Scintimammography with technetium-99m methoxyisobutylisonitrile: results of a prospective European multicentre trial

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Abstract. The aim of the trial was to determine the diagnostic accuracy of scintimmammography with technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI) in the detection of primary breast cancer and to verify its clinical usefulness. A total of 246 patients with a suspicious breast mass or positive mammogram were included in this prospective European multicentre trial. At 5 min and 60 min (optional) p.i. two lateral prone images were acquired for 10 min each; 30 min p.i. one anterior image was acquired for 10 min. There were 253 lesions (195 palpable and 58 non-palpable), in respect of which histology revealed 165 cancers and 88 benign lesions. Institutional and blinded read results were correlated to core laboratory histopathology results obtained during excisional biopsy. Diagnostic accuracy for the detection of breast cancer was calculated per lesion. The overall sensitivity and specificity of blinded read scintimammography were 71% and 69%, respectively. For palpable lesions, the sensitivity of blinded read and institutional read scintimammography was 83% and 91%, respectively. Sensitivity was not dependent on the density of the breast tissue. Invasive ductal and invasive lobular cancers showed similar sensitivity. The sensitivity and specificity of mammography were 91% and 42%, respectively, and did not depend on the tumour size. In 60% of false-negative mammograms, ^{99m}Tc-MIBI was able to diagnose malignancy (true-positive). High-quality imaging with ^{99m}Tc-MIBI has a high diagnostic accuracy for the detection of primary breast cancer. Used as a complementary method, scintimammography with ^{99m}Tc-MIBI can help to diagnose breast cancer at an earlier stage in patients with dense breasts.

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Introduction

Breast cancer accounts for the highest proportion of cancer-related deaths among women [1, 2]. Over recent decades, it has been shown that the incidence of this malignant disease has increased and is still increasing [3]; this is especially true in younger age groups. It seems possible that mortality might be reduced by therapeutic approaches as well as by efficient diagnostic methods. A significant benefit for the survival of breast cancer patients who are older than 50 years has been demonstrated using mammography as a screening method [4–6]. However, for patients younger than 50 years, a significant reduction of mortality could not be proven. Yet, it is in this patient group that major difficulties and frequent delays in the diagnosis of breast malignancies are often experienced [7]. The main reason for the diagnostic problems is dense or hyperproliferative glandular breast tissue which is typical for the premenopausal woman. Therefore, lumpy and mammographically dense breasts are frequent in this age group, and the sensitivity of palpation and mammography is significantly decreased [8].

Studies have shown that tumour size correlates with the frequency of axillary and distant metastases [9, 10]. For a cancer size of 1.5 cm, the rate of axillary disease has been calculated to be about 30%, whereas cancers with a size of 3 cm showed an increased rate of 48% [9]. Furthermore, 8 years after primary therapy of breast cancer, distant metastases occur with a probability of about 20% in the case of cancers of between 1 and 2.5 cm but with a probability of 40% when cancers are between 3.5 and 4 cm in size [11]. It has been shown that distant metastases correlate with mortality [12]. Thus, it is clear that the earlier tumours are detected, the better will be the survival rate of patients.

Recently, encouraging results have been obtained by means of nuclear breast imaging using different radiopharmaceuticals such as fluorine-18 fluordeoxyglucose, technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI), thallium-201 chloride, ^{99m}Tc tetrofosmin, ^{99m}Tc methylene diphosphonate, radiolabeled antibodies and iodine-123 oestradiol [13–40]. A number of studies have demonstrated high diagnostic accuracy of ^{99m}Tc-MIBI for the detection of breast cancer [22–32]. Therefore, this multicentre trial was set up to confirm the value of scintimammography using ^{99m}Tc-MIBI.

Material and methods

Study design

The study has been a prospective open-label multicentre trial to determine the diagnostic accuracy of ^{99m}Tc-MIBI scintigraphy for the identification of malignant breast lesions in two groups of patients (Fig. 1): (1) patients with mammographically detected, non-palpable breast abnormalities; (2) patients with breast abnormalities detected by palpation. Further objectives have been: (3) to compare the diagnostic accuracy of sestamibi imaging with that of mammography, (4) to establish whether the diagnostic performance of the imaging technique can be improved by modifying the method of interpretation and (5) to acertain whether use of the two techniques, scintigraphy and mammography, in conjunction provides a better predictive capability than either technique used alone.

Axillary tracer uptake had been documented on the case report forms. Since only a few patients showed axillary uptake of ^{99m}Tc-MIBI, these data are not presented in this paper. It was not the aim of the trial to evaluate ^{99m}Tc-MIBI for the detection of lymph node metastases.

Subjects who have undergone mammography and are positive for (a) at least one palpable breast abnormality detected by physical examination

OR

(b) at least one breast abnormality detected by mammography within the previous 3 weeks and are scheduled to undergo excisional biopsy are ENROLLED

⇓

Bolus injection of ^{99m}Tc-MIBI administered within 3 weeks of mammography and physical examination

⇓

5 min p.i. start of 10-min lateral image acquisitions, followed by anterior image

⇓

10-min lateral acquisition repeated 1 h p.i. (optional)

⇓

EXCISIONAL BIOPSY performed within 6 weeks following ^{99m}Tc-MIBI study

Fig. 1. Flow chart of the prospective trial with ^{99m}Tc-MIBI.

Patients

Inclusion and exclusion criteria for entry into the trial are listed in Table 1. Data were received for 246 patients (Table 2), from a total of nine sites (Italy 71 patients, France 64 patients, Spain 42 patients, Germany 37 patients, Belgium including two centres, 21 patients, Great Britain 7 patients, Switzerland 4 patients). The data of centres recruiting less than 20 patients were pooled. Since no

Table 1. Inclusion and exclusion criteria for entry into the trial

INCLUSION CRITERIA
1. Female older than 21 years, non-pregnant, non-lactating
2a. Suspicious lesion of the breast detected by physical examination and scheduled for mammography within the next 3 weeks
2b. Suspicious lesion detected by mammography in the previous 3 weeks
3. Recommendation for excisional biopsy, after mammography, but within 6 weeks following ^{99m}Tc-MIBI study
4. Informed consent.
EXCLUSION CRITERIA
1. Previous mastectomy (modified) of breast with suspicious lesion
2. Local tumour recurrence
3. Fine-needle biopsy within 1 week prior to scintimammography
4. Receipt of an investigational drug within 10 physical half-lives prior to ^{99m} Tc- MIBI

Table 2. Patient population of the trial

Data collection: 246 patients	*Centre*	*Number*
	Italy	71
	France	64
	Spain	42
	Germany	37
	Pooled centres	32
Efficacy population		
Patients:	232 patients, after exclusion of 14 patients	
Lesions:	253 lesions (21 patients with 2 examined lesions	
	195 palpable and 58 non-palpable lesions	
Mean age:	54.5 years	
Mean weight.	64.0 kg	
Post-/peri-/premenopausal:	62%/8%/30%	

excisional biopsy had been performed, 14 patients were excluded from the efficacy population, thus leaving 232 patients in this population. The overall ratio of palpable to mammographically detected lesions was about 3:1. The number of lesions in the "by lesion" efficacy population was 253 (195 lesions detected by palpation and 58 lesions detected by mammography). In 21 cases, patients had two pathological lesions of the breast (ten bilateral cancers).

The mean age and weight for patients with palpable lesions and mammographically detected lesions were 53.4 years and 63.1 kg and 56.4 years and 65.5 kg, respectively (range 21–87 years and 40–159 kg). The majority (95.5%) of patients were Caucasian. A history of pregnancy was indicated for 74% of patients, with age at first pregnancy varying between 15 and 39 years (mean 24.5). In 18% of patients, a family history of breast cancer was present. Oral contraceptive usage and hormone replacement therapy were indicated in 10% and 7%, respectively. Sixty percent of women were postmenopausal. Pre- and perimenopausal status was documented in 30% and 8% of patients, respectively. Surgical biopsy, found to be benign, had been previously conducted in 14% of patients. Mastectomy and lumpectomy of the contralateral breast had been carried out in 4% and 6% of patients.

Scintigraphy

Radiopharmaceutical. The radiolabelling and quality control procedures for the preparation of ^{99m}Tc-MIBI (Dupont Pharma) were carried out according to the manufacturer's instruction. The vial preparation requires reconstitution with sodium ^{99m}Tc pertechnetate followed by heating in a water bath. In order to be used, the radiochemical purity of the radiopharmaceutical had to be greater than or equal to 90%.

Patient preparation and administration. Each patient received an intravenous injection into the arm on the side contralateral to the breast lesion. A "cold" injection with 10 ml saline solution was administered after the injection of ^{99m}Tc-MIBI. The average dose was 20 mCi (range 18–30 mCi). No meal was consumed between injection and imaging; water intake was unrestricted, however. When both breasts had a palpable or mammographically determined abnormality, the injection was given in a dorsalis pedis vein.

The subject was initially examined in the prone position with the arms raised above the head, the shoulders flat against the table, and the head turned to one side. For lateral views, a special table overlay was used to provide maximal separation of breast tissue from the myocardium and the liver. This overlay consisted of a foam cushion with two cut-offs at the lateral side. Then the patient was imaged in the supine position.

Imaging. Planar imaging was started 5 min after the injection of ^{99m}Tc-MIBI. The imaging sequence was as follows: (1) 10-min lateral view 90° acquisition of the breast with the suspected lesion, (2) 10-min lateral view 90° acquisition of the other breast, following repositioning of the subject, (3) 10-min anterior view with the subject positioned supine and her arms raised behind her head. Delayed imaging 1 h post-injection was optional. Planar images were performed with a 256×256 matrix, a 10% window and an energy peak of 140 keV. A low-energy high-resolution collimated gamma camera without zoom was used. The camera was positioned as close as possible to the breast. A minimum number of 500 000 counts (field of view) per 40 cm head standardized had to be acquired. For the first two subjects enrolled in the study at each centre, 50 pixels in the breast were measured to allow comparative quantification.

Mammography

The analysis of mammograms is based on the institutional read. A standard mammographic examination had to be applied to all patients. The mammographer assigned a probability of malignancy (PM) for each lesion detected. If there was more than one lesion in a breast, the PM was taken as the maximum recorded level for that breast. When the probability was not given as a percentage, but descriptively instead, probabilities were assigned according to the following classification:

Description	*Percentage*
Low	20%
Medium/suspicious	50%
High	70%
Very suspicious	80%

If no lesion was detected mammographically in that breast, the PM was assigned as zero. For analysis, PMs were grouped into ordered categories: 0%–24%, 25%–49%, 50%–74% and 75%–100%. For the calculation of sensitivity/specificity statistics, mammography was taken as indicating malignancy if the assessed PM was 50% or greater.

Institutional and blinded read scintigraphy

For each lesion, a maximum of four images were assessed, an initial and a delayed image for both lateral and anterior views. The delayed image was optional. Each set of images was assessed by an institutional reader and a panel of four blinded readers. The institutional reader used both the initial and delayed images if available (but for the delayed image scored only the lateral view). The blinded readers scored the initial and the delayed views separately without knowing that they were from the same patient. For each view, the image was assessed in each of a number of segments [six per breast for the lateral view, four per breast for the anterior view plus the axillary nodes (one score per breast)]. Each segment was assessed using the following scale (Figs. 2 and 3):

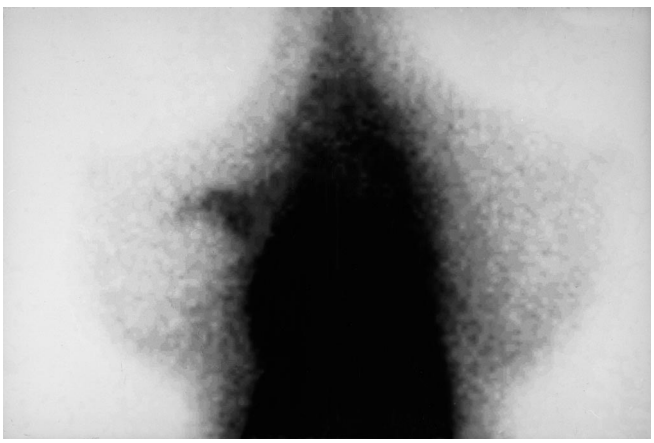

Fig. 2. Lateral scintimammography with ^{99m}Tc-MIBI in a 54-year-old patient with a palpable lesion in the left breast. Focal accumulation is observed in the upper part of the left breast, corresponding to a histopathologically confirmed invasive ductal cancer (diameter 2.0 cm). This scan was scored as 2 by the blinded read and considered as a true-positive scintigram for definition 1

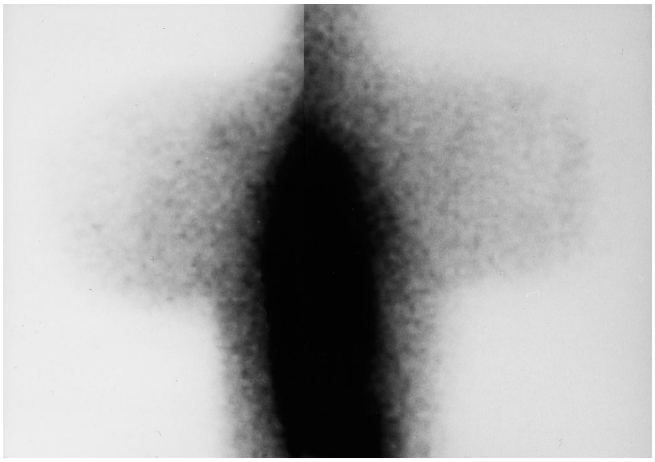

Fig. 3. Lateral scintimammography with ^{99m}Tc-MIBI in a 61-year-old patient with a palpable lesion in the left breast. Slightly increased tracer uptake is observed in the upper part of the left breast. Histopathology revealed an invasive ductal cancer with a maximum diameter of 1.1 cm. This scan was scored as 1 by the blinded read and considered as a true-positive scintigram for definition 2

0: Normal
1: Equivocal
2: Focal uptake – low intensity
3: Focal uptake – medium intensity
4: Focal uptake – high intensity

The blinded read was blinded in the sense that the assessors were ignorant of the centre at which the images were taken, and of any other ancillary medical information about the patient. Each assessor scored the images independently.

For the primary assessment of diagnostic accuracy, any breast with a maximum segment score of 2 or greater was interpreted as a positive result (definition 1). A secondary assessment was also made, in which a positive result was assumed if the maximum score was 1 or greater (definition 2). For the blinded read, the assessment based on the delayed view was made separately from that using the early views, but only the information from the early views was used for making comparisons with other assessment methods.

For the interpretation of the blinded read panel results, a breast was deemed to be positive if at least two of the four assessors scored the breast as such. As only in 3% of the blinded read scintigrams did two readers each score a scan positive and negative, there was no further consensus reading. Data had to be available for at least three of the assessors for this procedure to be applied; otherwise, the diagnosis was regarded as missing.

The blinded read assessors also scored the images for quality; each of the four images (early and delayed, lateral and anterior) was scored separately on a four-point scale: 1, excellent; 2, good; 3, fair; 4, poor. To obtain an overall assessment for each reader, an average value for the four scores was calculated. To obtain an average across readers, the numerical average of 16 observations (four readers by four views) was calculated.

Histopathology

An excisional biopsy was taken in all evaluated patients. This was diagnosed by the institutional pathologist and the diagnosis was later confirmed (in all but three cases) by the core centre pathologist. The measurement of the tumour size was based on the institutional results. Analysis by tumour size was done for the largest dimension given. Where two lesions were excised from the same breast, the size of the larger lesion was used. The core centre diagnosis was taken as indicating malignancy (for the primary analysis) if either of the following description boxes was ticked: (1) type of invasive cancer, (2) ductal carcinoma in situ (DCIS). For a secondary analysis, lobular carcinoma in situ (LCIS) and ductal and/or lobular hyperplasia as indicators for an increased breast cancer risk were also regarded as true-positive results.

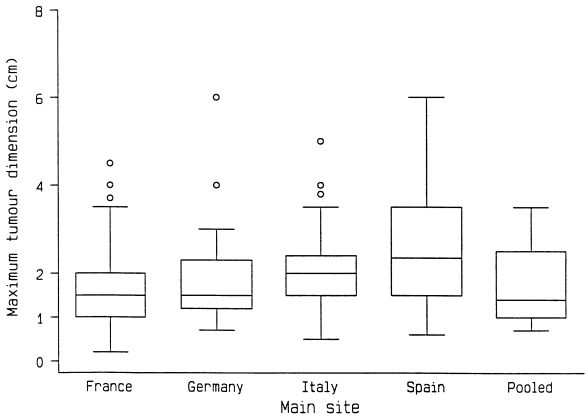

Fig. 4. Tumour size (mean maximum tumour dimension and range of tumour size) according to the site of the participating centre (pooled = all patients of the smaller centres)

Core centre histopathology diagnosed 109 invasive ductal and 29 invasive lobular cancers, 11 DCIS, two metastases, six tubular carcinoma, two medullary carcinomas and two papillary carcinomas. Furthermore, one mucinous cancer, one case of Paget's disease, one malignant cystosarcoma phylloides and one sarcoma have been revealed. Among the benign alterations, there were 37 fibroadenomas, 25 fibrocystic changes, six fat necrosis, five inflammatory processes, four LCIS, three scleradenosis, three normal breasts, two scars, two adenomas and one hemangioma.

The tumour sizes reported at the main participating centres are shown in Fig. 4. The average maximum tumour dimension ranged from 1.3 cm (pooled centres) over 1.5 cm (France, Germany) and 2.0 cm (Italy) to 2.4 cm (Spain). Forty-one cancers had a maximal diameter of below 1 cm, 37 a maximum diameter between 1.0 cm and 1.5 cm and 87 a maximum diameter of more than 1.5 cm.

Data analysis

All data were collected on case report forms (CRFs) which had been distributed to all participating centres. All CRF data were entered into a database and converted to SAS datasets for delivery and into STATA datasets for analysis.

The safety population of the trial consisted of all patients who received the ^{99m}Tc-MIBI imaging agent. To be included in the efficacy population patients had to meet the following criteria: (1) have had a biopsy for which a core centre microscopic diagnosis exists, (2) have blinded read data for the scintigraphy. The so called by lesion efficacy population consisted of all lesions for which a core centre microscopic diagnosis exists. Some classes of protocol violators were identified which were, however, not considered sufficient to warrant exclusion from the efficacy population. These were: (1) no mammography (two patients), (2) mammography more than 2 months prior to the scintigraphy (six patients who had no discrepancy between mammographic and scintigraphic results), (3) biopsy more than 6 weeks after the scintigraphy (19 patients, of whom four showed false-positive scintigrams

and one a false-negative scintigram). Among these 27 patients (12 malignant and 15 benign lesions), there were three false-negative and five false-positive blinded read scintigrams referring to definition 2. The exclusion of these patients did not result in any alteration in sensitivity and specificity as shown in the Results section. All efficacy analyses were made separately for each target group of patients: (1) mammographically detected breast abnormalities, (2) breast abnormalities detected by palpation.

The measurement of agreement between any two assessment methods was based on a two-by-two table, in which one of the classifying factors was the gold standard (e.g. core centre histopathological results). From the tables, the following statistics were derived: sensitivity, specificity, overall agreement, kappa, positive predictive value (PPV) and negative predictive value (NPV). For the assessment of whether one technique is better than another, four-by-four tables were created indicating false-negative and false-positive, and true-negative and true-positive results of the methods. Several different types of assessment were evaluated: (1) institutional centre sestamibi read (definition 1 and definition 2) compared to core centre histopathology, (2) blinded sestamibi read (definition 1 and definition 2) compared to core centre histopathology, 3. comparison between institutional and blinded read scintigraphy, (4) comparison between blinded read scintigraphy and mammography.

Safety assessment

The numbers of patients experiencing any adverse event were tabulated. Adverse events had to be classified by type of event and summarized accordingly. Any serious event had to be tabulated separately.

Results

Scintigraphic blinded read

When the results of the blinded read were compared with the histopathological results of the core centre, scintigraphy was true-positive in 117 of 165 cancers (definition 2). This resulted in an overall sensitivity of 71% (Table 3). In this group, sensitivity for palpable and non-palpable cancers was 83% and 30%, respectively. For tumours bigger than 1.5 cm, sensitivity was 90%. For tumours between 1.0 and 1.5 cm and for those smaller than 1 cm, sensitivity was 65% and 40%, respectively.

If only scintigrams scored 2 or more were taken into account (definition 1), overall sensitivity was only 61%. In this group, sensitivity was 72% for the palpable (n = 127) and 21% for the non-palpable cancers (n = 38; Tables 3 and 4). For tumours bigger than 1.5 cm, sensitivity was higher, with a value of 80%.

Among 88 benign alterations of the breast, there were 68 palpable and 20 non-palpable lesions (Table 5). Overall specificity was 69% (definition 2, 27/88 false-positives scans) and 81% (definition 1, 17/88 false-positive scans). For palpable lesions, specificity was 75% (defintion 2) and 79% (definition 1), respectively, and for lesions bigger than 1.5 cm, specificity was 72% (definition 2) and 78% (definition 1).

When the results of the blinded read were separated out by main sites, the sensitivities and specificities were as follows (definition 1, Table 6): 87% and 84% (Spain), 87% and 77% (Italy), 61% and 78% (Germany), 46% and 100% (pooled centres) and 40% and 71% (France). If the pooled smaller centres were excluded, the overall sensitivity improved slightly to 63.5% but the specificity remained constant at 80% (definition 1).

If the 27 patients with "acceptable" protocol violations were excluded, the overall sensitivity and specificity did not change, with values of 70.6% (108/153 true-positives) and 70% (51/73 true-negatives), respectively (definition 2).

Institutional read

If the histopathological results were correlated to the institutional read the overall sensitivity and specificity, the PPV and the NPV were 88%, 66%, 84% and 72%, respectively (for definition 2; Table 7). In this group, sen-

Table 3. Sensitivities (Sens) and specificities (Spec) of blinded read scintimammography according to the scoring mode

	All (Sens/Spec)	Palpable (Sens/Spec)	Non-palpable (Sens/Spec)
Definition 1	61%/81%	72%/79%	21%/85%
Definition 2	71%/69%	83%/75%	30%/50%

Definition 1 = all lesions scored as 2 or more considered positive, definition 2 = all lesions scored as 1 or more considered positive

Table 4. Results of blinded read scintimammography in respect of malignant lesions (numbers in parentheses), according to the scoring mode

	All (165)		Palpable (127)		Non-palpable (38)	
Scoring mode	TP	FN	TP	FN	TP	FN
Definition 1	100	65	92	35	8	30
Definition 2	117	48	106	21	11	27

Definition 1 = all lesions scored as 2 or more considered positive; definition 2 = all lesions scored as 1 or more considered positive; TP, true-positives; FN, false-negatives

Table 5. Results of blinded read scintimammography in respect of benign lesions (numbers within parentheses), according to the scoring mode

	All (88)		Palpable (68)		Non-palpable (20)	
Scoring mode	TN	FP	TN	FP	TN	FP
Definition 1	71	17	54	14	17	3
Definition 2	61	27	51	17	10	10

Definition 1 = all lesions scored as 2 or more considered positive; definition 2 = all lesions scored as 1 or more considered positive; TN, true-negatives, FP, false-positives

Table 6. Sensitivities and specificities of blinded read and institutional scintimammography separated by participating centres (referring to definition 1)

Centre	Italy	France	Spain	Germany	Pooled centre
Blinded read (Sens/Spec)	87%/77%	40%/71%	87%/84%	61%/78%	46%/100%
Institutional (Sens/Spec)	93%/83%	73%/43%	87%/80%	83%/56%	71%/100%

Sens, Sensitivity; Spec, Specificity

Table 7. Sensitivities (Sens) and specificities (Spec) of institutional read scintimammography depending on the scoring mode

	All (Sens/Spec)	Palpable (Sens/Spec)	Non-palpable (Sens/Spec)
Definition 1	81%/74%	86%/69%	63%/81%
Definition 2	88%/66%	91%/65%	60%/93%

Definition 1=all lesions scored as 2 or more considered positive; definition 2=all lesions scored as 1 or more considered positive

sitivity for palpable and non-palpable lesions was 91% and 60%, respectively. For tumours bigger than 1.5 cm, sensitivity was 95%. For tumours between 1.0 and 1.5 cm and for those smaller than 1 cm, sensitivity was 74% and 55%, respectively.

If definition 1 was used the overall sensitivity and specificity, the PPV and the NPV were calculated to be 81%, 74%, 86% and 65%, respectively. In this group, sensitivity and specificity for palpable and non-palpable lesions of the breast were 86% and 69%, and 63% and 81%, respectively.

The institutional results by main sites were as follows: sensitivity and specificifity were 93% and 83% for the Italian centre, 87% and 80% for the Spanish centre, 83% and 56% for the German centre, 73% and 43% for the French centre and 71% and 100% for the pooled centres (definition 1, Table 6). If the pooled smaller centres were excluded, the overall sensitivity improved slightly to 83% with a minimal decrease in specificity to 72% (definition 1).

Mammography

When comparing mammographic results with the core centre microscopy, mammography was true-positive in 152 of 165 cancers and true-negative in 37 of 88 benign alterations of the breast. This results in a sensitivity and specificity of 91% and 42%, respectively. Sensitivity was not dependent on the size of the breast tumour (for tumours >1.5 cm, 90.7%, for those between 1.0 and 1.5 cm, 96%, and for those <1.0 cm, 87%; non-palpable 88% and palpable 92%). In the category of probability of malignancy of 50%–74%, mammography underestimated the real cancer probability for palpable breasts but overestimated it for non-palpable breasts. If mammography and blinded read scintigraphy were compared, eight cancers scored true-positive by the blinded read scintigraphy had been indicated by mammography to be false-negative (Table 8). This means that in 61% of all false-negative mammograms scintigraphy could diagnose the cancer. The aforementioned eight cancers (seven palpable, one detected by ultrasonography) were studied by different centres participating in the trial. Except for one breast, the corresponding mammograms showed dense breast tissue. In five of the eight malignant tumours, no suspicious mass could be detected, and microcalcifications were present only in two breasts (Table 9). Just one patient was postmenopausal.

Table 8 Comparison of mammographic and blinded read scintigraphic results (referring to definition 2)

Mammographic results	Scintigraphic results			
	TP	FP	FN	TN
TP	109	–	43	–
FP	–	15	–	36
FN	8	–	5	–
TN	–	12	–	25

TP, True-positives; FP, false-positives; FN, false-negatives; TN, true-negatives

Table 9. Results of mammography, scintigraphy and histology in patients showing a false-negative mammogram and a true-positive scintigram

Patient	Breast density	MX	PM	SMM	Histology
1	HeD	MC, no mass	20%	Acc,2	Inv. duct, G2
2	ExD	MC, no mass	30%	Acc, 3	Medullary, G3
3	HeD	Mass	20%	Acc, 3	Inv. duct, G2
4	HeD	Mass	10%	Acc, 2	Metastasis
5	ExD	No mass	0%	Acc, 2	Inv. lobular G1
6	ExD	No mass	0%	Acc, 2	Inv. duct, G2
7	NvD	Mass	20%	Acc, 2	Inv. duct, G1
8	HeD	No mass	0%	Acc, 3	Inv. duct, G1

MX, Mammography; SMM, scintigraphy; PM, probability of malignancy; HeD, heterogeneously dense; ExD, extremely dense; NvD, numerous vague densities; MC, microcalcifications; Acc 2/3, focal accumulation with score 2 or 3; inv. duct, invasive ductal carcinoma; inv. lobular, invasive lobular carcinoma

Density of breasts

Sensitivity of blinded read scintigraphy was not dependent on the density of breast tissue. Of 165 cancers, 118 (72%) were categorized as located in a breast of mammographic grade I or II density (group 1) and 47 (28%) as located in a grade III/IV density breast (group 2). The mean tumour diameter in groups 1 and 2 was 1.9 and 1.8 cm, respectively. Overall-sensitivity of the blinded read scintigraphy (definition 2) for the first and second groups was 70% (83 true-positives from 118 cancers) and 72% (34 true-positives from 47 cancers), respectively.

Time of imaging

As delayed images were optional, comparison of the early and delayed blinded read scintigrams was confined to 176 breasts. Using definition 1, 30% of the breasts were found to be positive on the early reads as compared with 26% on the delayed reads. Using definition 2, reads of the early views yielded positive results in 38% compared with 31% for the delayed reads. Only in three cases did the early view give a false-negative result while the delayed read was true-positive.

Kappa-statistics

Overall, the agreement between the readers of the blinded scintigraphy read did not show a significant difference if definition 1 was compared with definition 2. Overall agreement referring to all breasts was high, at 0.812 and 0.793, respectively. In 97% of the cases, three or more readers agreed in scoring a scintigram either positive or negative (definition 1). The reader agreement was somehow better for palpable lesions than for mammographically detected lesions. This difference in kappa values was more significant if definition 1 was used. With decreasing quality of images, the kappa value fell slightly but always remained above 0.7. In each quality class, the same high percentage of reader agreement (three or more readers scoring either positive or negative) could be found with values of 94%–96%. One main reason for disagreement between the readers was the way axillary nodes have been handled. These were entered as axillary nodes by some readers but as being in one of the breast segments by others.

When comparing the blinded and the institutional read, the overall kappa value for the agreement was 0.63. For palpable lesions, the agreement was better, with a value of 0.7. The decrease in kappa values with the quality score was more significant than mentioned before between the blinded readers. The main reason for the differences in diagnoses of blinded and institutional reads was that the institutional readers assigned higher scores to lesions than did the blinded readers, especially where the lesion was indistinct.

Histopathology

With regard to the histopathological characterization of the cancer, the sensitivity of the blinded read (definition 2) for invasive ductal cancers (80 true-positives from 109), invasive lobular cancers (20 true-positives from 29) and ductal carcinoma in situ (seven true-positives from 11) was 74%, 69% and 64%, respectively. The blinded read correctly diagnosed two metastases, two medullary cancers, one sarcoma and one malignant cystosarcoma phylloides. Among six tubular and two papillary cancers, blinded read scintigraphy was true-positive in three and one cases, respectively, but could not diagnose one mucinous carcinoma and one case of Paget's disease (Table 10).

If the histopathological results of the benign alterations are taken into account, specificity for fibroadenomas and fibrocystic disease was 68% and 88% (definition 2), respectively. Among the six cases of fat necrosis, five inflammations of the breast, two scars and one haemangioma, blinded read scintigraphy was true-negative in four, two, one and one cases, respectively. In two adenomas and three cases of normal breast tissue, results were true-negative in two cases each. All three breasts with scleradenosis showed false-positive scintigrams (Table 11).

Table 10. Results of scintimammography (SMM; definition 2; blinded read) according to the histological type of breast cancer

Histology	No.	TP-SMM	FN-SMM
Inv. ductal	109	80	29
Inv. lobular	29	20	9
DCIS	11	7	4
Tubular	6	3	3
Others	10	7	3
All	165	117	48

Inv., Invasive; DCIS, ductal carcinoma in situ; TP-SMM, true-positive SMM; FN-SMM, false-negative SMM

Table 11. Results of scintimammography (SMM; definition 2; blinded read) according to the histological type in benign lesions

Histology	No.	TN-SMM	FP-SMM
Fibroadenoma	37	25	12
Fibrocystic tissue	25	22	3
Fat necrosis	6	4	2
Inflammation	5	2	3
LCIS	4	4	0
Others	11	4	7
All	88	61	27

LCIS, Lobular carcinoma in situ; TN-SMM, true-negative SMM; FP-SMM, false-positive SMM

Discussion

Recently, nuclear breast imaging has gained significant interest as several radionuclides have demonstrated promising results in the diagnosis of breast cancer. ^{99m}Tc-MIBI is a cationic complex which can accumulate in tumour cells [41]. The accumulation of ^{99m}Tc-MIBI in the tumour is dependent on the quantity of mitochondria in the tumour cell, on the electric membrane potential and on the expression of the multidrug resistance (MDR) gene [42–46].

Recent studies using ^{99m}Tc-MIBI for breast cancer detection have shown high sensitivity and specificity for palpable cancers [22–32]. For non-palpable breast lesions, diagnostic accuracy has been less favorable [25, 27, 29, 30]. In this trial, scintigraphy with ^{99m}Tc-MIBI read blinded achieved an overall sensitivity of 71%. For palpable tumours and tumours bigger than 1.5 cm, sensitivity was 83% and 90%, respectively. Specificity in these two groups was clearly over 70%. These values are slightly below those reported by previous studies [23–30]. Generally, it can be expected that it will be more difficult to obtain similar results if the method is assessed by a blinded multicentre study. Consequently, in this trial, the institutional read demonstrates an increase in the overall sensitivity in all centres up to a value of 88% when compared with the blinded read. It must be supposed that the clinical data such as size of lesion, location and probability of malignancy are important factors for the reader of scintigraphy and their knowledge will increase sensitivity. In the case of palpable lesions and lesions bigger than 1.5 cm, sensitivity increased to 91% and 96%, respectively, by the institutional read. These results are in agreement with a multicentre trial conducted in the United States and Canada which revealed an institutional sensitivity of 95% for palpable lesions [47].

In this study, it has been shown that sensitivity can be significantly increased if lesions which are scored as equivocal are considered as a malignant process. Even if this definition was used, specificity did not fall below a level of 70%. This means that any abnormality must be considered as suspicious for malignancy. In this way, a high sensitivity of scintimammography in association with an acceptable specificity can be achieved (Fig. 5). As demonstrated by the ROC curves, there will be a learning process for the interpretation of scintigrams resulting in an increase in sensitivity.

There are still significant limitations to the use of mammography for the detection of breast cancer, and these limitations persist in spite of technical improvements facilitating dianosis. Especially in younger women (less than 50 years old) with dense breasts, the diagnostic benefit of mammography is less favourable [7, 8]. Thus, there is a need for a non-invasive method to complement mammography and to help differentiate benign and malignant breast lesions in dense breasts. Such a method should be reliable and have a high sensitivity

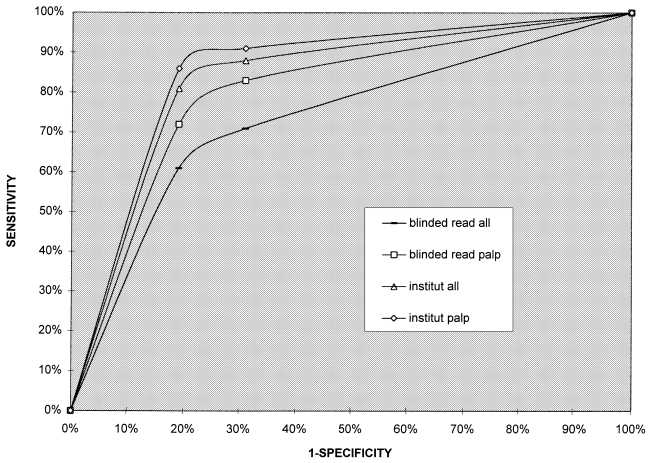

Fig. 5. ROC curves of blinded and institutional (*institut*) read scintigraphy for all and for palpable (*palp*) lesions. The first value of each curve refers to definition 1 and the second value of the curve refers to definition 2

and a high predictive value. In this trial, mammographic results were within the range of the values reported in the literature [48]. Overall sensitivity and specificity were 91% and 40%, respectively. Sensitivity of mammography was not dependent on the tumour size, and, therefore, no decrease in sensitivity in patients with non-palpable cancers was observed. In this trial, overall sensitivity of mammography was superior to that of scintigraphy, demonstrating that scintimammography, in its current state, is not suitable for breast cancer screening. For the mammograms, only an institutional read has been performed. This means that the mammographic results of this trial correspond to those of the clinical everyday practice of the radiologist.

However, this trial has shown that scintigraphy can provide additional information to mammography and help to detect breast cancer earlier in a subgroup of patients. In 60% of patients with a false-negative mammogram, scintigraphy could diagnose the breast cancer. This group consisted of younger patients with mammographically dense breast tissue resulting in a false-negative mammogram. As this study was able to prove, the diagnostic accuracy of scintimammography is not dependent on the density of breast tissue. This has also been reported by Khalkhali et al. [49, 50]. Consequently, premenopausal patients whose mortality from breast cancer cannot be decreased significantly by screening mammography will benefit most from scintimammography.

In the majority of the cases, the woman herself detects an alteration of the breast for which she consults the physician [51]. Sensitivity of breast palpation is not satisfactory, and often lumpy breasts make it difficult to characterize sufficiently a palpable nodule or mass in the breast [51]. If mammography performed in the further diagnostic work-up is indeterminate and suspicion of malignancy not high, the patient will be advised to return for a control mammography in 3–6 months. In this

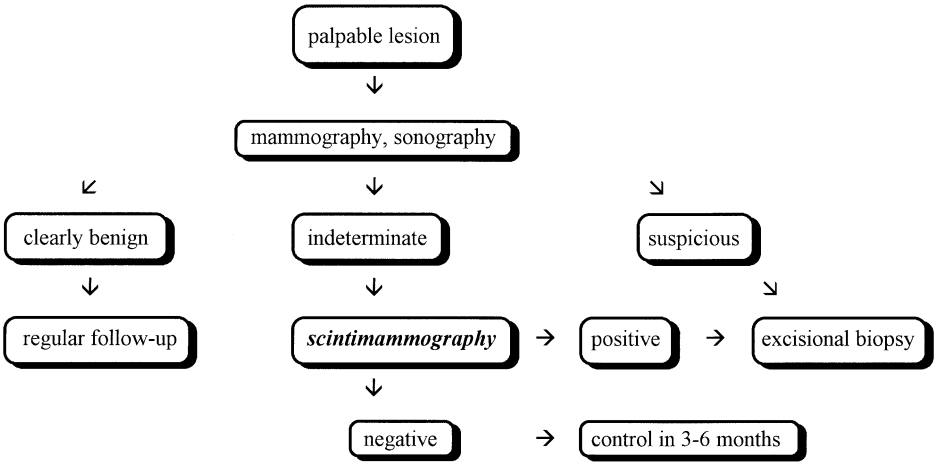

Fig. 6. Flow chart indicating the role of scintimammography in the diagnostic work-up of patients with palpable breast masses

patient group, the majority of which comprises premenopausal women, scintigraphy could help to diagnose breast cancer at an earlier point in time when it is used as a complementary method to mammography (Fig. 6).

It is important for a breast cancer imaging modality that sensitivity is not dependent on the histological type of the cancer. For invasive ductal and lobular carcinomas, the sensitivity of scintimammography did not show a significant difference. This group of malignant tumours represent 80%–85% of all breast cancers [52]. For DCIS, sensitivity was slightly lower than for invasive cancers. Furthermore, less frequent cancers such as medullary and tubular carcinomas and metastases could also be diagnosed by scintimammography. This makes scintigraphy suitable as a complementary imaging method.

False-positive results were obtained in patients with fibroadenoma, fibrocystic disease and local inflammation of the breast. Disease with a high inflammatory component might yield false-positive results, most likely due to increased local perfusion. Areas with increased mitochondrial activity and density, such as juvenile adenomas and hyperproliferative disease, can also cause false-positive MIBI uptake [22, 25, 27, 29]. However, patients with atypical hyperproliferative disease have a higher relative risk for breast cancer [52]. In these patients, a positive MIBI scan may be of prognostic value [53].

The exact localization of a MIBI-positive area remains a problem since neither planar imaging nor single-photon emission tomography provides the surgeon with sufficient information for biopsy of breast tissue. When scintimammography is indicative for breast cancer but other breast imaging modalities such as mammography, ultrasonography and magnetic resonance imaging are negative, the scintigram must be used for tumour localization. New approaches have been developed to allow scintigraphy-guided biopsy of breast lesions [54, 55].

It is known that mammogaphy is a very reader-dependent method. With regard to ultrasonography, this problem is even more important. The interreader agreement for scintimammography, however, is very high, with kappa values of 0.812. It is important for a diagnostic method that the interreader variation is low, especially when it is performed in a wide medical field of clinical everyday practice.

Khalkhali et al. have shown that the prone position with the breasts hanging freely is the best technique for the performance of lateral scintimammography because deeper regions of the breast can be visualized [23]. For this purpose different techniques may be used: a special table design with a lateral cut-off or a kind of foam cushion with lateral apertures as used in this trial. Regardless of which technique is used, the breast must not be compressed from either side. Furthermore, a high-resolution gamma camera should be used and the acquisition time must be at least 10 min if good quality images are to be obtained. Special attention must be drawn to the distance between the collimator and the breast, which, ideally, should touch the camera surface. Standardization of scintimammography will help to achieve a high quality level of this technique.

Use of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) and positron emission tomography (PET) has also been evaluated for the detection of breast cancer [14–21]. In a larger patient group, Avril et al. reported a sensitivity and specificity for the detection of primary breast cancer of 88% and 78%, respectively [18]. For small tumours, only low sensitivity was achieved. In a group of 20 patients, Palmedo et al. compared FDG PET and ^{99m}Tc-MIBI scintimammography [19]; however, in 40 breasts with 22 lesions, FDG PET could not detect additional cancer in comparison with Tc-99m MIBI scintigraphy. Comparing these two imaging modalities, PET has the advantage of providing better spatial resolution, but the availability of FDG and PET is limited and costs are significantly higher.

Conclusions

Scintimammography with ^{99m}Tc-MIBI has a high diagnostic accuracy in palpable breast lesions. Sensitivity is

not dependent on the mammographically determined density of the breast tissue. Scintimammography is suitable as a complementary method to mammography in patients with dense breasts and an intermediate or low probability of breast cancer. Further, patients with a high risk of breast cancer may benefit from radionuclide imaging with ^{99m}Tc-MIBI.

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