Comparison between ^{99m}Tc-Sestamibi Scintimammography and X-ray Mammography in the Characterization of Clusters of Microcalcifications: A Prospective Long-term Study

M. GROSSO[1], S. CHIACCHIO[1], F. BIANCHI[2], C. TRAINO[3], C. MARINI[4], A. CILOTTI[4], G. MANCA[1], D. VOLTERRANI[1], M. RONCELLA[5], L. RAMPIN[6], M.C. MARZOLA[6], D. RUBELLO[6] and G. MARIANI[1]

[1]*Regional Center of Nuclear Medicine,* [2]*Nuclear Medicine Unit, Department of Endocrinology,* [3]*Section of Medical Physics, Health Physics Unit,* [4]*Radiology Division, Imaging Department, and* [5]*Breast Surgery Unit, University Hospital, Pisa;* [6]*Department of Nuclear Medicine, PET Centre, "Santa Maria della Misericordia" Hospital, Rovigo, Italy*

Abstract. *Background: the early diagnosis of non-palpable breast cancer is the object of recent developments in the imaging procedures employed for screening purposes. In some patients, the presence of microcalcifications (MC) is the only indication of tumor. Although X-ray mammography (MRx) has high sensitivity in detecting MC, its specificity is however too low for diagnostic purposes. The aim of this study was to compare ^{99m}Tc-sestamibi scintimammography (SMM) and MRx in the differential diagnosis between benign and malignant clusters of MC and to assess the possible incremental value of SMM on specificity. Patients and Methods: A total of 283 consecutive women (mean age 53±8 years) with MC identified on X-ray mammograms underwent SMM. Scintigraphic images were acquired 10 minutes after the i.v. injection of ^{99m}Tc-sestamibi (740 MBq). Planar images of both breasts were simultaneously obtained in the lateral prone position and in the anterior and oblique projections using a dual head camera. Sixty-nine women underwent surgery, whereas the remaining 214 patients had completely negative follow-up for 5 years (a 5-year follow-up period is considered the "gold standard" for diagnosing benign lesions). Results: Histology demonstrated 32/69 primary breast carcinomas (prevalence of disease: 11% of all the 283 patients) and 37/69 benign lesions. The receiver operating characteristic (ROC) statistical technique was employed to compare the diagnostic value of Mrx alone to that of combined MRx and SMM. The detected difference between the areas under the MRx ROC curve (area=0.72, standard error 0.052) and the MRX and SMM ROC curve (area=0.86, standard error 0.039) was statistically significant ($p<0.01$). Moreover, the combination of MRx and SMM provided a significant improvement of the negative predictive value (NPV=98%) for MC with low-suspicion of malignancy at MRx. Conclusion: SMM can be considered as a complementary tool in the pre-operative work-up of patients with breast lesions. Furthermore, the high negative predictive value of this technique, makes it especially valuable in the perspective of reducing the number of negative breast biopsies or unnecessary surgical interventions.*

Correspondence to: Mariano Grosso, MD, Regional Center of Nuclear Medicine, University Hospital of Pisa, via Roma 67, Pisa, Italy. Tel: +39 50993127, Fax +39 50992126 e-mail: marianogrosso@yahoo.it

Key Words: Breast cancer, X-ray mammography, ^{99m}Tc-Sestamibi scintimammography, microcalcifications, negative predictive value, ROC curve analysis.

Breast cancer is a major health problem for women. It accounts for one-third of cancer diagnoses and 15% of cancer deaths in the U.S.A. with 192000 cases and 40000 deaths in 2001 it was the most common cancer (excluding superficial skin cancer) and second leading cause of cancer death (1).

In Italy the incidence is about 31,000 cases per year with a frequency of 60-70 cases/100,000 for year in the north and central regions and the mortality is 11,000 cases per year (2). At present, the primary strategy for reducing mortality due to this disease is early detection and treatment. Currently, early detection relies on patient self-examination, physical examination and X-ray mammography (MRx). MRx is the most frequently used screening method and a decrease in breast cancer mortality of 33% has been observed in women who have undergone mammographic screening (3).

In addition, MRx is the primary imaging modality used to detect nonpalpable breast cancer (4-7) and has proven to be the single most reliable method for detecting breast abnormalities, but the only way to exclude the possibility of breast cancer in patients with nonpalpable suspicious

mammographic masses is by biopsy and analysis of specimens. MRx is not able to distinguish between benign and malignant MC, and there is also a large interobserver variability in its interpretation (8). As the positive predictive value (PPV) of mammography ranges from 10% to 40%, a large number of unnecessary biopsies are performed (9). Therefore, most patients undergo a biopsy procedure unnecessarily. The development of a complementary non-invasive test to improve the specificity of mammography should be of importance. Despite its high sensitivity, it has a low specificity in the diagnosis of breast cancer and in certain cases, MRx has to be supplemented with additional imaging modalities. The limitation of MRx in patients with dense breasts, those who have previously undergone surgery and those with breast implants is well known (10, 11). Ultrasound is an established supplement in patients with dense breasts (12). Magnetic resonance imaging (MR) is most often used as a complement in cases with indeterminate X-ray mammograms and it has high sensitivity, but rather low specificity (13, 14).

The presence of microcalcifications (MC) without mass, such as asymmetric breast, focal architectural distortion, ductal asymmetry ("indirect signs"), is sometimes the only indication of the presence of cancer (15, 16). There is controversy as to whether the presence of indirect signs alone is grounds for a biopsy. In the event that MRx detects a localized abnormality without the pathognomonic signs of benignity, physicians have only the limited management options of either prompt excision, aspiration for cytology, or short-interval follow-up MRx to detect growth. Since a great number of benign lesions are found in patients with suspicious mammographic findings, a series of morphological and/or functional imaging complementary techniques [(ultrasound, MRI, scintimammography (SMM)] have been proposed to support MRx in the detection and characterization of breast anomalies.

SMM is useful for initial diagnosis of breast cancer, detection of recurrence, evaluation of tumour extention, diagnosis of primary breast tumours in patients with dense breasts (17), and its value has especially been emphasised in the evaluation of therapy response (18). Moreover, SMM may be considered a non-invasive method for the identification of (MDR)-positive patients, assisting in the choice of the most suitable therapy (19). High sensitivity ranging from 83% to 93.7% (20-23) and specificity ranging from 50% to 94.4% (16) for SMM have been reported. Increased diagnostic specificity of breast imaging, might reduce the number of unnecessary biopsies performed after mammographic indication.

The goal of this prospective study was to evaluate the additional diagnostic value of SMM in the diagnosis of nonpalpable breast lesions (microcalcifications) previously detected by MRx.

Patients and Methods

During the period between September 1996 December 2002, 283 consecutive patients aged 32-79 (mean 53±8,2), with MC of the breast detected by screening-MRx were included in the study. After informed consent was obtained, SMM was performed in all the patients. Inclusion criteria included: SMM within 2 weeks after conventional mammography; breast lesion operated upon within 1 month after SMM; a minimum follow-up of 5 years after SMM; mental capacity and age above 18 years. Exclusion criteria included: a palpable lesion suspicious of malignancy; palpable nodes in the axillary region; a history of prior carcinoma; prior fine-needle aspiration (FNAC) or core-biopsy (CB) within 1 week prior to SMM (because it has been suggested that recent trauma could lead to false-positive SMM images), pregnancy and lactation.

X-ray mammography. MRx was performed using a dedicated mammography unit (Metaltronica Compact Mammo HF, Pomezia, Italy). A standard two-view protocol of cranio-caudal and lateral oblique views was used. Magnification and coned compression techniques were used for all the lesions to clarify doubtful diagnoses. The images were interpreted by two skilled radiologist mammographers without knowledge of the patient's history, clinical presentation or the results of previous mammograms. Disagreements between readers were resolved by consensus, with a third experienced observer used as a referee. The MC on the mammograms were divided into three groups following the criteria previously published by the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) (24, 25) based on the suspicion of malignancy: BI-RADS 1, 2=low suspicion (L); BI-RADS 3=intermediate suspicion (I); BI-RADS 4, 5=high suspicion (H). In detail, group L included low suspicion MC, whose morphology was typically benign, coarse, round (<1 mm), spherical or lucent-centered, milk of calcium, dystrophic and punctate (<0.5 mm). Group I included intermediate suspicious MC whose morphology was amorphous or indistinct (round or flake). Group H comprised high suspicion MC, whose morphology was pleomorphic or heterogeneous (granular), fine and/or branching (casting), irregular, discontinuous, <0.5 mm in width (23).

Scintimammography. SMM was performed as second procedure on each patient after *i.v.* of 740 MBq of ^{99m}Tc-sestamibi in an antecubital vein of the arm opposite to the breast lesion. The dose was then flushed by injecting 20 ml of saline solution. ^{99m}Tc-sestamibi was prepared according to the manufacturer's recommendations (Cardiolite®, Bristol-Myers Squibb Medical Imaging, North Billerica, MA, USA). Five minutes after the injection the patient was positioned prone on a dedicated table adaptor, with raised arms in order to expose the axillae and with the detectors touching the patient's side for improved resolution. Fifteen lateral planar images were simultaneusly acquired. A dual head large field-of-view (LFOV) gamma camera (GE Medical Systems, Millennium MG, Milwaukee, WI, USA), equipped with low energy, high resolution (LEHR) collimators on a matrix of 256×256 pixels (zoom factor 1.6) was used. Further anterior and oblique planar images were later acquired on a matrix 128×128 without zoom factor with the patient supine and with raised arms to better visualize the axillae and medial breast regions. All the planar images were obtained with a 10% window centered at 140 keV of the ^{99m}Tc energy peak.

Table I. *Results of hystopathological diagnosis versus mammographic (MRx), scintigraphic (SMM) and mammographic+scintigraphic (MRx+SMM) suspicion of malignancy.*

Histology	MRx			SMM			MRx+SMM		
	L	I	H	L	I	H	L	I	H
Ductale invasive	3	5	6	4		10	1	2	11
Ductal *in situ*	3	5	4	3	6	3	1	4	7
Lobular invasive		1	1			2			2
Lobular *in situ*		1	1			2			2
Papillar *in situ*		1			1			1	
Mucinous			1			1			1
Total malignant	6	13	13	7	7	18	2	7	23
Dysplasia	9	18	7	26	7	1	9	18	7
Fibroadenoma	1		1		1	1		1	1
Nipple adenoma			1			1			1
Follow-up	110	95	9	181	32	1	103	101	10
Total benign	120	113	18	207	40	4	112	120	19

Suspicion of malignancy: L, low; I, intermediate; H, high.

The SMM was scored by two experienced observers blinded to clinical and MRx information. Disagreements between readers were resolved by consensus, with a third experienced observer used as a referee.

The mammoscintigrams were classified in three groups, based on the uptake of the lesion: 1=total absence of uptake (group L); 2=indeterminate (group I); 3=malignant uptake (group H). In detail, the breast images with homogeneous uptake of tracer in both breasts were classified as normal; non-homogeneous ^{99m}Tc-sestamibi uptake without focal uptake was interpreted as equivocal or indeterminate because it was impossible to state whether a small tumour could be present within the breast, but was obscured by physiological uptake of ^{99m}Tc-sestamibi. Any focal uptake with moderate or high intensity was considered to be malignant.

Combined MRx and SMM. Based on the results of MRx and SMM, the MRx-SMM combination was evaluated in three groups, based on the suspicion of malignancy (from L=low suspicion to H=high suspicion of malignancy).

Data analysis. The results obtained were compared to the definitive histological diagnosis by surgical biopsy in 69 patients and the results of follow-up to 5 years in 214 patients (gold standard) in whom the mammographies remained unchanged.

Histology revealed 32 malignant and 37 benign lesions. In Table I the type of pathology is shown. Combination imaging was defined as MRx followed by SMM and the combined result was determined by the highest score obtained with either modality. The comparison between MRx and the MRx-SMM combination was analysed by the receiver operating characteristic (ROC) curves method. The area under the ROC curves was evaluated by the nonparametric Wilcoxon test. The areas were then compared by the method previously described in (26). The Pearson product-moment correlation was used to calculate the correlation coefficient r between the areas (25). A p-value less than 0.05 was considered as significant.

Follow-up consisted of periodic clinical examination, MRx, ultrasound and ^{99m}Tc-sestamibi scintimammography when appropriate. The minimum follow-up period was 5 years (range 5 to 12.4 years, median 8.7 years).

Results

A total of 69 breast lesions out of the 283 in the study were operated upon (Group 1). Carcinoma was found in 32 of these lesions (46%) and benign lesions in 37 (54%); six different histologic types of breast tumor were identified. The other 214 patients had follow-up for at least 5 years (Group 2) (Table I).

The SMM results were positive in 18 patients out of the 32 (56.2%) malignant lesions. There were 14 breast carcinomas that were false negative on SMM and out of these 7 were evaluated as benign and 7 as indeterminate. False-positive uptake of ^{99m}Tc-sestamibi was reported in 3 patients, while 8 patients were evaluated as indeterminate.

The X-ray mammograms were interpreted as revealing breast cancer in 13 patients out of the 32 (40.6%), while the remaining 19 cases were reported as benign lesions (6 lesions) or indeterminate (13 lesions). There were 10 true negative and 18 indeterminate findings out of the 37 benign lesions. In the remaining group consisting of 214 patients not operated on, with a median negative follow-up of 8.7 years (evaluated as true-negative), SMM was negative in 181 cases and indeterminate in 32 cases. Therefore, the sensitivity,

Table II. *Calculated values of sensitivity (TPF), specificity (TNF), false positive fraction (FFP), false-negative fraction (FFN), positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy (DA). These values are calculated depending on diagnostic threshold.*

	MRx		SMM		MRx + SMM	
Diagnostic threshold	1=non malignant	1, 2=non malignant	1=non malignant	1, 2=non malignant	1=non malignant	1, 2=non malignant
TPF	0.81	0.41	0.78	0.53	0.94	0.75
TNF	0.47	0.93	0.82	0.98	0.44	0.92
FFP	0.53	0.07	0.18	0.02	0.56	0.08
FFN	0.19	0.59	0.22	0.47	0.06	0.25
PPV	0.17	0.42	0.36	0.81	0.18	0.55
NPV	0.95	0.92	0.97	0.94	0.98	0.97
ICC	0.62	1.06	1.00	1.14	0.60	1.10
Ind Youden	0.28	0.33	0.60	0.52	0.37	0.67

specificity, PPV and negative predictive value (NPV) of SMM were, 78% , 82% , 36% and 97% , respectively.

MRx was negative in 110 and indeterminate in 95 out of the 214 patients. Its sensitivity, specificity, PPV and NPV were, 81% , 47% , 17% and 95% , respectively.

Table I shows that 13 out of the 31 (41%) lesions with a high mammographic suspicion of malignancy (group H), were malignant [6 ductal carcinomas, 4 ductal carcinomas *in situ* (DCIS) and three other type], 13 out of the 126 (10%) lesions with intermediate suspicion of malignancy (group I) were malignant (5 ductal carcinomas, 5 DCIS and three other type), and only six of 126 (5%) lesions with a low mammographic suspicion of malignancy (groups L) were malignant (3 ductal carcinomas, 3 DCIS).

Eighteen out of the 22 (82%) lesions with high scintigraphic suspicion of malignancy (group H) were malignant (10 ductal carcinomas, 2 lobular invasive, 2 lobular *in situ*, 3 DCIS and 1 mucinous carcinoma), 7 out of the 47 (15%) lesions with intermediate scintigraphic suspicion of malignancy (group I) were malignant (6 DCIS and 1 papillar *in situ*), and only 7 out of the 214 (3%) lesions with a low scintigraphic suspicion of malignancy (group L) were malignant (4 ductal carcinomas and 3 DCIS). Taking into account the diagnostic results of the mammography-mammoscintigraphy combination, Table I shows that 23 out of the 42 (55%) lesions with a high suspicion of malignancy (group H) were malignant, 7 out of the 127 (5%) lesions with intermediate suspicion of malignancy (group I) were malignant, and only 2 out of the 114 (2%) lesions with a low suspicion of malignancy (group L) were really malignant.

However, if a combination of the two methods was used (MRx followed by SMM), sensitivity for identifying cancer was 94% , specificity was 44% , PPV 18% and NPV 98% .

The areas under the ROC curves for MRx, SMM and the combination of MRx and SMM imaging were respectively 0.72±0.052, 0.84±0.046 and 0.86±0.039. A highly significant difference (*t*-test $p<0.01$) was found between the areas under the ROC curves corresponding to MRx and SMM and between the areas under the ROC curves corresponding to MRx and the MRx and SMM combination imaging.

If the groups with low and indeterminate suspicion were considered as negative, the sensitivity of the two methods used (MRx followed by SMM) was 75% , specificity 92% , PPV 55% and NPV 97% (Table II).

Discussion

Functional imaging using tumour-avid radiopharmaceutical may be useful in those cases in which anatomic imaging alone proves to be inconclusive. Breast cancer, like other carcinomas, shows significant affinity for the radiopharmaceutical ^{99m}Tc-sestamibi. It is a marker of cellular activity and has significant uptake with high tumour/non-tumour ratios (27). Although the precise uptake mechanism of ^{99m}Tc-sestamibi into tumour cells is not clearly understood, the main factors that appear to affect the uptake are tumoural perfusion, accumulation in the lipid component of the cell membrane, passive membrane diffusion and the electrostatic attraction between the positive charge of the ^{99m}Tc-sestamibi molecule and the negative charge of the mitochondria (28). Similarly, there appears to be a relationship between the cellular washout of ^{99m}Tc-sestamibi and the cellular expression of the P-glycoprotein, which is considered to be an MDR agent (29).

Several studies have reported the use of SM as an adjunct to MRx for the diagnosis of breast cancer. Taillefer in a meta-analysis of the literature showed that the sensitivity and specificity of SM ranged between 83% and 95% , and 77% and 96% respectively (30). Khalkhali *et al*. in a multicentre trial enrolled 673 women, and found that the specificity of SMM was higher than for non-palpable lesions (31). Recently, Liberman *et al*. in a meta-analysis of the literature reported data on a total of 5,340 patients assessed for breast

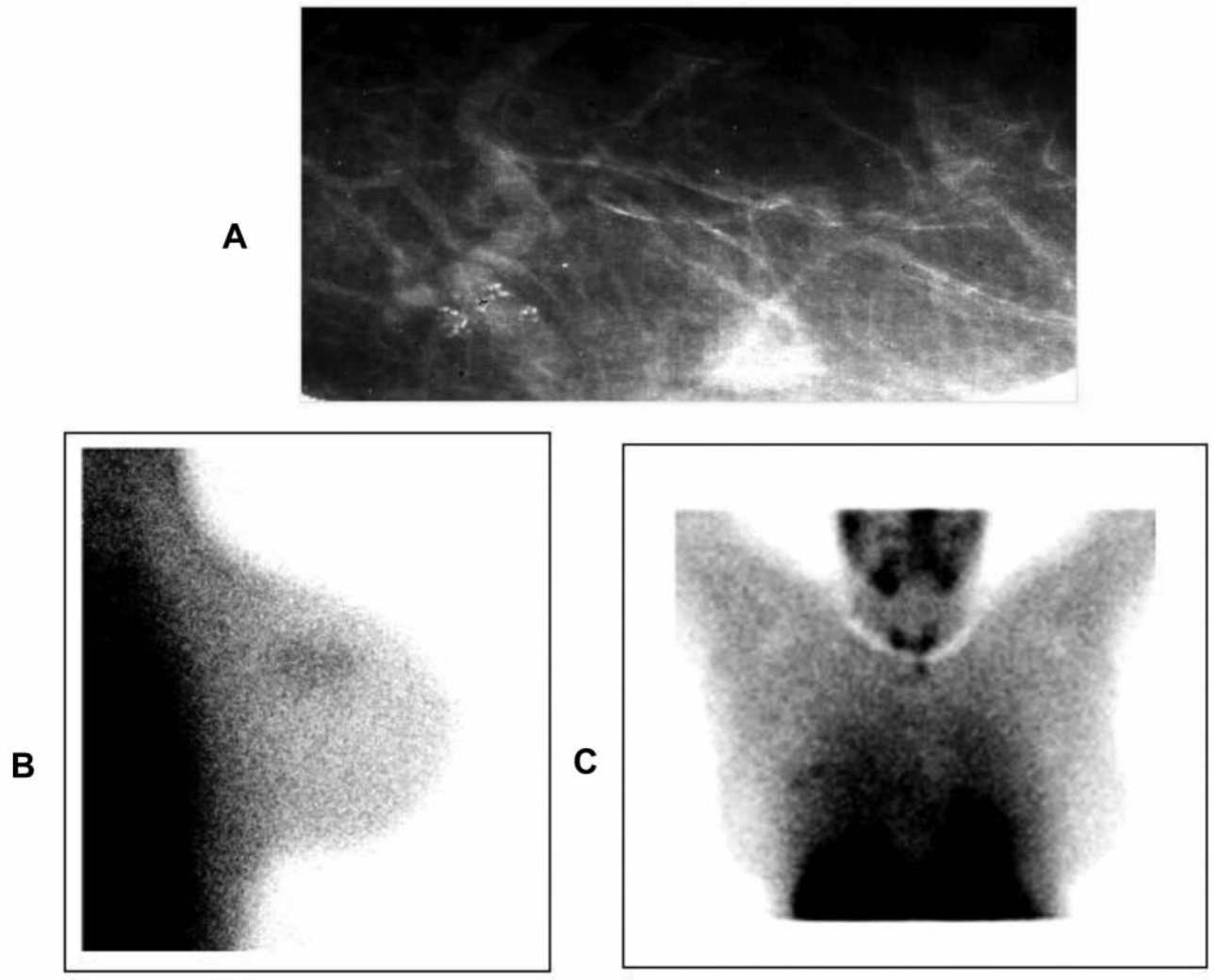

Figure 1. *Example of mammographic intermediate suspicious (group I) isolated clusters of MC (A). The corresponding lateral view ^{99m}Tc-sestamibi scintimammography (B) shows an area of pathological uptake in the upper quadrant of the right breast, and (C) the anterior view shows two areas of significant pathological uptake (two infiltrant ductal carcinoma, size 0.6 and 0.9 mm).*

cancer with SMM (32). The aggregated summary estimates at these patients gave sensitivity of 85.2% and specificity of 86.6% . For patients without a palpable mass the sensitivity was 66.8% and that for specificity was 86.9% , while in patients with a palpable mass they were 87.8% and 87.5% respectly, showing that SMM may be used effectively as an adjunct to MRx and physical examination in the diagnosis of breast cancer. By this multimodality diagnostic approach, the rates of negative biopsies and breast surgery could be significantly reduced. Patients with equivocal or unremarkable mammograms that have other risk factors including a positive physical examination, family history and previous cancer may also benefit from the additional information provided by SMM. In addition, younger women with dense breasts and women with implants may also benefit from SMM, since the latter technique is not affected by breast density and it is permeable to implants (17, 32).

In the present study the sensitivity of SMM was 78% , more than the value (71%) found by Palmedo *et al*. (31, 33, 34). The FP could be due to the focal areas of radiopharmaceutical uptake in fibroadenomas and areas of fibrocystic change with high mitotic activity or local inflammation (35); the FN were possibly due to carcinoma *in situ* (since their endo-ductal growth causes a low uptake of sestamibi and the size and biological patterns vary greatly) and to clusters of MC in a small field (<0.7 mm), which are a difficult diagnostic problem to solve with MRx (33).

Among the 32 patients with breast cancer, 14 were infiltrative ductal carcinoma and 12 were DCIS. SMM was resulted positive in 10 out of the 14 cases (4 negative were <1

cm in size) and in 3 out of the 12 respectively. This finding did not seem to be associated with grading, but with lesion size (35). To our knowledge, there are no studies concerning the sensitivity of SMM in diagnosing DCIS. It is generally accepted that the sensitivity of SMM for the detection of breast cancer lesions less than 1 cm in size is reduced compared with the sensitivity in respect of larger lesion (33). In one patient SMM detected two contiguous neoplastic foci (0.6 and 0.9 cm) which appeared benign on MRx (Figure 1).

Lobular carcinoma is a diagnostic challenge for MRx and for conventional assessment (36). Indeed, in the present series, lobular carcinoma was present in four patients (12.5% of the total carcinomas). It is worth noting that SMM gave true positives in the detection of 2/2 infiltrative lobular carcinoma (size 0.8 and 0.5 cm) and in the detection of 2/2 lobular carcinoma *in situ*, lesions which often lack clinical and mammographic signs (Figure 2). In a series of 46 patients, Leidenius *et al*. found that SMM was positive in 3/6 lobular carcinomas (sensitivity of 50%) (37) while SMM was positive in 3/3 lobular carcinoma of Prats *et al*. (38), in 7/9 cases of Buscombe *et al*. (39) and in 18/21 cases of Mathieu *et al*. (40) (sensitivity of 86%). Therefore, SM can accurately detect lobular carcinoma and may play an important role in the diagnosis of this type of cancer if the high incidence of multifocality and bilaterality in this group of lesions is considered.

The present data also showed that considering only grade 1 as non-malignant, the NPV of SMM and MRx combined imaging was 98%. Considering grade 1 and 2 as non-malignant, the NPV of SMM and MRx combined imaging was 97% and NPV of MRx was 92%. The results of the current study strongly support the implementation of SMM in current practice, in particular the use of SMM as an adjunct to MRx and physical examination would probably reduce the number of unnecessary excisional biopsies in patients with intermediate suspicious mammograms (BI-RADS 2-3).

Conclusion

SMM shows an acceptable degree of certainty for diagnosis and could to be used as a routine second-line test in the investigation of breast cancer and in the pre-operative work-up of patients with breast lesions. Furthermore, the high NPV of this technique makes it especially valuable in reducing the number of negative breast biopsies or unnecessary surgical interventions. Therefore, the current study findings further support the implementation of SMM in the diagnostic evaluation of breast cancer.

Acknowledgements

This work is dedicated to Dr. C.R. Bellina, member of the Nuclear Medicine staff of the University of Pisa (who unfortunately died nine years ago), for his invaluable help in design of the study.

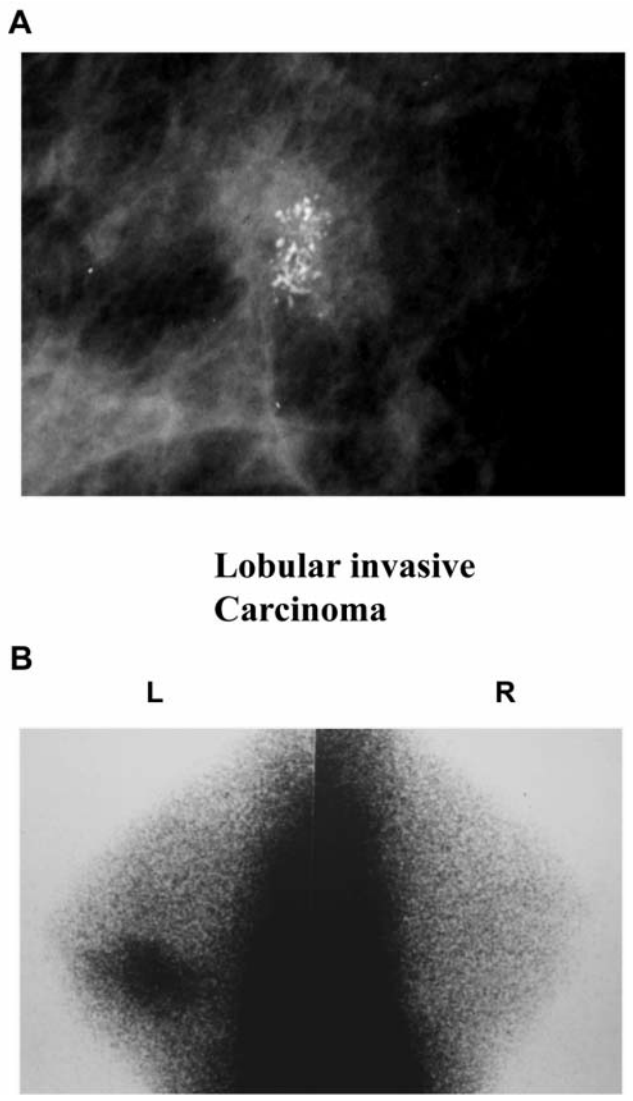

Figure 2. *Example of mammographic high suspicious (group H) isolated clusters of MC (A). The corresponding ^{99m}Tc-sestamibi scintimammography (B) shows a focal area of malignant uptake (lobular invasive carcinoma).*

References

1 Lacey JV Jr, Devesa SS and Brinton LA: Recent trends in breast cancer incidence and mortality. Environ Mol Mutagen *39(2-3)*: 82-88, 2002.

2 Decarli A and La vecchia C: Cancer mortality in Italy, 1991. Tumori *80(6)*: 405-415, 1994.

3 Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B and Rutqvist LE: Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet *359*: 909-919, 2002.

4 Sickles EA: Mammographic features of 300 consecutive non-palpable breast cancer. AJR *146*: 661-663, 1986.

5 Basset LW, Liu TH, Giuliano AE and Gold RH: The prevalence of carcinoma in palpable *vs*. impalpable, mammographically detected lesions. AJR 157: 21-24, 1991.
6 Stomper PC, Davis SP, Weidner N and Meyer JE: Clinically occult, noncalcified breast cancer: serial radiologic-pathologic correlation in 27 cases. Radiology *169*: 621-626, 1988.
7 Rogers JV and Powell RW: Mammographic indications for biopsy of clinically normal breasts: correlation with pathologic findings in 72 cases. AJR *115*: 794-800, 1972.
8 Elmore J G, Wells C K, Lee C H, Howard D H and Feinstein A: Variability in radiologists' interpretations of mammograms. N Engl J Med *331*: 1493-1499, 1994.
9 Kopans D B: The positive predictive value of mammography. Am J Radiol *158*: 521-526, 1992.
10 Bird RE, Wallace TW and Yankaskas BC: Analysis of cancers misses at screening mammography. Radiology *184*: 613-617, 1994.
11 Kerlikowske K, Grady D, Barclay J, Sickles EA and Ernster V: Effect of age, breast density, and family history on sensitivity of first screening mammography. JAMA *276*: 33-38, 1996.
12 Flobbe K, Nelemans PJ, Kessels AG, Beets GL, von Meyenfeldt MF and van Engelshoven JM: The role of ultrasonography as an adjunct to mammography in the detection of breast cancer: a systematic review. Eur J Cancer *38*: 1044-1050, 2002.
13 Tiling R, Khalkhali I, Sommeret H, *et al*: Role of technetium-99m sestamibi scintimammography and contrast-enhanced magnetic resonance imaging for the evaluation of indeterminate mammograms. Eur J Nucl Med 24: 1221-1229, 1997.
14 Bagni B, Franceschetto A, Casolo A *et al*: Scintimammography with ^{99m}Tc-MIBI and magnetic resonance imaging in the evaluation of breast cancer. Eur J Nucl Med Mol Imaging *30*: 1383-1388, 2003.
15 Homer MJ: Imaging features and management of characteristically benign and probably benign lesions. Radiol Clin North Am *25*: 939-951, 1987.
16 Kopans DB: Breast Imaging. Philadelphia: Lippincott pp. 134-135, 1983.
17 Khalkhali I, Baum JK, Villanueva-Meyer *et al*: ^{99m}Tc Sestamibi breast imaging for the examination of patients with dense and fatty breasts: multicenter study. Radiology *222*: 149-155, 2002.
18 Mubashar M, Harrington KJ, Chaudhary KS *et al*: ^{99m}Tc-sestamibi imaging in the assessment of toremifene as a modulator of multidrug resistance in patients with breast cancer. J Nucl Med *43*: 519-525, 2002.
19 Palmedo H: What can we expect from MDR breast cancer imaging with sestamibi? J Nucl Med *43*: 526-530, 2002.
20 Khalkhali I, Cutrone JA, Mena IG, *et al*: Scintimammography: the complementary role of Tc-99m sestamibi prone breast imaging for the diagnosis of breast carcinoma. Radiology *196*: 421-426, 1995.
21 Bombardieri E, Crippa F, Maffioli L and Greco M: Nuclear medicine techniques for the study of breast cancer. Eur J Nucl Med *24*: 809-824, 1997.
22 Hussain R, Buscombe JR: A meta-analysis of scintimammography: an evidence-based approach to its clinical utility. Nucl Med Commun *27(7)*: 589-594, 2006.
23 Gommans GM, van der Zant FM, van Dongen A *et al*: (99M)Technetium-sestamibi scintimammography in non-palpable breast lesions found on screening X-ray mammography. Eur J Surg Oncol *33(1)*: 23-27, 2007.
24 Monsees BS: Evaluation of breast microcalcifications. Radiol Clin North Am *33*: 1109-1119, 1995.
25 American College of Radiology: Breast Imaging Reporting and Data System (BIRADS) 3rd ed. Reston VA. American College of Radiology, 1998.
26 Hanley JA and Mc Neil BJ: A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology *148*: 839-843, 1983.
27 Khalkhali I, Mena I, Jouanne E *et al*: Prone scintimammography in patients with suspicion of carcinoma of the breast. J Am Coll Surg *178*: 491-497, 1994.
28 Pauwels E K J, McCready V R, Stoot JHMB and van Deurzen DFP: The mechanism of accumulation of tumour-localising radiopharmaceuticals. Eur J Nucl Med *25*: 277-305, 1998.
29 Picwnica-Worms D, Chiu ML, Budding M, Kronague JF, Kramer RA and Croop LM: Functional imaging of multidrug-resistant P-glycoprotein with an organotechnetium complex. Cancer Res *53*: 977-984, 1993.
30 Taillefer R: The role of ^{99m}Tc-sestamibi and other conventional radiopharmaceuticals in breast cancer diagnosis. Semin Nucl Med *29(1)*: 16-40, 1999.
31 Khalkhali I, Villanueva-Meyer J, Edell SL *et al*: Diagnostic accuracy of ^{99m}Tc-sestamibi breast imaging: multicenter trial results. J Nucl Med *41(12)*: 1973-1979, 2000.
32 Liberman M, Sampalis F, Mulder DS and Sampalis JS: Breast cancer diagnosis by scintimammography: a meta-analysis and review of the literature. Breast Cancer *89*: 115-126, 2003.
33 Howarth D, Sillar R, Clark D and Lan L: Technetium-99m sestamibi scintimammography: the influence of histopathological characteristics, lesion size and the presence of carcinoma *in situ* in the detection of breast carcinoma. Eur J Nucl Med *26(11)*: 1475-1481, 1999.
34 Palmedo H, Biersack HJ, Lastoria S *et al*: Scintimammography with technetium-99m methoxyisobutylisonitrile: results of a prospective European multicentre trial. Eur J Nucl Med 25: 375-385, 1998.
35 Scopinaro F, Schillaci O, Ussof W *et al*: A three-center study on the diagnostic accuracy of ^{99m}Tc-MIBI scintimammography. Anticancer Res 17(3B): 1631-1634, 1997.
36 Berg WA, Gutierrez L, NessAiver MS *et al*: Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology *233*: 830-849, 2004.
37 Leidenius MH, Leppanen EA, Tykka HT and von Smitten KA: The role of Tc99m-sestamibi scintimammography in combination with the triple assessment of primary breast cancer. Eur J Surg Oncol *28*: 108-112, 2002.
38 Prats E, Aisa F, Abos MD *et al*: Mammography and ^{99m}Tc-MIBI scintimammography in suspected breast cancer. J Nucl Med *40*: 296-301, 1999.
39 Buscombe JR, Cwikla JB, Holloway B and Hilson AJ: Prediction of the usefulness of combined mammography and scintimammography in suspected primary breast cancer using ROC curves. J Nucl Med *42*: 3-8, 2001.
40 Mathieu I, Mazy S, Willemart B *et al*: Inconclusive triple diagnosis in breast cancer imaging: is there a place for scintimammography? J Nucl Med *46*: 1574-1581, 2005.

Received April 25, 2009
Revised July 3, 2009
Accepted July 15, 2009