cancer detection. With the current technology available, routine use of SPECT imaging alone is certainly not recommended. However, SPECT imaging may be valuable when planar images are not conclusive (especially when a lesion is in projection of the heart or upper part of the liver on planar view), to better characterize multicentric or multifocal lesions, or in the detection of axillary metastases.[48,49] It is likely that with the use of dedicated breast imager and/or imaging devices adapted for SPECT imaging, this procedure will play a more significant clinical role. Table 1 summarizes the results of different studies published in the medical literature on ^{99m}Tc-sestamibi scintimammography.[50-80] There is no significant statistical difference between planar and SPECT ^{99m}Tc-sestamibi breast imaging in detection of breast cancer.

Clinical Results With ^{99m}Tc-Sestamibi Scintimammography

Although few case reports have been initially described,[81-83] the first study on the use of ^{99m}Tc-sestamibi in the detection of breast cancer to be performed in a relatively large number of patients has been reported in 1994. Khalkhali and coworkers[41] conducted ^{99m}Tc-sestamibi scintimammography in 59 female patients with abnormal mammography and physical examination and scheduled for biopsy or fine-needle aspiration cytology. Prone lateral and posterior oblique planar images were obtained at 5 and 60 min after the injection of 20 mCi of ^{99m}Tc-sestamibi. The results of this pilot study were very promising: the sensitivity was 95.8%, the specificity 86.8%, and the positive and negative predictive values 82.1% and 97.1%, respectively. The authors concluded that ^{99m}Tc-sestamibi scintimammography could improve the specificity of standard mammography and potentially reduce the number of mammographically indicated biopsies of the breast (yielding a low positive predictive value). Burak and coworkers[43] studied 41 patients with palpable masses. Planar ^{99m}Tc-sestamibi imaging was performed in anterior, anterior oblique, and lateral supine projections. They found a sensitivity of 93% and a specificity of 87%. Lu and coworkers[42] studied 44 patients with a breast mass or suspected metastases post mastectomy and 10 controls with ^{99m}Tc-sestamibi planar imaging performed at 15 minutes and 3 hours. Scintimammography was able to differentiate benign and malignant breast mass with a sensitivity of 93%, a specificity of 84% and a diagnostic accuracy of 87%. Fibroadenomas (4 of 7 in their study) with histologically proven hypercellularity were shown to exhibit focal ^{99m}Tc-sestamibi uptake and thus lead to false-positive result. However, other benign lesions such as papilloma, abscess, chronic inflammation and fibrous hyperplasia did not show any significant ^{99m}Tc-sestamibi uptake. The authors also concluded that delayed imaging at 3 hours post injection was not beneficial, because it did not show incremental diagnostic value.

The results of a multicenter clinical trial performed in more than 30 North American institutions and involving 673 female patients also have been reported.[49] The number of palpable abnormalities (n = 286) and nonpalpable mammographically detected breast lesions (n = 387) was certainly more representative of the type of patient population seen in a general medical community than in the studies previously reported. Using blinded reading (which is not the case in clinical practice where the reviewer has access to the clinical history and the result of mammography or knows if the lesion is palpable or not and its location), the overall diagnostic sensitivity was 80% and the specificity was 81% in the detection of breast cancers. While the sensitivity and the specificity for the detection of palpable lesions were 95% and 74% respectively, the sensitivity and the specificity of nonpalpable lesions were 72% and 86% respectively.

The results of prospective evaluation on the use of ^{99m}Tc-sestamibi scintimammography have been recently reported.[78] This study performed in 1243 patients confirmed that ^{99m}Tc-sestamibi scintimammography is an accurate diagnostic procedure and can be a useful adjunct to mammography for the detection of breast cancer. There were 503 (40%) of the women who were postmenopausal and 69 (6%) who were perimenopausal. Breast density was graded as dense for 381(30%), normal for 970 (78%), and fatty for 381 (30%). Of the 1243 women in the study, 417 (33%) had a palpable mass on physical examination and the mammographic results using breast imaging reporting and data system (BIRADS) were classified as follows: 16% BIRADS 5, 12% BIRADS 4, 16% BIRADS 3, and the remaining 56% BIRADS 2 and 1. Of the 201 malignant lesions scintimammography correctly identified as positive 186 (93%). There were 1042 women without a malignant lesion, of which scintimammography correctly identified 906 (87%). From a total of 322 positive scintimammographies 186 (58%) were proven to be true positive. True negative scintimammographies were seen in 906 of 921 (98%). Therefore, the sensitivity and specificity of scintimammography for the detection of breast cancer

Table 1 ^{99m}Tc-Sestamibi Scintigraphiy for Breast Imaging

Authors	Year	Patients/ Lesions	Inclusion Criteria	Palpable/ Non-palpable	Imaging			Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
					Modality	Timing	Dose					
Burack et al[43]	1994	41	BM	41/0	Planar	10 min	20 mCi	93% (25/27)	87% (12/14)	93% (25/27)	86% (12/14)	90% (37/41)
Kao et al[50]	1994	38	BM	38/0	Planar	10 min	20 mCi	84% (27/32)	100% (6/6)	100% (27/27)	55% (6/11)	87% (33/38)
Khalkhali et al[41]	1994	147/153	PM/BM	113/40	Planar	5 min, 60 min	20 mCi	92% (47/51)	89% (91/102)	81% (47/58)	96% (91/95)	90% (138/153)
Lu et al[42]	1995	44/40	BM	44/0	Planar	15 min, 3 h	15 mCi	91% (10/11)	83% (24/29)	67% (10/15)	96% (24/25)	85% (34/40)
Taillefer et al[44]	1995	65	PM/BM	44/21	Planar	15 min	25-30 mCi	92% (43/47)	95% (17/18)	98% (43/44)	81% (17/21)	92% (60/65)
Khalkhali et al[41]	1995	100/106	PM/BM	85/21	Planar	5 min, 60 min	20 mCi	94% (30/32)	88% (65/74)	77% (30/39)	97% (65/67)	90% (95/106)
Villanueva-Meyer et al[51]	1996	66	PM/BM	46/20	Planar	15 min	20 mCi	83% (29/35)	94% (29/31)	94% (29/31)	88% (29/33)	88% (58/66)
Palmedo et al[47]	1996	54	PM/BM	40/14	Planar,	5-10 min	20 mCi	88% (21/24)	87% (26/30)	84% (21/25)	90% (26/29)	87% (47/54)
					Spect	30 min	20 mCi	83% (20/24)	83% (25/30)	80% (20/25)	86% (25/29)	83% (45/54)
Maffiou et al[52]	1996	24	PM	0/24	Planar	30-40 min	20 mCi	50% (7/14)	90% (9/10)	88% (7/8)	56% (9/16)	67% (16/24)
Clifford et al[53]	1996	147/148	PM/BM	89/59	Planar	5 min, 60 min	20 mCi	84% (36/43)	95% (100/105)	88% (36/41)	93% (100/107)	92% (136/148)
Carril et al[54]	1997	41	PM	0/41	Planar	10 min	20 mCi	86% (19/22)	58% (11/19)	70% (19/27)	79% (11/14)	73% (30/41)
Buscombe et al[55]	1997	74	BM	74/0	Planar	10 min	20 mCi	91% (48/53)	71% (15/21)	89% (48/54)	75% (15/20)	85% (63/74)
Anbrus et al[56]	1997	51	BM	51/0	Planar	5 min, 2 h	20 mCi	95% (38/40)	73% (8/11)	93% (38/41)	80% (8/10)	90% (46/51)
Chen et al[57]	1997	61/63	PM	61/0	Planar	10 min, 2 h	20 mCi	78% (25/32)	90% (28/31)	89% (25/28)	80% (28/35)	84% (53/63)
Becherer et al[48]	1997	70	PM/BM	45/25	Planar,	15 min	20 mCi	67% (18/27)	96% (115/120)	78% (18/23)	93% (115/124)	90% (133/147)
					Spect	30 min	20 mCi	88% (22/25)	91% (107/118)	67% (22/33)	97% (107/110)	90% (129/143)
Scopinaro et al[58]	1997	420/449	PM/BM	283/166	Planar	1-2 h	20 mCi	85% (300/355)	90% (85/94)	97% (300/309)	61% (85/140)	86% (385/449)
Tiling et al[59]	1997	56	PM/BM	43/13	Planar	5 min	20 mCi	88% (29/33)	83% (19/23)	88% (29/33)	83% (19/23)	86% (48/56)
Helbich et al[60]	1997	75	PM/BM	73/02	Planar,	15 min	17-20 mCi	62% (16/26)	88% (43/49)	73% (16/22)	81% (43/53)	79% (59/75)
					Spect	30 min		83% (20/24)	80% (39/49)	67% (20/30)	91% (39/43)	81% (59/73)
Colella et al[61]	1997	227	–	–	Planar	–	–	82% (128/156)	89% (42/47)	96% (128/133)	60% (42/70)	84% (170/203)
Mekhmandarov et al[62]	1998	140	PM/BM	85/55	Planar	10-20 min	20 mCi	84% (71/85)	85% (47/55)	90% (71/79)	77% (47/61)	84% (118/140)
Cwikla et al[63]	1998	70/74	BM/PM	63/11	Planar	10 min	20 mCi	89% (47/53)	57% (12/21)	84% (47/56)	67% (12/18)	80% (59/74)
Tiling et al[64]	1998	44	BM/PM	15/29	Planar	10 min	20 mCi	63% (15/24)	85% (17/20)	83% (15/18)	65% (17/26)	73% (32/44)
Tolmos et al[65]	1998	70	PM	0/70	Planar	10 min	20 mCi	56% (5/9)	87% (53/61)	38% (5/13)	93% (53/57)	83% (58/70)
Flanagan et al[66]	1998	79/80	BM/PM	34/46	Planar	10 min	20 mCi	81% (17/21)	81% (48/59)	61% (17/28)	92% (48/52)	81% (65/80)
Danielsson et al[67]	1999	96/121	BM/PM	–	Planar	10 min	20 mCi	84% (72/86)	74% (26/35)	89% (72/81)	65% (26/40)	81% (98/121)
Howarth et al[68]	1999	117/123	BM/PM	9/114	Planar	–	20 mCi	84% (87/103)	80% (16/20)	96% (87/91)	50% (16/32)	84% (103/123)
Melloul et al[69]	1999	121	BM/PM	79/42	Planar	5, 90-120 min	20-25 mCi	89% (16/18)	88% (91/103)	57% (16/28)	98% (91/93)	88% (107/121)
Horne et al[70]	2000	34	BM/PM	–	Planar	5 min	20-25 mCi	89% (17/19)	80% (12/15)	85% (17/20)	86% (12/14)	85% (29/34)
Paz et al[45]	2000	322	BM/PM	213/109	Planar	5, 90 min	20-25 mCi	90% (53/59)	94% (248/263)	78% (53/68)	98% (248/254)	93% (301/322)
Lumachi et al[71]	2001	87	PM	0/87	P + S	5-10 mCi	20 mCi	81% (58/72)	93% (14/15)	98% (58/59)	50% (14/28)	83% (72/87)
Alonso et al[72]	2001	238/245	BM	245/0	Planar	10, 60 min	20-30 mCi	83% (157/189)	77% (43/56)	92% (157/170)	57% (43/75)	82% (200/245)
Lumachi et al[73]	2001	239	BM/PM	–	Planar	5-10 min	20 mCi	88% (182/207)	94% (30/32)	99% (182-184)	55% (30/55)	89% (212/239)
Sun et al[74]	2001	32	BM	32/0	Planar	10 min	20 mCi	83% (20/24)	88% (7/8)	83% (20/24)	88% (7/8)	84% (27/32)
Khalkhali et al[75]	2002	558/584	BM/PM	264/320	Planar	5-10 min	20-30 mCi	Fatty 72% (84/116)	80% (133/166)	72% (84/117)	81% (133/165)	77% (217/282)
								Dense 70% (69/98)	78% (122/156)	67% (69/103)	81% (122/151)	75% (191/254)
Leidenius et al[76]	2002	46/49	BM/PM	25/49	Planar	20	20 mCi	77% (24/32)	61% (11/18)	77% (24-31)	61% (11/18)	71% (35/49)
Lumachi et al[77]	2002	73	PM	0/73	Planar	5-10 min	20 mCi	85% (44/52)	91% (19/21)	96% (44/46)	70% (19/27)	86% (63/77)
Sampalis et al[78]	2003	1243	BM/PM	417/826	Planar	5-10 min	20-30 mCi	93% (186/201)	87% (906/1042)	58% (186/322)	98% (906/921)	88% (1092/1243)
Bone et al[79]	2003	90/111	BM/PM	–	Planar	10 min	20 mCi	82% (65/79)	75% (24/32)	89% (65/73)	63% (24/38)	80% (89/111)
Krishnaiah et al[80]	2003	95/104	BM/PM	59/45	Planar	–	20-30 mCi	83% (20/24)	83% (66/80)	59% (20/34)	94% (66/70)	83% (86/104)
Total		5663		4165/2322 (1.79)	Planar,			83.8% (2205/2631)	86.4% (2690/3112)	83.8% (2205/2630)	86.4% (2690/3112)	85.2% (4895/5743)
					Spect			84.9% (62/73)	86.8% (171/197)	70.5% (62/88)	94.0% (171/182)	86.3% (233/270)

BM, breast mass; PM, positive mammography.

were 93% and 87%, respectively. The positive predictive value was 58% and the negative predictive value was 98% with a diagnostic accuracy of 88%. In this sample with a pretest probability of 13%, a positive scintimammography result would change the estimated probability to 51%, which is equivalent to a 400% change from the pretest value. Therefore, a positive scintimammography result significantly increases the ability to predict the presence of malignant disease in this type of population.

Several other studies have been published since the initial reports regarding the use of ^{99m}Tc-sestamibi scintimammography in the evaluation of breast cancer. The major conclusions of these studies can be summarized as follows.

Sensitivity of Scintimammography

In more than 5660 cases (Table 1) reported so far, the sensitivity of ^{99m}Tc-sestamibi scintimammography in the detection of primary breast cancer varies between 80% and 90% with an average of 84%. The sensitivity for palpable abnormalities is significantly higher than that of nonpalpable lesions. Furthermore, the sensitivity for lesions measuring less than 10 mm is rather low and, so far, no lesion detection of less than 5 mm has been described with the use of currently available standard detectors. Because of this limitation, ^{99m}Tc-sestamibi scintimammography cannot be used as a screening test for breast cancer detection. On the other hand, the sensitivity of ^{99m}Tc-sestamibi scintimammography is not affected by the density of the breast tissue, contrary to radiological mammography, in which high-density breast tissue may have a negative impact on the detection of some lesions. The sensitivity of ^{99m}Tc-sestamibi breast imaging seems also to be superior to that seen with radiological mammography in patients suspected of having recurrent disease with architectural distortions secondary to previous surgery, chemotherapy, radiotherapy or breast implants.

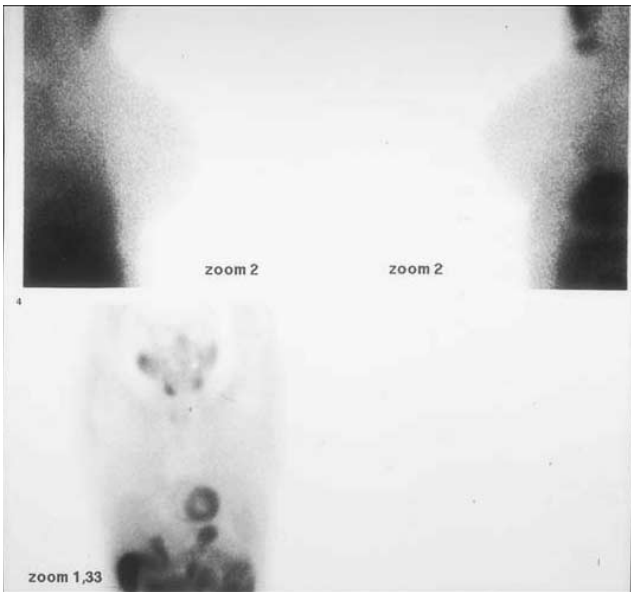

Figure 1 Normal ^{99m}Tc-sestamibi scintimammography. There is a relative uniform uptake of the radiotracer in both breasts on the right and left lateral prone views and in the anterior supine view. The absolute breast uptake is lower compared with the cardiac uptake, which is approximately 2% of the total injected dose of radiotracer.

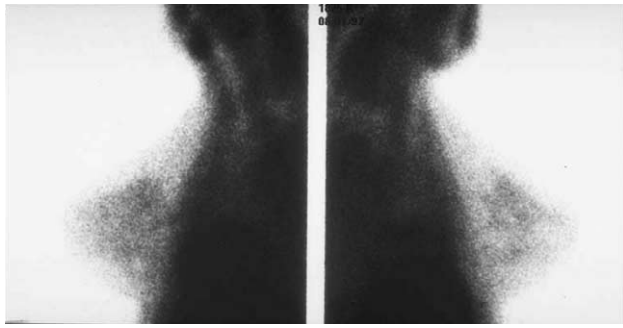

Figure 2 Fibrocystic disease. The study shows bilateral, diffuse, and moderate abnormal uptake of ^{99m}Tc-sestamibi in lesions that are not well delineated. This is a typical scintigraphic pattern of fibrocystic disease.

Specificity of Scintimammography

The specificity of ^{99m}Tc-sestamibi scintimammography is somewhat higher than its sensitivity with an average of 86.4%. Criteria of interpretation for a positive lesion for breast cancer on ^{99m}Tc-sestamibi have not been well defined in initial reports. Since then, more specific criteria were described. Although ^{99m}Tc-sestamibi is most avidly concentrated in breast cancers, increased uptake of the radiotracer also can be detected in various types of benign breast diseases (Figs. 1-3). More extensive clinical experience has lead investigators to recognize some ^{99m}Tc-sestamibi uptake patterns in hyperproliferative fibrocystic breast disease. The following criteria, although not accurate at 100%, provide some guidelines in interpreting ^{99m}Tc-sestamibi breast imaging in pa-

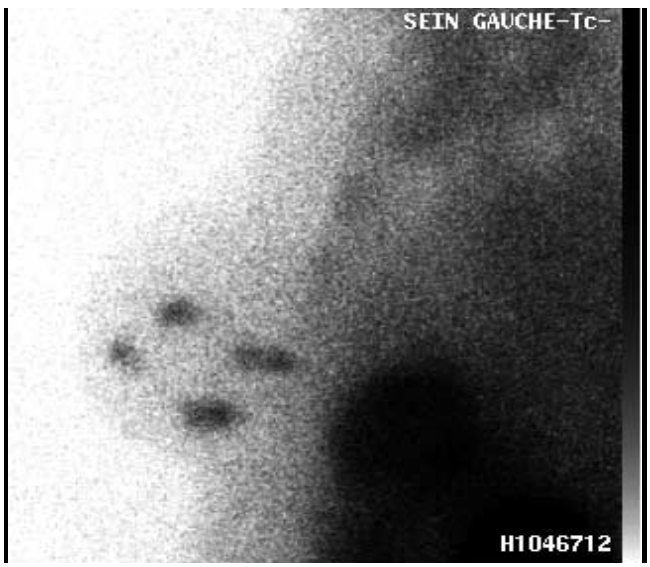

Figure 3 Scintimammography performed in a lactating patient with multiple abscesses of the left breast . Acute mastitis is also a cause of abnormal ^{99m}Tc-sestamibi increased uptake.

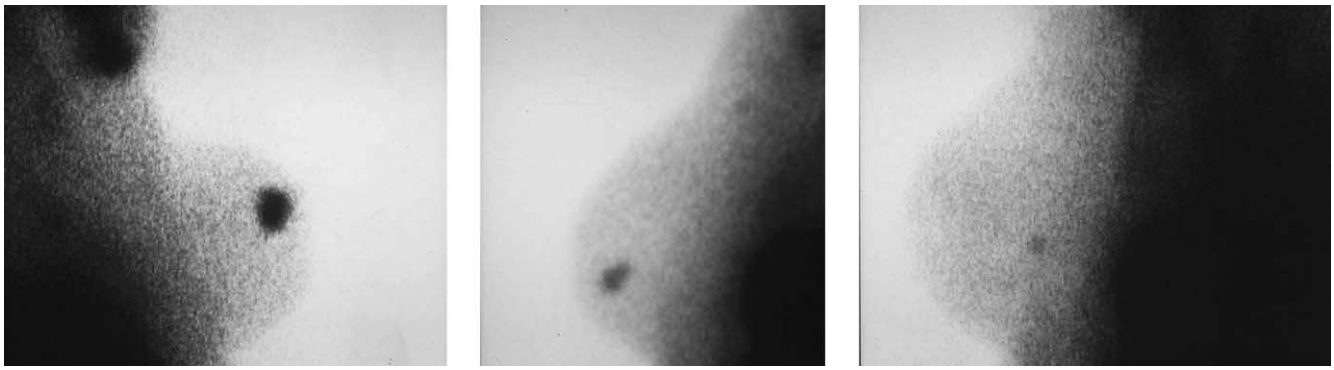

Figure 4 ^{99m}Tc-sestamibi scintimammography obtained in 3 different patients with primary breast cancers (invasive ductal carcinomas), measuring between 1 and 2 cm in diameter. Contrary to fibrocystic disease, the abnormal uptake is more focalized, well-circumscribed, and moderate-to-important in intensity.

tients with benign breast disease. Most of the time, fibrocystic disease will be seen on ^{99m}Tc-sestamibi breast scintigraphy as a region or regions of slight-to-moderate increased uptake, more diffuse than focalized, often bilateral, having contours that are not well delineated, and often presenting a "patchy" uptake. Most of the other benign diseases of the breast will not show a significantly increased ^{99m}Tc-sestamibi uptake. Usually, these lesions are not ^{99m}Tc-sestamibi avid. Acute mastitis or juvenile fibroadenomas are exceptions.

Contrary to most benign disease of the breast, primary breast cancers are usually much more well focalized (although there are some exceptions such as inflammatory cancers which are more diffuse), their contours are usually relatively well delineated and unilateral most of the time (Figs. 4-6). The intensity of ^{99m}Tc-sestamibi uptake varies from mild to very intense depending on several factors, such as the size, type, location, and hormonal factors. Those criteria are still subjective and remain reader dependent. Investigators have attempted to use semiquantitative analyses with tumor-to-background activity ratio determination. Although a ratio greater than 1.2 to 1.4 has been shown to suggest the presence of a malignant lesion, many benign tumors, such as highly mitotic juvenile adenomas, or other benign conditions, such as papillomas, abscess, local inflammation, or hyperproliferative breast disease, will exhibit ratios even greater than 1.5. Nonetheless, the use of more specific criteria than a "positive" focus of increased uptake in the breast greatly improves the specificity of ^{99m}Tc-sestamibi scintimammography in differentiation between benign and malignant lesions. Table 2 summarizes the major causes of false positive ^{99m}Tc-sestamibi studies for breast cancer that have been published so far. Tiling and coworkers[59] compared ^{99m}Tc-sestamibi breast imaging and pre- and postcontrast enhanced magnetic resonance imaging (MRI) in 56 patients with suspicion of breast cancer. Although MRI showed a slightly better sensitivity than ^{99m}Tc-sestamibi scintimammography (91% versus 88% respectively), its specificity was considerably lower (52% versus 83% for ^{99m}Tc-sestamibi imaging), especially in patients with indeterminate mammographic findings. Boné and coworkers[79] compared the diagnostic accuracy of planar ^{99m}Tc-sestamibi scintimammography with dynamic contrast-enhanced MRI on the basis of histopathologic results obtained from 90 patients. They showed that MRI had a higher sensitivity (94% versus 82%, $P = 0.008$) but a lower specificity (47% versus 75%) than scintimammography.

Detection of Axillary Node Involvement

The axillary lymph node chains are the major regional drainage sites for the breast. Because axillary lymph node involvement has been shown to be one of the most important prognostic factors for determining survival in patients with newly diagnosed primary breast cancer, almost every patients with invasive, and many patients with noninvasive cancer will undergo an axillary dissection once the breast cancer diagnosis has been made. Although axillary dissection provides important staging and prognostic information and identifies patient subgroups for adjuvant therapy, is positive influence for breast cancer patients is controversial. It is accompanied by non-negligible morbidity, including arm edema, lymphostasis, and subsequent infections of the ipsilateral extremity. A noninvasive technique to detect breast cancer that

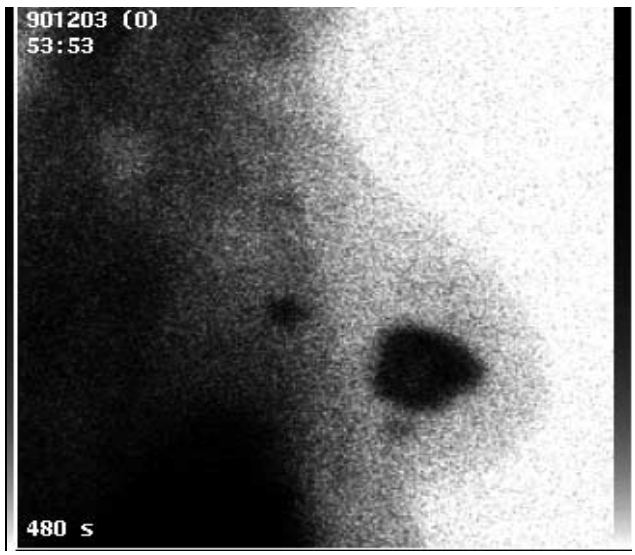

Figure 5 Patient with inflammatory left breast cancer with satellites lesions.

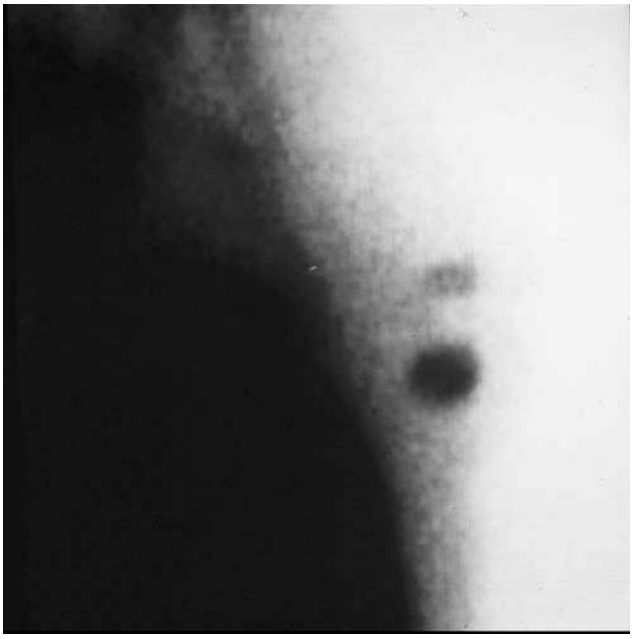

Figure 6 ^{99m}Tc-sestamibi scintimammography in a patient with dense breast and two primary cancers in the right breast. Only the larger lesion has been detected on mammography.

has metastasized to the axillary lymph nodes could permit better selection of patients for axillary dissection. So far, imaging modalities have played a very limited clinical role in this condition. Different radionuclide imaging procedures such as axillary lymphoscintigraphy, immunolymphoscintigraphy, ^{18}F-FDG PET or SPECT imaging, and more recently lymphoscintigraphy with an intraoperative gamma probe for sentinel node detection, have been proposed to assess metastatic involvement of axillary lymph nodes.[84,85]

Taking the advantage of the whole-body distribution of ^{99m}Tc-sestamibi after its injection, different authors have studied the uptake of this radiopharmaceutical in the axillary lymph nodes in patients with primary breast cancers. In a relatively recent review of the literature,[86] ^{99m}Tc-sestamibi breast imaging was reported to have a sensitivity and a specificity of 77% and 89%, respectively, in the detection of axillary lymph node metastatic involvement in patients with primary breast cancer. The associated positive and negative predictive values are 86% and 84%, respectively. In a prospective study performed in 100 consecutive patients with breast cancer, Taillefer and coworkers[44] showed that the sensitivity of ^{99m}Tc-sestamibi scintimammography in detecting metastatic axillary lymph node involvement was 79.2% (38/48), the specificity was 84.6% (44/52), and the positive and negative predictive values were 82.6% (38/46) and 81.5% (44/54), respectively. No patients with more than 4 histologically proven metastatic nodes have been missed by scintimammography. They noted, however, that there was no correlation between the number of positives nodes detected by scintimammography and the number of nodes that were found histologically positive for metastases. This is not a surprising finding since most of the lymph nodes have a small volume, a relatively low absolute radiotracer uptake, are close to each other, and the gamma camera has a limited spatial resolution. Table 3 summarizes the results of various studies using ^{99m}Tc-sestamibi in detection of axillary lymph node involvement in patients with primary breast cancer.[87-91] The average sensitivity is 76%, the specificity 88%, the positive predictive value 83%, the negative predictive value 81%, for an overall diagnostic accuracy of 81%.

Clinical Applications of Scintimammography

So far, the great majority of scintimammographic studies share the same inclusion criteria bias, which is the inclusion of patients having known breast lesion on either mammography or on physical examination with subsequent histopathologic correlation with fine needle, core biopsy, excisional biopsy or surgery. These initial studies had to be performed that way to establish the overall diagnostic accuracy of scintimammography with its advantages and limitations in terms of sensitivity, specificity, and positive and negative predictive values. Now that these numbers are known through several prospective studies, the time has come to position scintimammography in the algorithm of clinical investigation for breast cancer detection. However, although there are many ongoing prospective studies evaluating the clinical role of scintimammography performed in very specific types of patient populations to determine the best niches for it, several data are missing to definitely present scintimammography as an established diagnostic procedure for breast cancer evaluation. Nevertheless, clinical experience acquired so far in several institutions permits to define the areas where scintimammography is most likely to play a significant role in clinical practice.

Radiologic mammography is a very well-established diagnostic procedure that is relatively inexpensive, widely available, and serves as the best screening tool available today for breast cancer detection. Given the limited sensitivity of scintimammography in detection of breast cancer measuring less than 10 mm, all investigators agree that this procedure

Table 2 Sestamibi Breast Imaging: Major Causes of False-Positive Study for Primary Breast Cancer

Fibrocystic disease
Fibroadenoma
Papillomatosis
Focal atypical hyperplasia (ductal, lobular)
Benign phyllodes tumor
Ductal ectasia with hyperplasia
Hyperplastic breast disease with “radial scan”
Inflammation with foreign body granuloma
Sclerosing adenitis
Intraductal papilloma
Chronic granuloma
Mastitis
Intramammary lymph node
Lymphoma
Gynecomastia

Table 3 ^{99m}Tc-Sestamibi in Detection of Axillary Lymph Node Involvement in Patients With Primary Breast Cancer

Authors	Year	Number of Patients	Method	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Burak et al[43]	1994	27	Planar	57% (8/14)	–	–	–
Kao et al[50]	1994	12	Planar	67% (8/12)	–	–	–
Lu et al[42]	1995	11	Planar	100% (4/4)	100% (7/7)	100% (4/4)	100% (7/7)
Taillefer et al[44]	1995	41	Planar	84% (16/19)	91% (20/22)	89% (16/18)	87% (20/23)
Lam et al[87]	1995	31	Planar	64% (7/11)	90% (18/20)	78% (7/9)	82% (18/22)
Palmedo et al[47]	1996	11	Planar	82% (9/11)	–	–	–
			Spect	82% (9/11)	–	–	–
Schillaci et al[88]	1997	49	Planar	81% (17/21)	93% (26/28)	89% (17/19)	87% (26/30)
			Spect	62% (13/21)	96% (27/28)	93% (13/14)	77% (27/35)
Perre et al[89]	1997	36	Planar	91% (20/22)	64% (9/14)	80% (20/25)	82% (9/11)
Chiti et al[90]	1997	28	Spect	82% (9/11)	100% (17/17)	100% (9/9)	89% (17/19)
Taillefer et al[91]	1998	100	Planar	79% (38/48)	85% (44/52)	83% (38/46)	81% (44/54)
Cwikla et al[63]	1998	54	Planar	43% (10/23)	77% (24/31)	56% (10/18)	65% (24/37)
Lumachi et al[71]	2001	62	Planar	82% (51/62)	–	–	–
Total		461		76% (219/290)	88% (192/219)	83% (134/162)	81% (192/238)

Overall diagnostic accuracy: 81% (411/509).

should not be used and is not indicated as a screening test in asymptomatic patients. Therefore, scintimammography should rather be considered as a complementary diagnostic procedure to mammography when this later is nondiagnostic or difficult to interpret. Different select subgroups of patients that may benefit from scintimammography have been identified by many investigators and can be summarized as follows.

Patients With Dense Breast Tissue on Mammography

Despite recent improvement in the overall quality of mammography, dense breasts still represent a diagnostic challenge. It has been shown that the density of the breast tissue is a significant limiting factor for the sensitivity of the test. The detection of breast cancer is more difficult because its radiograph attenuation properties are similar to that of dense glandular and fibrous tissue. Unless the lesion is superimposed or delimited by fat (instead of glandular tissue), the breast cancer will not be easily visualized. It is estimated that approximately 25% of women have dense breast tissue, which is more common among young women but may be seen at any age group. It is not surprising to have a lower sensitivity for mammography in patients aged 40 to 49 years (with more dense breast tissue) in comparison with older women (usually with fatty breast). Contrary to mammography, ^{99m}Tc-sestamibi scintimammography has been shown to be independent of the breast density or structural distortions, and the sensitivity for detection of breast cancer is not affected by the density of breast tissue. Therefore, it is not surprising to find that ^{99m}Tc-sestamibi scintimammography was more accurate than mammography with a better sensitivity and specificity in women with dense breasts on mammography. Patients with a palpable breast mass that is not detected on mammography showing dense breast tissue may benefit from a scintimammography, especially if a previous biopsy of the mass was nondiagnostic. Furthermore, a palpable mass that does not concentrate ^{99m}Tc-sestamibi is likely to be benign because the sensitivity of scintimammography is very high when the lesion measures more than 10 mm (which is usually the case for palpable lesions).

Khalkhali and coworkers[75] reported the results of a multicenter study performed in 558 women prospectively enrolled from 42 north American centers. The analyses were based on 580 breasts with an abnormality. Of the 580 breasts, 276 were dense. The diagnostic properties for scintimammography of fatty breast versus dense breast were very similar (no significant statistical difference) with, respectively, a sensitivity of 72% versus 70%, a specificity of 80% versus 78%, a positive predictive value of 72% versus 68%, a negative predictive value of 81% versus 81%, and an accuracy of 77% versus 75%. This large study concluded that the diagnostic accuracy of ^{99m}Tc-sestamibi breast scintigraphy is not affected by breast density. This is an important observation from a clinical point of view. In this study, there were 45 dense breasts with a palpable mass but negative mammographic findings. Among the 45 breasts, there were 6 with a malignancy not detected at mammography. The scintimammography was positive for three and equivocal for one of the six breasts. Therefore, scintimammography depicted 67% of the cancers that were missed at mammography. The false-negative rate of scintimammography was 7% (2 of 24) compared with 13% (6 of 45) for mammography.

Lumachi and coworkers[71] evaluated the usefulness of ^{99m}Tc-sestamibi scintimammography and x-ray mammography in 87 premenopausal patients with small (<2 cm) suspicious breast lesions. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of x-ray mammography and scintimammography were 81% versus 81%, 60% versus 93%, 91% versus 98%,

39% versus 50%, and 77% versus 83%, respectively. Tumors undetected by both mammography and scintimammography were significantly smaller than those correctly diagnosed. Patients with false-negative mammography were younger than those with tumors correctly detected, while scintimammography sensitivity was independent (P = ns) of age and also density of the breast. Sun and coworkers[92] studied 32 patients with indeterminate mammographic probability of malignancy because of mammographically dense breasts. ^{99m}Tc-sestamibi scintimammography showed a sensitivity of 83%, a specificity of 88%, and an accuracy of 84% in this patient population with radiologic mammograms, which were difficult to interpret.

Patients With "Iatrogenic" Architectural Distortion of the Breast

If there has been architectural distortion of the breast tissue from a previous breast surgery, radiation therapy, chemotherapy or biopsy, mammographic findings will be much less specific than that on a "virgin" breast. Scarring caused by these "iatrogenic" treatments in the breast will render mammographic assessment more difficult and uncertain. Scintimammography findings are not affected by the morphologic changes of the breast tissue but rather by the metabolic changes. Therefore, scintimammography can be more specific than mammography in patients with architectural distortions of the breast from the above-mentioned reasons. It also can be useful to determine the presence of recurrent disease in these circumstances. Babuccu and coworkers[93] studied the value of ^{99m}Tc-scintimammography in 12 women undergoing a reduction mammoplasty operation using the McKissock technique. Mammography is known to be unreliable in reduction mammoplasty, which results in fat necrosis, architectural distortion, and heavy scarring of the breast. Mammography and scintimammography were performed before and 6 months after the surgery. Although mammography showed postoperative parenchymal redistribution, retroareolar fibrotic bands and cysts, scintimammography did not show any significant modification of the radiotracer uptake in this patient population without breast cancer.

Patients With Breast Implants

Mammographic findings are sometimes difficult to assess in patients with breast implants. However, scintimammography is not affected by the "attenuation" from the implant. The implant is seen as a photopenic defect which, in fact, improves the overall quality of the procedure since there is no or very few activity detected in projection of the implant, facilitating the detection of breast lesions (Fig. 7). Therefore, scintimammography is indicated when mammography is difficult or nondiagnostic in patients with breast implants.

Patients With Palpable Mass and Normal or Equivocal Mammography

It is not infrequent that a palpable breast mass is difficult to evaluate on mammography, especially in patients with dense breast and fibrocystic changes. Although many of the patients with this condition will have a breast biopsy, in others, for different reasons, a follow-up study will be suggested. Because the positive and negative predictive values of scintimammography are high in patients with palpable breast lesions, this procedure could be performed immediately after mammography, instead of waiting for a 6- to 12-month period as a follow-up. This would also decrease the level of anxiety of the patient. If scintimammography is positive, then it will be important to obtain a histopathological result as soon as possible. Scintimammography can also be useful to provide additional information in patients who are hesitant to undergo either a biopsy or a resection or in whom the biopsy may be relatively contraindicated.

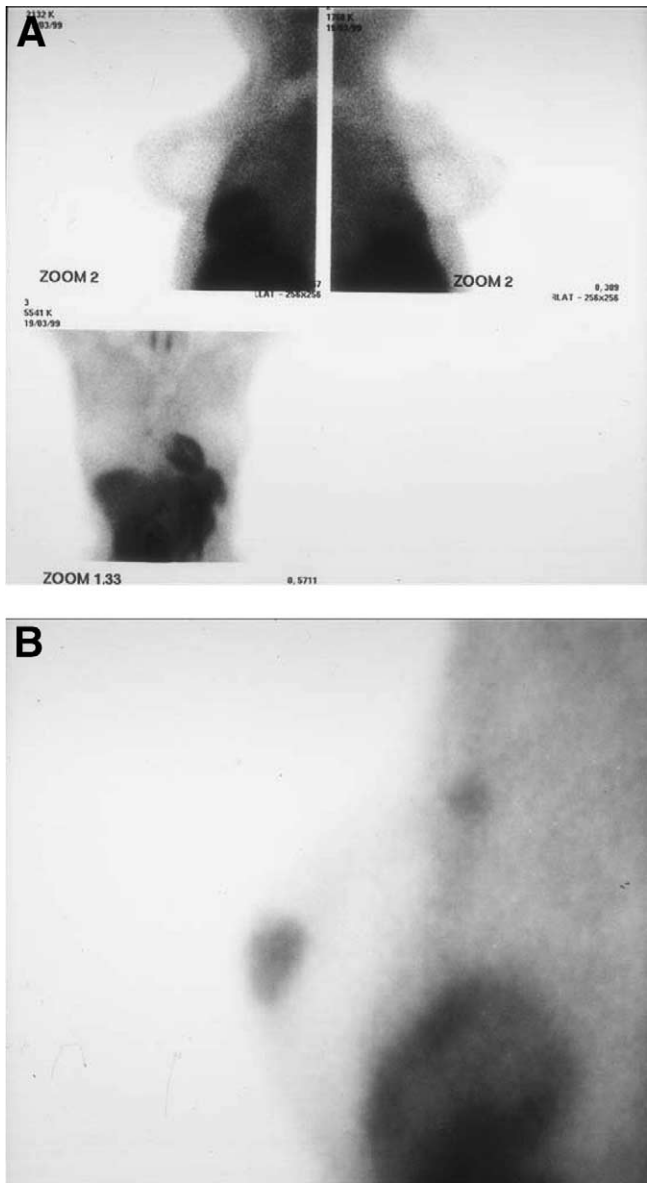

Figure 7 (A) Normal ^{99m}Tc-sestamibi scintimammography in a patient with bilateral breast implants (seen as relative decreased uptake). (B) Patient with a breast implant and a primary breast carcinoma with metastatic involvment of the left axillary lymph nodes shown on scintimammography.

Assessment of Multifocal Disease of the Breast

Patients who are scheduled for a lumpectomy but had a normal or nondiagnostic mammography may benefit from a scintimammography to evaluate the presence of multifocal disease. Because scintimammography is not affected by the density or the type of breast tissue, it can demonstrate the presence of one or more focus of increased uptake. A lumpectomy will be considered if there is only one site of tumor. However, if multifocal disease is discovered, the type of surgery will differ. Because both breasts are imaged at the same time, it also is possible to discover a breast cancer contralateral to the suspected one. Derebek and coworkers[94] described a case of bilateral multifocal breast cancer in whom ^{99m}Tc-sestamibi scintimammography correctly identified the lesions missed by mammography and dynamic MRI.

Evaluation of High-Risk Patients for Breast Cancer

It has been demonstrated that there are some factors that increase the risk of developing breast cancer. These include a family history of breast cancer, genetic predisposition (BRCA1, BRCA2, Li Fraumeni syndrome), secondary breast radiation, prior lumpectomy and radiation therapy, histological atypia, and hormonal contraceptives. Although scintimammography cannot be used as a screening test for breast cancer detection, high-risk patients with dense breast tissue for example might be an exception. Because mammography and ultrasound cannot always be effective to these patients as a screening procedure, it might be interesting to follow these patients with another imaging modality which is not dependent on the density of the breast tissue as previously stated. However, it will take many years with long-term follow-up prospective studies to confirm or infirm the cost-effectiveness of "screening" scintimammography in this very specific niche.

Evaluation of Tumor Response to Chemotherapy

As previously discussed, ^{99m}Tc-sestamibi is a P-glycoprotein transport substrate which responsible for the multidrug resistance. It has been shown that ^{99m}Tc-sestamibi uptake can be significantly decreased in tumor cells overexpressing MDR1 gene. Therefore, scintimammography can provide functional imaging for the evaluation of the susceptibility of a breast cancer to chemotherapeutic agents. Many studies are currently evaluating the clinical role of ^{99m}Tc-sestamibi scintimammography in patients undergoing chemotherapy for breast cancers, especially to predict the response or the nonresponse to chemotherapeutic agents.

Neoadjuvant or induction chemotherapy is increasingly used in the treatment of patients with locally advanced breast carcinoma and inflammatory breast cancer, followed by surgical treatment. The primary goal of this approach is to increase tumor resectability and to enable breast-conserving therapy. The optimal intensity and duration of neoadjuvant chemotherapy for locally advanced breast cancer remain controversial, in part because of the difficulty of evaluating response to therapy. Studies have demonstrated significant discrepancies between the clinical assessment of response to chemotherapy and the pathologic assessment of the response.[95] Mammography also is not always reliable in this condition. An imaging procedure able to quantitatively evaluate the amount of viable residual disease over the course of chemotherapy would result in the ability to treat effectively to maximal response. Such a noninvasive imaging method also would be useful in planning the optimal timing of surgical therapy after chemotherapy.

Mankoff and coworkers[96] prospectively evaluated 32 patients receiving neoadjuvant chemotherapy for locally advanced breast cancer with ^{99m}Tc-sestamibi scintimammography before therapy at 2 months after therapy and close to the completion of chemotherapy, before surgery. They calculated a lesion-to-normal radiotracer uptake ratio on each image. In the clinical responders, the ratio decreased by 35%, whereas it increased by 17% in the nonresponders ($P < 0.001$). In patients achieving a pathologic primary tumor macroscopic complete response, the mean change in ^{99m}Tc-sestamibi tumoral uptake on the presurgical study decreased by 58% versus 18% for patients with a partial pathologic response ($P < 0.005$). The authors also found that a decrease of more than 40% in the radiotracer ratio identified complete responses with a sensitivity of 100% and a specificity of 89%.

Tiling and coworkers[97] compared ^{18}F-FDG positron emission tomography and ^{99m}Tc-sestamibi planar and SPECT scintimammography in a small group of 7 patients with locally advanced breast cancer before beginning chemotherapy, after the first 2 cycles of chemotherapy, and after completing chemotherapy before surgery. There was a highly significant correlation between standard uptake value (SUV) mean, SUVmax, and the tumor-to-lung ^{99m}Tc-sestamibi ratio in the studies performed before and after chemotherapy. They concluded that both radionuclide techniques were equally useful methods for monitoring tumor response to neoadjuvant chemotherapy.

Cayre and coworkers[98] studied 45 patients with primary breast cancer with mammography, ^{99m}Tc-sestamibi scintimammography, and biopsy for histopathological diagnosis before and after neoadjuvant therapy. Expression of MDR1 and MRP mRNA (multidrug resistance-related protein) were determined by reverse transcription polymerase chain reaction on fine-needle aspirations. Their results showed that ^{99m}Tc-sestamibi scintimammography predicted the reduction of tumor size measured by ultrasound and the pathological response. A negative scintimammography predicted chemoresistance with a specificity of 100% and the uptake of ^{99m}Tc-sestamibi was inversely correlated to the expression of MDR1 ($P < 0.05$) in invasive ductal carcinoma. Therefore, they concluded that a low ^{99m}Tc-sestamibi uptake before neoadjuvant chemotherapy in locally invasive breast carcinoma correlated to MDR1 chemoresistance and was highly specific of a lack of pathological response to chemotherapy.

Evaluation of Metastatic Axillary Lymph Nodes

Although the diagnostic accuracy of scintimammography to detect metastatic axillary lymph node involvement varies between 80% and 85%, this number is still too low to advocate its use to avoid axillary node dissection in patients with proven invasive primary breast cancer. However, the information on the axillary node status obtained during a scintimammographic study (without any particular "effort") can be useful to the clinician in specific circumstances (Fig. 8). A patient who is reluctant to be submitted to an axillary dissection for any reason can be motivated to have one if scintimammography shows a positive axillary uptake. However, if the primary breast tumor shows an increased uptake of the radiotracer but the axilla is negative, the surgeon may decide to not perform the axillary dissection if the patient is very obese or elderly. Obviously, the biopsy of the sentinel node may be a useful adjunct in these circumstances. Scintimammography also can be useful to assess patients who present with axillary metastatic adenocarcinoma of unknown origin without clinical or mammographic evidence of primary breast tumor.

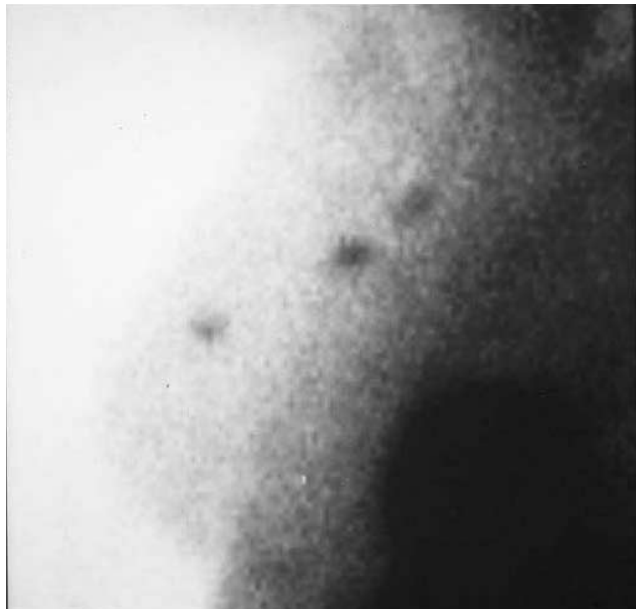

Figure 8 Scintimammography in a patient with primary left breast cancer and 2 metastatic lymph nodes in the axilla.

Miscellaneous

Some patients who have had a bad experience from previous mammography or lack of confidence in it either because of the related pain from breast compression or because they had negative biopsies for suspicious lesion or cancer which were missed by a previous mammography may be reluctant to be submitted to another mammography. In these special cases, the accuracy of scintimammography is high enough to offer it as an alternative method to mammography. Some institutions may also use the high predictive value of scintimammography to perform it on a routine basis as a complementary procedure to a mammography showing a probably benign result. A negative scintimammography can increase the diagnostic certainty that there is no cancer and that the result of mammography is effectively normal. It can also be performed for detection of breast cancer in male patients[99] or bilateral breast cancers.[100]

Scintimammography in Clinical Practice

Now that the diagnostic accuracy of scintimammography has been assessed in different groups of patients, that its positive and negative predictive value are relatively high, and that the advantages and limitations of scintimammography are known, more specific studies are necessary to specify the clinical niches of this test. Taking into consideration the above-mentioned advantages of scintimammography clinical algorithms can be developed to position the test where it may act as a useful complementary procedure to difficult or nondiagnostic mammography and ultrasound. Obviously, the clinical relevance of any algorithm will depend on several factors, such as the availability of scintimammography, the technical and medical expertise, the collaboration between radiologists, nuclear medicine physicians, and referring physicians, and the clinical practice in a given institution or area which can vary significantly from a place to another. It is likely that many suggested indications for scintimammography cannot be applied in various centers but this procedure can be considered in situations where other imaging modalities are not optimal. In summary, scintimammography can be used when mammography is nondiagnostic or when it is difficult to interpret, to better characterize the ≪ functional≫ aspect of architectural distortions, to evaluate the multicentricity of a proven primary breast cancer, or to serve as a complementary diagnostic procedure when a 6- to 12-month follow-up is suggested. A rapidly performed scintimammography, especially a negative one, can be reassuring to the patient.

Future Applications and Cost Effectiveness

As previously stated, one of the major limiting factor of scintimammography is the spatial resolution of the standard gamma camera. No lesion measuring less than 5 to 7 mm has been detected so far with such imaging system. Given the recent enormous interest of the nuclear medicine community for breast imaging, different dedicated cameras specifically designed for scintimammography are currently under development and tested in various clinical sites. Different collimators, cameras (different types and sizes), views, and imaging tables have been tested.[101] One of the interesting development is the use of semiconductor camera. Unfortunately, over the last few years, breast studies using new radionuclide imaging modalities or procedures have not been really successful or consistent in showing significant improvement in the spatial resolution and ultimately in the diagnostic accu-

racy. Most of the recently published clinical data on ^{99m}Tc-sestamibi scintimammography still were performed using "standard" imaging procedures and equipment. If scintimammography is to survive as a useful clinical diagnostic tool in breast cancer detection in a very competitive diagnostic field where many types of new imaging techniques are considered, the overall principle of external tumor detection will have to improve, especially for both contrast and spatial resolution. Planar and SPECT breast imaging, as currently practiced, imposes a significant drawback to a more widespread diagnostic application of ^{99m}Tc-setamibi scintimammography in clinical practice.

One of the frequent questions raised by scintimammography is how can a cancer be located if it concentrates ^{99m}Tc-sestamibi but is not seen on mammography and is not palpable? At the present time, there are 3 different ways to locate the lesion for a biopsy or an excision. The first and simplest way is to use a skin marker to locate the lesion from an anterior supine view and then, if possible, to perform a lateral view in this position to evaluate the depth of the lesion. Although this is an easy procedure that is usually accurate to determine the quadrant of the involved breast, it is less accurate to measure the depth; therefore, it is a rather gross localization method. The second method introduced by Khalkhali and coworkers[102] uses a radionuclide-guided stereotactic prebiopsy needle localization device that allows the physician or technician to localize an abnormality detected on scintimammography. A postbiopsy specimen scintigraphy is obtained to confirm removal of suspicious areas of increased radiotracer uptake seen on scintimammography. The third way to locate the lesion, especially during surgery, is to use an intraoperative gamma hand-held probe, such as the one used for sentinel lymph node localization, in the operating room. After the injection, the surgeon can manipulate the probe to more precisely locate the area of increased radiotracer uptake.

In this managed care era, cost-effectiveness is an important factor to considered when a new diagnostic procedure is introduced. Hillner[103] demonstrated that substantial cost savings can be obtained with the use of ^{99m}Tc-sestamibi scintimammography or stereotactic core biopsy compared with surgery with a slight compromise in the rate of early cancer detection in patients with nonpalpable breast abnormalities. In the recent years, conflicting results on the cost effectiveness of ^{99m}Tc-sestamibi scintimammography, especially for the screening of women with dense breasts for breast cancer have been reported. Allen and coworkers[104] have studied the impact of scintimammography on the cost effective management of women with dense breasts by addressing the issue quantitatively with three different strategies: conventional mammography alone (strategy A), scintimammography after a negative mammogram (strategy B), and scintimammography as the only screening test for women already identified as having dense breasts by a previous mammogram (strategy C). They evaluated the impact of these strategies based on approximately 3 million women older than 40 with very dense breasts without palpable masses who have had one or more prior x-ray mammogram, who undergo routine screening each year. Strategies B and C reduced the number of false negative diagnoses by 62% and 8%, respectively. The calculated incremental cost effectiveness ratio was $632,000 and $3.18 mol/L per life year for strategy B and C, respectively. They calculated that, to be effective, the pretest probability of cancer in the study population must be greater than 3% for strategy B or the cost of scintimammography must be less than $50 for strategy C. Therefore, they concluded that the cost effectiveness of scintimammography was beyond the range of many other routinely performed medical interventions. However, the same group of authors[105] in another study showed the cost effectiveness of using a mammography and ^{99m}Tc-sestamibi scintimammography based strategy to avoid unnecessary biopsies for screening patients with breast cancer.

Chen and coworkers[106] described a decision analysis model comparing ^{99m}Tc-sestamibi scintimammography and excisional biopsy as breast cancer evaluation strategies for a hypothetical cohort of estimated 40,000 Taiwanese women with indeterminate mammographic probability of malignancy because of mammographically dense breasts. Using a quantitative decision tree sensitivity analysis, two different strategies were compared: conventional excision biopsy alone (strategy A), screening with ^{99m}Tc-sestamibi scintimammography before excision biopsy after an indeterminate mammogram (strategy B). Strategy B showed a significant cost saving compared with strategy A, and scintimammography can save the cost of unnecessary biopsies in women with nondiagnostic mammogram because of mammographically dense breasts. More data will be needed to better qualitatively assess the cost effectiveness of ^{99m}Tc-sestamibi scintimammography in clinical practice.

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