Original article

Scintimammography with 99mTc-MIBI and magnetic resonance imaging in the evaluation of breast cancer

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Received: 2 March 2003 / Accepted: 18 June 2003 / Published online: 9 August 2003

Abstract. This study was performed to evaluate the sensitivity and specificity of technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI) scintimammography (SMM) and contrast-enhanced magnetic resonance imaging (MRI) in patients with breast masses, using the histological findings as the gold standard. Forty-five consecutive patients with a breast lesion, detected by self-examination, physical examination or screening mammography, underwent SMM and MRI. In 38 cases (84.5%), the histopathology was malignant; the breast cancers ranged from 3 to 100 mm in diameter (mean 22 mm). In the overall patient group, MRI showed a slightly higher sensitivity than SMM (92% vs 84%), but SMM showed a better specificity: 71% vs 42%. The accuracy was 82% and 84% for SMM and MRI respectively. To evaluate the influence of lesion size on the results, patients with lesions ≤20 mm and ≤15 mm were examined. In patients with lesions ≤20 mm, the sensitivity of SMM and MRI decreased to 64% and 82% respectively, while SMM again displayed considerably better specificity: 83% vs 50% for MRI. The accuracy of SMM and MRI was 64% and 82% respectively. In patients with lesions ≤15 mm, SMM again showed better specificity (75% vs 50%), while MRI displayed better sensitivity and accuracy (sensitivity, 81% vs 62%; accuracy, 75% vs 65%). In this study the specificity of SMM in patients with breast lesions was thus superior to that of MRI. The combination of SMM and MRI may be used in those patients with equivocal findings at mammography and ultrasound to reduce the number of unnecessary surgical biopsies.

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Keywords: Breast cancer – Scintimammography – ^{99m}Tc-MIBI – Magnetic resonance imaging

Eur J Nucl Med Mol Imaging (2003) 30:1383–1388
DOI 10.1007/s00259-003-1262-6

Introduction

Several imaging techniques are used to evaluate breast cancer in women. Mammography is the most frequently used screening method, and a decrease in mortality of 33% has been observed for breast cancer in women who have undergone mammographic screening [1]. Although mammography is capable of detecting cancer in its early stages, and has a reasonable cost, it displays low sensitivity and specificity in patients with dense breasts, those who have previously undergone surgery and those with breast implants [2, 3, 4].

Since a great number of benign lesions are found in patients with suspicious mammographic findings, complementary methods to increase diagnostic specificity have been proposed. Due to the high spatial resolution of the most recent ultrasound (US) transducers (7.5–13 MHz) and the use of echo-enhanced colour power Doppler US, suspicious areas at mammography can be more accurately evaluated on US, reducing the number of false positives [4, 5, 6, 7, 8, 9, 10]. However, variable values for sensitivity and specificity are still reported in the literature, depending on the anatomical position and dimensions of the suspicious lesion, on the experience of the physician and on the quality of the US device [11].

Magnetic resonance imaging (MRI) has been demonstrated to further improve the sensitivity of mammography and US; in fact it gives excellent images of breast structure and can detect lesions of a few millimetres [12]. Even though the specificity of MRI is relatively

low for identifying primary breast cancer, some improvement has been achieved by the use of contrast media (gadolinium-DTPA) [13, 14]. MRI has also been demonstrated to be useful in the evaluation of axillary lymph node metastasis [14, 15].

Breast cancer, like other cancers, shows significant affinity for the radiopharmaceutical technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI), with high tumour/non-tumour ratios [16]. ^{99m}Tc-MIBI is a lipophilic agent and furthermore is a substrate of P-glycoprotein (Pgp), which is considered one of the multi-drug resistance (MDR) agents [17]. Scintimammography (SMM) has been demonstrated to be useful in the diagnosis of primary breast tumours in patients with dense breasts [18], and its value has especially been emphasised in the evaluation of therapy response [19, 20]. 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, 20, 21]. Our study goal was to evaluate the sensitivity and specificity of SMM and MRI, using the histological findings as the gold standard.

Materials and methods

Patient population. We examined 45 consecutive patients (age range 32–84 years, mean 51 years) with a suspicious breast lesion detected by self-examination, physical examination or screening mammography. Afterwards all the patients underwent US. Mammography and US were performed according to standard procedures. The patients underwent MRI and SMM prior to fine-needle aspiration biopsy (FNAB). The patients with breast cancer at FNAB underwent surgery, and malignancies were classified by the pathologist according to WHO nomenclature and staged as follows: pT1is (carcinoma in situ), pT1a (1–5 mm in largest diameter), pT1b (6–10 mm), pT1c (11–20 mm), pT2 (21–50 mm) or pT3 (>51 mm without involvement of the chest wall or the skin). The size of benign lesions was determined by US.

Magnetic resonance imaging. MRI was obtained with a General Electric device at 1.5 Tesla using a dedicated breast coil, enabling the simultaneous imaging of both breasts with the patient in the prone position. The data acquisition was performed directly before and after i.v. injection of gadolinium-DTPA using appropriate 3D gradient and spin echo sequences with fat tissue subtraction; 20–50 continuous transverse slices were obtained. The qualitative and quantitative analysis of gadolinium-DTPA enhancement was performed using regions of interest and flow curves. Lesions with marked, rapid enhancement and the washout sign and those with inhomogeneous or rim enhancement and irregular outlines were classified as malignant or probably malignant and interpreted as positive. MRI images were considered true positive when the malignant or probably malignant lesion was confirmed by histopathology. MRI was interpreted as true negative when the images and histopathology excluded breast cancer.

Scintimammography. SMM was performed with a Picker Axis dual-headed gamma camera, equipped with a parallel-hole, low-energy, high-resolution collimator. The test was performed using the standard technique: 740 MBq ^{99m}Tc-MIBI was injected i.v. in the opposite arm to the breast with the suspected lesion. In all patients, planar imaging was performed using a 256×256 matrix with an acquisition time of 10–15 min, in both lateral and anterior views, at 20–30 min after injection. Patients were examined in the prone position using an imaging table with breast "cut-outs". To avoid interference from the opposite breast, a layer of lead was used as a shield. The SMM images were classified based on visual interpretation. Focal tracer accumulation in the breast was interpreted as suspicious or probably malignant and such scintigrams were classified as positive. The suspicious or probably malignant images were considered true positive when confirmed by histopathology. The SMM was interpreted as true negative when the images and histopathology excluded breast cancer.

Image interpretation. The MR and SMM images were interpreted separately by three expert radiologists and three expert nuclear medicine physicians who worked independently. They were blinded to the results of MRI or SMM.

Results

The lesion size in the entire patient group ranged from 3 to 100 mm, with a mean of 22 mm. In 7 of 45 cases (15.5%), the histopathology was benign, revealing hyperplasia (two patients), sclerosing adenosis (two patients), granuloma (one patient), fibroadenoma (one pa-

Table 1. Results of SSM and MRI in patients with benign disease

Patients	Age (years)	Histopathology	Size (mm)	SSM				MRI			
				TP	TN	FP	FN	TP	TN	FP	FN
1	33	Granuloma	15		+				+		
2	48	Hyperplasia	13		+					+	
3	46	Fibroadenoma	10		+				+		
4	55	Hyperplasia	15		+					+	
5	84	Breast involution	16			+			+		
6	70	SC-AD	25			+				+	
7	72	SC-AD	10		+					+	
Overall					5	2			3	4	

SC-AD, Sclerosing adenosis; TP, true positive; TN, true negative; FP, false positive; FN, false negative

Table 2. Results of SSM and MRI in patients with breast cancer

Patients	Age (years)	Histopathology	Staging (pT)	SSM				MRI			
				TP	TN	FP	FN	TP	TN	FP	FN
1	37	DC	pT2	+				+			
2	39	DC	pT3	+				+			
3	49	DC	pT3	+				+			
4	65	N	pT1a				+				+
5	60	DC	pT2	+				+			
6	56	DC	pT2	+				+			
7	47	DC	pT2	+				+			
8	45	DC	pT2	+				+			
9	54	DC	pTis				+	+			
10	50	DC	pT2	+				+			
11	56	DC	pT2	+				+			
12	45	DC	pT2	+				+			
13	67	DC	pT3	+				+			
14	43	LC	pT2	+				+			
15	56	LC	pT1c	+				+			
16	66	DC	pT2	+				+			
17	38	DC	pT1c	+				+			
18	58	DC	pT1b				+				+
19	48	DC	pT1c	+				+			
20	65	LC	pT1a	+				+			
21	43	DC	pT1c	+				+			
22	70	DC	pT1c	+				+			
23	40	DC	pT2	+				+			
24	37	DC	pT2	+				+			
25	37	DC	pTis				+				+
26	36	DC	pT2	+				+			
27	59	DC	pT1c	+				+			
28	64	DC	pT1c	+				+			
29	43	DC	pT2	+				+			
30	46	LC	pT1b				+	+			
31	45	DC	pT2	+				+			
32	48	DC	pT1b				+	+			
33	47	DC	pT2	+				+			
34	61	DC	pT2	+				+			
35	65	DC	pT1c	+				+			
36	41	DC	pT1c	+				+			
37	47	DC	pT1c	+				+			
38	38	DC	pT2	+				+			
Overall				32			6	35			3

TP, True positive; TN, true negative; FP, false positive; FN, false negative; DC, ductal carcinoma; LC, lobular carcinoma; N, neuroendocrine carcinoma

tient) or breast involution (one patient) (Table 1). The size of these lesions ranged from 10 to 25 mm (mean 22 mm).

The malignant lesions (84.5% of patients) had a diameter of 3–100 mm (mean 23 mm) and included 33 ductal carcinomas, four lobular carcinomas and one case of neuroendocrine carcinoma (Table 2). Of these lesions, 5.3% were classified as pT1is, 5.3% as pT1a, 7.9% as pT1b, 26.3% as pT1c, 47.3% as pT2 and 7.9% as pT3.

SMM was true positive in 32 lesions and false negative in six (two ductal carcinomas in situ and four carcinomas up to 10 mm: two ductal carcinomas, one lobular carcinoma and one neuroendocrine carcinoma). MRI appeared true positive in 35 breast cancer and false negative in three (one ductal carcinoma in situ and two carcinomas up to 8 mm: a neuroendocrine carcinoma and a ductal carcinoma).

SMM was false positive in a patient with breast involution and in a case of sclerosing adenosis. MRI appeared false positive in four patients: two with hyperplasia and two with sclerosing adenosis.

The value of SMM and MRI as diagnostic tests is shown in Table 3. In our population of patients, MRI

Table 3. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of SSM and MRI in the overall patient group

	Sensitivity	Specificity	PPV	NPV	Accuracy
SSM	84	71	94	45	82
MRI	92	42	89	50	84

PPV, Positive predictive value; NPV, negative predictive value

Table 4. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy in lesions ≤20 mm and ≤15 mm

	Sensitivity		Specificity		PPV		NPV		Accuracy	
Size (mm)	≤20	≤15	≤20	≤15	≤20	≤15	≤20	≤15	≤20	≤15
SSM	64	62	83	75	91	90	45	33	64	65
MRI	82	81	50	50	82	86	50	40	82	75

PPV, Positive predictive value; NPV, negative predictive value

showed a slightly better sensitivity than SMM (92% vs 84%) whereas SMM displayed a clearly higher specificity: 71% vs 42%. The positive predictive value was similar for SMM and MRI (94% vs 89% respectively), as was the negative predictive value (45% vs 50% respectively). We found an accuracy of 82% and 84% for SMM and MRI respectively.

To evaluate the influence of lesion size on our results, we examined patients with lesions ≤20 mm and with lesions ≤15 mm (Table 4). In the subgroup of patients with lesions ≤20 mm, the sensitivity of SMM and MRI decreased to 64% and 82% respectively, while SMM again displayed considerably better specificity: 83% vs 50% for MRI. The positive and negative predictive values of SMM and MRI remained practically unchanged compared with the overall patient group. The accuracy of SMM and MRI was 64% and 82% respectively.

In the subgroup of patients with lesions ≤15 mm, SMM continued to show better specificity (75% vs 50%), while MRI again displayed higher sensitivity and accuracy (sensitivity, 81% vs 62%; accuracy, 75% vs 65%). The positive and negative predictive values were 90% and 33% for SMM, and 86% and 40% for MRI respectively.

Discussion

Mammographic screening programmes have proved useful for the early detection of breast cancer but, as already mentioned, the sensitivity and specificity of mammography are reduced in dense glandular breasts, in patients who have previously undergone surgery and in those with breast implants. Consequently a large number of excisional biopsies are performed in such patients [2, 3, 4]. To improve the diagnostic outcome of mammography, US and echo-enhanced colour Doppler have been employed as a complementary tool and indeed reduce the number of false positives. For instance, US has proved useful in patients with dense breasts, breasts with architectural distortion, or breasts with suspicious spiculate lesions, as well as in differentiating cysts from solid masses [4].

Among the additional techniques used to improve the sensitivity and the specificity in identifying breast cancer, MRI and SMM have yielded good results. MRI has shown high sensitivity in the detection of breast cancer (a few millimetres in thickness) thanks to the development of high-resolution surface coils, fast imaging sequences, fat suppression and the use of gadolinium-DTPA. However, MRI has a low specificity, since some carcinomas behave atypically, enhancing only slightly and gradually (lobular carcinoma) or being well defined (papillary and mucinous carcinomas). Ductal carcinoma and ductal carcinoma in situ have a variable appearance on MRI, depending on the neoangiogenesis, and it is not possible to differentiate inflammatory carcinoma from other benign causes of inflammation [22]. In addition, some benign lesions display enhancement after gadolinium-DTPA, e.g. fibroadenomas [22].

For about a decade, SMM has been a promising technique for the imaging of breast cancer, though unfortunately its specificity and sensitivity have depended on lesion size (with low sensitivity and high specificity in small lesions). Various published studies have compared SMM and MRI. Palmedo et al. [23], in a group of 56 patients, reported an overall sensitivity and specificity of 93% and 21% respectively for MRI, while the sensitivity and specificity of SMM were 85% and 66% respectively. Tiling et al. [24] performed SMM and MRI in 82 patients with indeterminate mammograms. When indeterminate findings were included in the group of positive diagnoses, the sensitivity and specificity of SMM were 79% and 70%, and those of MRI 84% and 49% respectively. When indeterminate results were considered negative, SMM showed a sensitivity and specificity of 62% and 83%, while the sensitivity and specificity of MRI were 56% and 79%, respectively. In a group of 49 patients with equivocal mammographic findings, Imbriaco et al. [25] reported a sensitivity of 80% and a specificity

of 88% for SMM, as compared with figures of 96% and 75%, respectively, for MRI.

In our patients, in accordance with previous studies, SMM showed a higher overall specificity in comparison with MRI (71% vs 42%). This was probably due to the presence of benign lesions which enhanced after gadolinium-DTPA, a likely expression of a high degree of neovascularity; by contrast, ^{99m}Tc-MIBI uptake depends on the metabolic activity of the cells (mitochondrial concentration in the cells).

As shown previously, MRI displayed a higher sensitivity than SMM (92% vs 84%). In particular, the two ductal carcinomas in situ and the neuroendocrine carcinoma were below the intrinsic spatial resolution of the gamma camera detector. For the smaller lesions (≤15 mm), the sensitivity and specificity of SMM were 62% and 75%, as compared with 75% and 50% for MRI. These values are slightly lower than those reported by Imbriaco et al. [25], who found the sensitivity and specificity of SMM to be 77% and 88% in patients with lesions ≤15 mm, as compared with 100% and 75%, respectively, for MRI. Our data were similar to those reported by Palmedo et al. [23], who found that for non-palpable lesions, SMM showed lower sensitivity than MRI (60% vs 100%) (two of four missed carcinomas were <8 mm) but higher specificity (75% vs 50%).

The three lesions larger than 15 mm that were nevertheless false negative on SMM (two ductal carcinomas and one lobular carcinoma) were sited at the inner quadrants of the breast (where scatter radiation from the liver and the myocardium may have an effect) or near the chest wall. Improvement in the sensitivity of SMM for the detection of such lesions will occur with the development of a high-resolution, small-field-of-view breast-specific gamma camera, as demonstrated by the preliminary results using a prototype gamma camera [26].

We found the overall diagnostic accuracy of SMM and MRI to be 82% and 84% respectively; these are similar to the values reported by Imbriaco et al. [25]. The accuracy was lower for smaller lesions, and this was more evident for SMM (65%) than for MRI (75%). The overall positive predictive value was also similar between SMM and MRI (94% and 89%, respectively), and lesion size did not significantly affect this value (in lesions ≤15 mm the positive predictive value was 90% for SMM and 86% for MRI).

We conclude that in this study the specificity of SMM in patients with breast lesions was superior to that of MRI. Unfortunately, the sensitivity of SMM is still unsatisfactory owing to the intrinsic spatial resolution of gamma camera detector and high variability in the uptake of ^{99m}Tc-MIBI. Given the simplicity of the procedure and the lower costs, SMM may be preferred to MRI in the evaluation of equivocal breast lesions larger than 10 mm and of lesions in dense glandular breasts. MRI is to be preferred in clinical practice if high spatial resolution is needed; moreover, MRI can be recommended in the local staging of breast cancer for the planning of surgery. On the basis of the obtained results, however, it is doubtful whether these expensive and time-consuming imaging techniques can be applied in daily routine in patients in whom biopsy allows easy and inexpensive evaluation.

Even though the low negative predictive value of SMM and MRI leads surgeons to continue to perform biopsies of equivocal breast lesions, thereby minimising the number of missed carcinomas, the combination of SMM and MRI may be proposed as a second-line approach in those patients in whom mammography and US are non-diagnostic or difficult to interpret, e.g. those with very dense breasts, mammographically occult tumours, suspected multifocality or multicentricity, or suspected chest wall involvement. In these situations, SMM and MRI can help by guiding the biopsy to assure that the samples are taken from the correct site.

Acknowledgements. We wish to thank Professor Ignac Fogelman for his review of the manuscript.

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