The efficacy of ^{99m}Tc-MIBI scintimammography in the evaluation of breast lesions and axillary involvement: a comparison with X-rays mammography, ultrasonography and magnetic resonance imaging

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Abstract

This study was performed because the efficacy of technetium-99m methoxyisobutyl isonitrile scintimammography (^{99m}Tc-MIBI-SM) in the evaluation of the breast lesions and axillary lymph node involvement in comparison with X-rays mammography (XRM), ultrasonography (US) and magnetic resonance imaging (MRI) has not been fully investigated. *Forty six female patients* were included in this study, with suspicious lesions detected in their breasts by palpation, by imaging modalities or clinically. All patients underwent ^{99m}Tc-MIBI-SM, US and MRI for the evaluation of breast lesions. All patients according to clinical situation and imaging studies underwent fine needle aspiration, mass extirpation, core biopsy, modified radical mastectomy or partial lumpectomy in order to confirm the nature of the lesions. *Our results* showed that ^{99m}Tc-MIBI-SM detected 15 of 16, US 11 of 16, XRM 13 of 16 and MRI 13 of 16 malignant lesions. Sensitivities were 93%, 68%, 81% and 81%, respectively. Among these cases there were 4 of 15 false positive (FP) results on SM whereas 4 of 11 on US, 11 of 13 on XRM and 8 of 13 on MRI. The specificities of the above modalities were 86%, 87%, 63% and 73%, respectively. The sensitivities of the above imaging modalities for the detection of axillary lymph node metastases were 55%, 55%, 11% and 77% for SM, US, XRM and MRI, respectively. The sensitivity and specificity of SM for the palpable lesions (n=31) were 100% and 84% and for the nonpalpable lesions (n=15) were 75% and 90%, respectively. *In conclusion,* although the number of patients studied was small it is the opinion of the authors that ^{99m}Tc-MIBI-SM has a much better sensitivity and less FP results in detecting malignant breast lesions than the other 3 modalities and also better sensitivity than XRM and MRI. Thus ^{99m}Tc-MIBI-SM can be included in the diagnostic algorithms for detecting malignancy in breast tumors.

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Introduction

Breast cancer (BC) is one of the leading health problems of women. Its incidence in European countries is steadily increasing during the last 40 years. It is the most frequently encountered type of cancer in women in Europe, Australia, North America and in a great part of Latin America [1]. One in 12 women is in the risk of developing BC during her life time and in some countries this ratio rises up to 1 in 8 [2, 3]. Early and accurate diagnosis of the disease has an impact on prognosis and the outcome of the disease. For this reason in most countries screening programs are performed using X-rays mammography (XRM). Randomized controlled studies showed that there is a 17% decrease in mortality in women between 40-49 years of age, and in women over 50 years of age a 25%-30% decrease in mortality is detected [4-7]. Although XRM has a high specificity, it is not reliable enough in patients with dense breasts, dysplastic diseases, breast implants, or in the evaluation of patients after breast surgery or radiotherapy. Additionally, its specifity is not high in order to discriminate between benign and malignant masses. Biopsies performed according to XRM findings, frequently give false negative (FN) results. In some developed countries, every 1 in 4 women undergoes surgical biopsy for the clarification of suspicious breast lesions [1]. Unnecessary biopsies evoke anxiety and stress in women and biopsy scars may cause FP results in XRM. For this reason, in order to increase the specificity of XRM, other imaging modalities are applied, like ultrasound (US), color Doppler US, computerized tomography (CT), magnetic resonanse imaging (MRI) and nuclear medicine techniques.

In this study we aimed to assess the efficacy of technetium-99m methoxyisobutyl isonitrile scintigraphy (^{99m}Tc-MIBI-SM) in the detection of benign or malignant breast lesions.

Patients and methods

Forty six patients aged 46.10±13.31yr (range: 22-82yr) were enrolled in this study. In these patients suspicious lesions were detected in their breasts clinically, by palpation or by imaging modalities. All patients underwent physical examination and then ^{99m}Tc-MIBI-SM, XRM, MRI and breast US examinations during the two weeks before biopsy or operation.

The MRI images were obtained with a 1.5 T MRI (Magnetom Vision Plus; Siemens, Erlangen, Germany) by using dedicated breast coil which enables visualization of both breasts. Imaging was performed before and immediately after intravenous (i.v.) injection of gadolinium-DTPA (0.2mg/kg) and then serial images were obtained with T1-weighted spin-echo and 3D gradient-spin-echo sequences. Nineteen slices each, with a thickness of 5mm were obtained. Post gadolinium quantitative analysis was performed with an automatic regions of interest (ROI) method. All patients underwent bilateral XRM of both breasts. Ultrasound examination of the breasts having lesion was performed with a 5-MHz probe (Toshiba XG Aplio, 2006 Italy). The ^{99m}Tc-MIBI used was prepared and quality controlled according to the instructions of the manufacturer (Monrol, Turkey). Each patient was i.v. injected with 925MBq of ^{99m}Tc-MIBI into the contralateral to the lesion pedal through a catheter, so that if the lesions were bilateral, to avoid FP findings resulting from lymph nodes uptake due to possibly extravasated radiopharma- ceutical. Before and after the injection of ^{99m}Tc-MIBI, the catheter was flushed with saline to eliminate any possible extravasation and ensure the complete infusion of the tracer. Imaging study was performed in our department, with a single head single photon emission tomography (SPET) camera equipped with low-energy, general purpose collimator (LEGP), ADAC, USA in our department. Starting 10min after the injection of ^{99m}Tc-MIBI, lateral and then anterior images of both breasts were obtained. Imaging was undertaken with the patient lying prone with her head resting on her arms. In order to prevent the “shine through” phenomenon, the breast to be imaged was freely pendent , while the opposite breast was behind a specially designed lead shield and compressed on the couch. We didn’t use a special matress for this purpose (Fig. 1). All projections were taken for 10min in a 256x256 matrix with a LEGP collimator. Semiquantitative analysis of the lesions was done by calculating the count ratios obtained from the counts of the ROI drawn around the lesions, to the background (bg) counts obtained from ROI of equal number of pixels drawn at the surrounding normal breast parenchyma.

Figure 1. The patient lying prone on the couch and the left breast is freely pendent , while the opposite breast was compressed on the couch.

When a lesion, irregular and dense or having microcalcifications on the XRM was detected, it was evaluated as: suspicious, probably malignant or malignant. The rest of the lesions were categorized as: normal, benign or probably benign.

The MRI images were graded according to a) the intensity of gadolinium uptake as: no uptake, low, moderate and high uptake, b) the configuration of the lesion that shows uptake and c) the dynamics of contrast uptake: rapid uptake that reaches to maximum at the first post-contrast images and slow uptake with a constant increase in signal intensity and contrast wash-out after the early post-contrast images. According to these criteria, the lesions were classified as normal, probably benign, suspicious and probably malignant. The lesions after the US test were classified as: benign cystic, normal, solid probably benign, solid probably malignant and malignant. The evaluation of the lesions was done visually. The lesions which showed increased uptake compared to the surrounding breast parenchyma were regarded as positive and the rest of the lesions as negative on the ^{99m}Tc-MIBI-SM (Fig. 2).

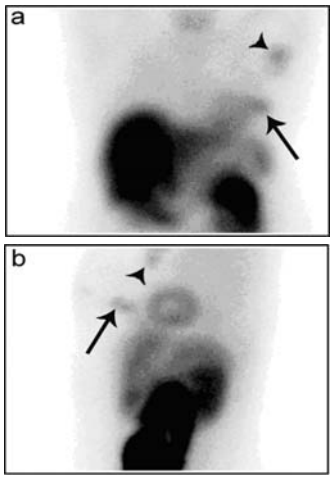

Figure 2. Pathologically increased ^{99m}Tc-MIBI uptake in a mass lesion at left lower quadrant of left breast (arrow) in a patient with invasive ductal carcinoma. Accumulation of ^{99m}Tc-MIBI at left axillary region was consistent with metastatic invasion of lymph nodes (arrow head).

Axillary regions were evaluated for lymph node metastases by all imaging modalities.

Imaging findings were reported by two nuclear medicine physicians (T.O. and F.O.) and XRM, MRI and US were reported by an experienced radiologist (H.D.)

After imaging studies were completed, patients underwent one of the surgical interventions chosen according to the clinical situation of the patient and imaging findings: fine needle aspiration, mass extirpation, core biopsy, modified radical mastectomy or partial lumpectomy. In 3 cases, there were palpable lesions but findings on XMR, US, MRI and ^{99m}Tc-MIBI-SM were suggestive of benign disease, and the patients didn’t undergo any further intervention.

In cases in which cancer was confirmed histopatho - logically and US, MRI, and XRM imaging studies were scored as: suspicious, probably malignant or malignant, and ^{99m}Tc-MIBI-SM was reported as positive, the findings were described as true positive (TP). If cancer was ruled out histopathologically and US, MRI, and XRM imaging studies was scored as normal, probably benign, or benign, and ^{99m}Tc-MIBI-SM was reported as negative, findings were interpreted as true negative (TN).

Statistical analysis

Statistical analysis comparing the average count ratios of the tumor/bg region of interest (ROI) of the malignant

tumors to the same average of the benign tumors was calculated by Levene's test [8] and Students t-test. For this purpose semicircular background ROIs were drawn over the breast parenchyme surrounding the lesions. For evaluation of the accuracy of the imaging techniques, a) the sensitivity was defined as the ratio of the number of TP to the sum of TP and FN cases, b) the specificity was defined as the ratio of the number of TN to the sum of TN and FP cases, c) the positive predictive value (PPV) was defined as the ratio of the TP tests to the sum of the TP and false positives (FP) and d) the negative predictive value (NPV) was defined as the ratio of the TN to the sum of the TN and FN cases.

Ethical approval

The study protocol was approved by the Ethics Committee of Okmeydanı Hospital. Each patient gave her written, informed consent, before participation in the study.

Results

In our 46 patients there were 31 palpable and 15 nonpalpable lesions. Malignancy was confirmed histopathologically in 16 of 46 and benign lesions in 27 of the 46 patients. In 3 patients lesions were accepted as benign depending on findings on US, MRI, 99mTc-MIBI-SM and XRM. Twelve of the 16 malignant lesions were palpable. Technetium-99m-MIBI-SM detected 15 of 16 malignant lesions, US detected 11, XRM 13 and MRI detected 13 of the 16 lesions. The sensitivities of the above modalities were 93%, 68%, 81% and 81%, respectively (Table 1).

Tecnhetium-99m-MIBI and XRM showed FN results in only one case with invasive ductal carcinoma, while this case was interpreted correctly as malignant by US and MRI.

In 3 out of the 30 patients whose histopathologies were benign, the lesions were palpable, and nonpalpable in the rest of the patients. Among these cases there were 4 FP results on SM, 4 on US, 11 on XRM and 8 on MRI.

Thus, specificities of the above modalities were 86%, 87%, 63% and 73%, respectively. Detailed findings for every patient with all imaging modalities examined, the biopsy and histopathology findings are described in Table 2.

Table 1. *Comparison of the diagnostic accuracies of the imaging modalities*

	SM	US	Mammography	MRI
Sensitivity	93%	68%	81%	81%
Specificity	86%	87%	63%	73%
PPV	78%	73%	54%	61%
NPV	96%	83%	86%	88%

PPV: Positive predictive value; NPV: Negative predictive value

Table 2. *Results of 99mTc-MIBI scintimammography (SM), ultrasonography (US), X-rays mammography (XRM) and magnetic resonance imaging (MRI) studies in patients evaluated for breast lesions*.

Patients initials	Age	Palpable (+) or non (-)	SM	T/B	US	XRM	MRI	Biopsy/ Operation	Histopathological diagnosis
HA	35	+	pos	0.86	SPB	PB	S	FNAB	Granulomatous mastitis
SB	52	+	»	1.67	M	PM	PM	MRM	Invasive ductal carcinoma
FA	29	+	»	2.17	PM	»	»	Mass extirpation	» » »
RA	82	+	»	2. 07	SPB	»	M	Core biopsy	» » »
NA	74	+	»	3.28	SPM	»	»	MRM	» » »
LA	62	+	»	1.57	M	MM	PM	FNAB	» » »
SA	42	+	»	1.70	S	Normal	PB	Mass extirpation	Fibroadenoma
HC	36	+	neg	-	BC	S	»	FNAB	Fibrocystic disease
HC	57	+	pos	5.05	M	M	PM	MRM	Invasive ductal carcinoma
UG	60	+	»	3.06	»	Insufficient	»	»	» » & lobular »
GI	56	-	neg	-	S	Normal	S	Mass extirpation	Fibrocystic disease
NK	35	-	»	-	SPM	»	PM	»	Invasive ductal carcinoma
FK	36	-	pos	1.91	»	PB	»	MRM	» » »
GO	65	+	»	1.30	SPB	PM	PB	»	» » »
FS	48	-	»	1.10	BC	B	»	FNAB	Fibrocystic disease
MT	52	+	»	3.60	SPB	PM	»	MRM	Invasive ductal carcinoma
MT	64	+	»	3.07	SPM	S	»	»	» » »
HT	35	+	»	1.40	S	PM	Normal	Mass extirpation	Fibroadenoma
TY	31	+	»	2.60	SPM	»	PM	MRM	Invasive lobular carcinoma
SA	37	+	neg	-	Normal	PB	S	Mass extirpation	Fibroadenoma
ZV	30	-	»	-	»	»	Normal	FNAB	Fibrous tissue
GG	41	-	»	-	BC	»	»	»	Fibrocystic mastopathy
AG	40	+	»	-	»	Normal	PB	»	Simple cyst & Fibroadenoma
CS	51	-	»	-	Normal	PB	Normal	»	Fibrous tissue
FP	41	+	»	-	BC	S	»	»	Fibrocystic disease
AY	42	+	neg	-	BC	Normal	PB	FNAB	Fibrocystic disease
ST	60	+	»	-	»	»	»	»	» » & Sclerozing adenitis
HS	52	-	pos	1.67	Normal	PM	S	»	Invasive ductal carcinoma
FA	60	+	neg	-	»	»	PM	Excisional biopsy	Fibrocystic disease
FD	47	-	»	-	»	PB	Normal	FNAB	Fibrous tissue
NY	22	+	»	-	SPB	S	»	On follow up	-
NY	23	+	»	-	»	»	PB	»	-
AS	41	-	»	-	BC	PB	S	FNAB	Fibrocystic disease
AT	49	-	pos	1.40	SPB	PM	PM	MRM	Infiltrative ductal carcinom
AG	65	+	»	1.80	SPB + BC	»	S	»	» » »
AB	35	+	neg	-	S	PB	PB	Excisional biopsy	Fibroadenoma & Lipoma
ME	44	-	»	-	Normal	Normal	»	FNAB	Granulomatous mastitis
DC	36	+	»	-	BC	S	PM	Excisional biopsy	Fibrocystic disease
SA	35	+	»	-	»	»	S	Partial mastectomy	» »
NE	52	+	»	-	Normal	Normal	Normal	On follow up	-
FK	32	+	»	-	BC	»	PB	FNAB	Chronic infection
HO	53	+	»	-	»	S	»	»	Fibrocystic disease
GO	50	-	»	-	»	B	Normal	»	» »
GS	46	-	»	-	»	»	PB	»	Simple cyst
CY	28	+	»	-	SPB	S	»	Mass extirpation	Fibroadenoma & Lipoma
HZ	34	-	»	-	BC	»	S	Excisional biopsy	Fibrocystic disease

SPB: Solid probably benign, M: Malignant, PM: Probably malignant, SPM: Solid probably malignant, S: Suspicious, PB: Probably benign, BC: Benign cystic, FNAB: Fine needle aspiration biopsy, MRM: Modified radical mastectomy, T/B: Tumor/Background uptake ratio, pos: positive, neg: negative

Sensitivity, specificity PPV and NPV of all studied modalities for the 31 palpable lesions are shown in Table 3.

Table 3. *Comparison of the diagnostic accuracies of the imaging modalities in* 31 *palpable lesions*

	SM	US	XRM	MRI
Sensitivity	100%	66%	91%	75%
Specificity	84%	84 %	47%	73%
PPV	80%	72%	52%	64%
NPV	100%	80%	90%	82%

PPV: Positive predictive value; NPV: Negative predictive value

Sensitivity, specificity, PPV and NPV of all studied modalities for the 15 patients with non palpable lesions are shown in Table 4.

The average of the ratios of the counts obtained from the ROI drawn around the lesions and at the bg in the group of patients with positive SM was 2.41±1.03, (1.3-5.05) for malignant lesions and 1.26±0.36 (0.86-1.7) for benign lesions. The difference between the averages of the two groups were found to be statistically significant (P=0,046 in 95% confidence interval). Table 5 and 6 show the T/B count ratios in malignant and benign tumors.

Table 4. *Comparison of the diagnostic accuracies of the imaging modalities in 15 nonpalpable lesions.*

	SM	US	XRM	MRI
Sensitivity	75%	50%	50%	100%
Specificity	90%	90%	90%	57%
PPV	75%	66%	66%	100%
NPV	90%	83%	100%	72%

PPV: Positive predictive value; NPV: Negative predictive value

Both axillae were evaluated by the imaging modalities for lymph node metastases. In 9 out of 16 patients with malignant diseases, metastases in axillary lymph nodes were detected. The sensitivities of the imaging modalities for the detection of these metastases were 55%, 55%, 11% and 77% for SM, US, XRM and MRI, respectively.

Table 5. *T/B count ratios in malignant tumors*

Histopathology:	IDC	IDC	IDC	IDC	IDC	IDC	IDC & ILC	IDC	IDC	IDC	IDC	IDC	IDC	IDC	IDC
T/B:	1.67	2.17	2.07	3.28	1.57	5.05	3.06	1.91	1.3	3.6	3.07	2.6	1.67	1.4	1.8

IDC: Invasive ductal cancer; ILC: Invasive lobular cancer; T/B: Tumor/Background uptake ratio

Table 6. *T/B count ratios in benign tumors*

Histopathology:	Fibroadenoma	Fibrocystic disease	Fibroadenoma	Granulomatous mastitis
T/B:	1.4	1.1	1.7	0.86

Discussion

In our study sensitivity of SM in detecting malignant breast lesions was found 93%. Similar results of 78.1%-94% were reported in the literature [9-15]. Scintimammography was more sensitive than the other three modalities. The sensitivity and specificity we found by SM for the detection of malignancy palpable lesions was 100% and 84% while others found 97% and 84%, respectively [13]. For non-palpable lesions, SM had a sensitivity and specificity of 75% and 90%, respectively. Thus SM was found to be, more sensitive for palpable malignant and more specific for non-palpable malignant lesions.

It is known that histologically hypercellular types of fibroadenomas may show focal ^{99m}Tc-MIBI uptake. There are few papers in the literature reporting ^{99m}Tc-MIBI uptake in abscesses [16] as in our case of granulamatous mastitis. Thus infectious diseases should also be considered in the differential diagnosis of cases of increased ^{99m}Tc-MIBI uptake. The pattern of the uptake in infections is diffuse or heterogenous, while in malignant diseases it is focal. Others showed that ^{99m}Tc-MIBI uptake in benign lesions like usual-type ductal epithelial hyperplasia and apocrine metaplasia does not seem to be related to cell proliferation index (Ki-67) and the presence of estrogen receptors (ERs) so it could not be a useful indicator of the probability of these lesions to progress to atypical hyperplasia, ductal carcinoma in situ or invasive tumors [17].

In our study the specificity of the SM was higher than in XRM (86% vs 63%). This is clinically important because one of the major limitations of XRM is its relatively lower specificity and PPV and as a result fine needle aspiration biopsy (FNAB) is performed. Although FNAB and also stereotactic core biopsy, which may follow are not so invasive as is excisional biopsy, they may be insufficient for the early diagnosis of cancer and sampling errors may also occur. On the other hand excisional biopsies may expose the patient to the risk of surgical interventions, high morbidity and high costs. In that context, complementary techniques like SM that is suggested in our study would increase the specificity of XRM. In the literature it is reported that the specificity of SM in detecting BC is 69%-85.4% whereas for XRM is 42%-56% [11, 13, 18].

Others reported that, SM in 41% of the cases decreased futile biopsies which were performed after depending on the XRM results [19] In our study, SM was TN in 8 of 11 patients who had FP results in XRM and thus decreased the futile biopsies in these 8/11 cases.

According to our results the PPV for XRM was 54% and for SM 78%.

Nevertheless, XRM has a high sensitivity in elderly womens' breasts, rich of fat tissue. In some studies, FN 25%-45% were reported principally in dense breasts, dysplastic disease, breast implants, or in patients evaluated after operation or radiation treatment [20].

The MRI examination is known to be a highly sensitive imaging technique (86%-100%) but its specificity is varying, 27%-97% [21]. In our study its sensitivity was 81% and specificity 73%.

There are variable reports on the sensitivity of US in the detection of BC. In some studies FN results 0.3%-45% were reported [22-25]. Others reported sensitivity of 100% and specificity of 48% [26]. In our study these sensitivity and specificity values were 68% and 87%, respectively. The sensitivity of US is decreased by microcalcifications without accompanying mass lesions and by solid lesions which are embedded in fat tissue. The relatively high specificity of US found in our study can be attributed to the high number of cystic lesions. The well known discrimination by US between cystic and solid lesions was confirmed in our study; among benign lesions, US correctly diagnosed 15 of 16 lesions which (all) had cystic components as shown by histopathology.

In our study, the sensitivities of the imaging modalities in detecting axillary lymph node metastases were 55%, 55%, 11% and 77% for SM, US, XRM and MRI, respectively.

In the literature, SM for the detection of axillary lymph node metastases has a sensitivity between 57% to 100% [27-29]. Others compared the ^{99m}Tc-MIB-SM and fluorine-18-fluoro-2-deoxyglucose, positron emission tomography (^{18}F-FDG PET) in the detection of lymph node metastases and found that ^{18}F-FDG PET was superior to SM in that respect [30]. In a multicenter trial the authors concluded that non tomographic ^{99m}Tc-sestamibi SM had a very low detection rate for axillary lymph node involvement and it should not be applied for clinical assessment of breast cancer [31].

In the present study, the average of the T/B ratios of the malignant lesions were significantly higher than those of the FP lesions, (2.41±1.03 vs 1.26±0.36 P=0.046). In another study, the diagnostic accuracy of T/B ratio examined by ^{99m}Tc-MIBI was 1.5±0.5 for TP tumor lesions and 1.2±0.2 for the benign lesions [32]. In a study performed to evaluate and compare the diagnostic accuracy of pentavalent ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-(V)DMSA) and ^{99m}Tc-MIBI in the detection of primary breast cancer and metastatic lymph node involvement, T/B ratios were almost identical for the two agents and were significantly higher than those for benign lesions [33]. For BC, T/B ratio cut off values of 1.2-1.4 and for benign breast tumors, values even higher than 1.5 have been proposed [34].

Planar SM with a high-resolution dedicated breast camera (DBC) has been shown to have higher sensitivity in the detection of BC, in comparison to planar SM acquired with a conventional gamma camera, even when the lesions are small in size [35, 36].

Technetium-99m-MIBI-SM was also found useful for the monitoring of tumour response to neoadjuvant chemotherapy, with an efficacy comparable to that of ^{18}F-FDG PET [37].

A higher number of patients studied, semiquantitative analysis, and more specific criteria than focal uptake as a sign for malignancy would increase the specificity of the SM technique.

In conclusion, our study shows that ^{99m}Tc-MIBI SM has a sensitivity of 93% in detecting malignancy in breast lesions better than MRI, US and XRM. In palpable breast tumors the sensitivity of SM was 100%. Thus, SM can be applied as a better alternative to XRM especially in specific cases like dense breast tissue etc. Conversely, ^{99m}Tc-MIBI-SM was not quite sensitive for the detection of axillary lymph node metastases.

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