The role of ^{99m}Tc-MIBI scintimammography in diagnosis of breast cancer

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ABSTRACT

Scintimammogrphy (SMM) is a new non-invasive method of imaging breast tumors which in various studies the overall sensitivity of 83%-95.8% and specificity of 52%-95% is reported.The purpose of our study was to evaluate the usefullness of ^{99m}Tc-MIBI SMM in our environement in detecting breast cancer and in reducing the rate of biopsy. 65 patients aged 23-70 years were included in this study. The overall sensitivity and specificity of SMM were 84.6% and 71.8%, respectively. The PPV of 66.6% and NPV of 87.5% were similar to that obtained by others. These results showed that, SMM did not increase the specificity and PPV of mammography. However SMM is a useful method for evaluating patients with low suspicion or indeterminate mammographic or palpable findings or lesions larger than 1.5 cm.

Key words: ^{99m}Tc-MIBI scintimammgraphy, Breast cancer

Introduction

Mammography is a highly sensitive technique in the diagnosis of breast cancer,but it is frequently incapable of differentiating malignant lesions from benign ones (PPV=10% - 40%).Thus a complementary diagnostic procedure that, complete the study of mammography becomes clear [1].

It was the research of Waxman et al. and Khalkhali et al. that generated the clinical interest in evaluating breast cancer with ^{99m}Tc-MIBI. The purpose of this study was (a) to confirm in our environement the usefulness of ^{99m}Tc-MIBI SMM fundamentally, (b) to determine whether a diagnostic protocol based on the joint use of mammography and SMM is capable of reducing the number of biopsies required in patient with suspected breast cancer.

Materials and Methods

69 women aged 23 to 70 years were enrolled in this study from September 2000 to January 2002. Each patient had a physical examination and standard 2 view mammography, using a dedicated mammography unit (General Electric, model: Z.5002B.4651824 & Philips: Mamo Diagnost S). The study entry criteria comprised either a positive finding on mammogram, and /or a mass

palpated on physical examination that required biopsy or FNA(fine needle aspiration) cytology.Mammograms were interpreted and categorized according to BI-RADS criteria, and graded using five point grading system.

All these patients referred to nuclear medicine department of Nemazee hospital with a maximum interval of 4 weeks after mammography. SMM was performed using a single head gamma camera(Siemens) equipped with a large field, low energy all purpose collimator. The spectrometer was centered at 140 kev with a 10% window. Patients were imaged in the upright and prone position using a plastic table overlay that allowed the breast being imaged freely dependent from the image table. In all views، the arms were raised and axillary regions were included in the field of view. Each patient received 20 mCi ^{99m}Tc-MIBI injected intravenously in the arm contralateral to the breast with the abnormality. For patients with suspected lesions in both breast, the injection of ^{99m}Tc-MIBI was given in a pedal vein. Planar images were obtained 10 to 15 minutes after injection.All scintimammograms were analyzed by one nuclear medicine physician, who was blinded to the clinical status, physical examination، radiologic mammogram and histopathologic result. However، the side of the intravenous injection of ^{99m}Tc-MIBI (and thus، indirectly the side of the suspected breast lesion) was specified before interpretation in order to avoid false positive axillary lymph node uptake secondary to extravasation of the radiopharmaceutical at the injection site and any subsequent drainage through local and regional lymphatic vessels. Two different types of display were available for the data analysis: hard copy of the analog film and direct reading from the computer screen.

Excisional biopsy of the 47 lesions and FNA cytology of the 44 lesions were performed no more than 2 weeks after scintimammography. In 16 patients with deep seated and / or non-palpable lesions with probably benign or equivocal criteria a follow up physical examination and mammography after six months was performed. All the data were analyzed by SPSS and EPI-INFO statistical analysis program.

Results

Of 69 patients, the data from 4 patients were excluded in final statistical calculation. One patient with category 5 refused biopsy, in 2 of them the results of physical examination and /or SMM or mammography were missed and one refused follow up examination. 62 lesions were found in mammograms. The mammograms of 3 patients were normal (category 1), one had focal hard area in palpation, one had palpable malignant-looking axillary lymph node, and one had hard nipple with bloody discharge. In those patients with multiple lesions in mammograms, the lesions with higher category included in this study. The mammographic size of the lesions were between 1 to 6 cm. 26 (40%) women had normal physical examination (non-palpable) and 39 women (60%) had palpable lesions. 47 of total women underwent excisional biopsy. 21(44.7%) lesions were benign and 26(55.3%) were malignant. In 16 patients biopsy was not done and follow up mammography after 6 months was normal or not changed. Two of patients had only FNA(blood and cyst without malignant cell).

TABLE 1. Results of ^{99m} Tc- MIBI scintigraphy

	Total	Physical exam		Size*(mm)		Category*		
		Pallpable	Non- palpable	<15	≥15	3	4	5
Total	65	39	26	24	38	28	23	11
True-positive	22	20	2	3	18	1	9	11
True-negative	28	9	19	16	11	17	10	0
False-positive	11	8	3	2	8	7	3	0
False-negative	4	2	2	3	1	3	1	0
Sensitivity%	84.5	91	50	50	94.7	25	90	100
Specificty%	71	53	88.8	88	57.8	70.8	76.3	100
PPV%	66.6	71.5	40	60	69.2	12.5	75	100
NPV%	87.5	81.8	90.4	84	91.6	85	90.9	100
Accuracy%	76.9	76.9	88.7	79.1	76.3	64.2	82.6	100

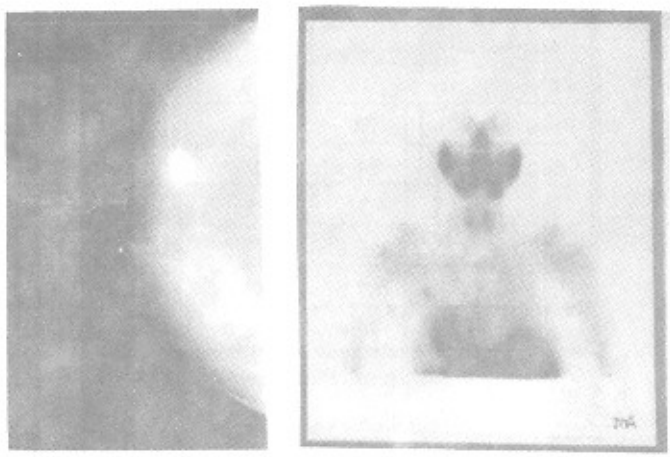
* 3 of patients had normal (category 1) mammograms which is not included in this table.

TABLE 2.Definitive Diagnosis Results of ^{99m} Tc-MIBI ScintigraphyAccording to Mammographic Degrees of Malignancy

Probability of malignancy According to mammography	Diagnosis	scintimammography	
		+	
Normal (n=3)	Nipple adenoma	1	
	Medullary carcinoma	1	
	Negative follow up mammogram		1
Probably benign finding (low, n=28)	Infiltrative ductal carcinoma	1	1
	Medullary carcinoma		1
	Intraductal carcinoma		1
	Phylloides tumor	1	
	Fibrocystic disease	1	2
	Fibroadenoma	3	5
	Leiomyoma	1	
	Cyst		1
	Normal breast tissue		1
	Negative followup mammogram	1	8
Suspicious of malignancy (Intermediate, n=23)	Infiltrative ductal carcinoma	8	1
	Medullary carcinoma	1	
	Fibrocystic disease	3	
	Fibroadenoma		2
	Normal breast tissue		1
	Hematoma		1
	Negative follow up mammogram		6
Highly suggestive of malignancy (High, n=11)	Infiltrative ductal carcinoma	11	

TABLE 3. Axillary Node Detection in SMM

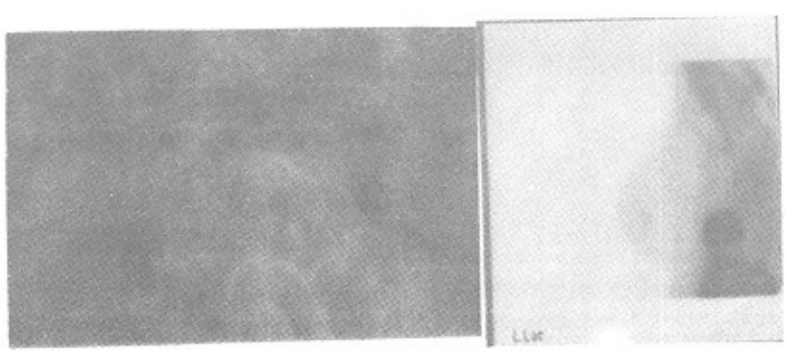
malignancy	True- positive	True-negative	False- positive	False- nagative
26	5	14	7	6



(a) (b)

Fig 1: A 42-year-old patient with lesion considered highly suggestive of malignancy on x-ray mammogram (a) SMM showed active lesion in the breast and both axillary lymph nodes (b). Histology confirmed infiltrative ductal carcinoma with axillary nodes involvement.

Fig 2: A 40-year-old patient with palpable axillary node, not detected on mammogram and considered as normal mammogram. On SMM a focus of increased uptake was seen in left breast, not axilla. Medulary carcinoma of breast was confirmed with axillary node involvement. Note that mild to moderate and superficial ^{99m}Tc-MIBI increased uptake in left axilla corresponding to cutaneous activity, should not be misinterpreted as positive metastatic lymph node (compare with Fig 1).



(a) (b)

Fig 3: A 40-year-old patient with palpable breast mass not seen on mammogram (a). but was considered as cancer on SMM (b). An infiltrative ductal carcinoma was confirmed at biopsy.

Discussion

In previous studies for evaluation of SMM in diagnosis of breast cancer, sensitivity between 83% to 95.8% and specificity between 52% and 95% is reported [1,3-8]. In our study, a sensitivity of 84.5% and a specificity of 71% was demonstrated. Thus SMM did not increase the specificity and PPV of mammography which were 71%, and 64% respectively, as previously reported [1,4].

There was a high accuracy of SMM in identifying breast cancer and, it reflected the findings of other recent studies [4,5]. Like previous study by J.B Cwikla et al. [4], our study was performed in population with a lower pre-test probability of breast cancer and with a higher proportion of benign tumors. This may explain why the specifcity of the results from this series was lower than that previously noted by khalkhali et al.,Who reported a sensitivity of 95.8% and a specificity of 86.8% [2].

We observed a higher sensitivity of SMM in palpable breast masses than in non palpable nodules (91% vs 50%, pv<0.000). Most observers had reported a sensitivity between 94% and 98% for palpable breast cancer, all of them have shown that, SMM was more sensitive in palpable masses than non-palpable ones [5,6,9]. Like most previous studies [5,6,9], there is significant higher specificity (86.3%, pv<0.000) for non-palpable lesions than palpable ones. In some studies usefullness of SMM in detection of breast cancer, and reduction of the unnecessary biopsies in non-palpable nodules was shown [10,11]. However, considering low sensitivity (50%) and low PPV (40%) in our study, we could not suggest SMM as adjunct investigation for detection of primary breast cancer in non-palpable masses.

There is direct relation between size of the lesions and radiotracer uptake in SMM. This demonstrated that sensitivity of SMM for detection of breast cancer strongly depended on not only palpability, but also size of the tumor. The low sensitivity of SMM, made us to reject its use in lesions less than 1.5 cm in diameter. Khalkhali et al belived that, size itself appears not to be the only factor affecting the uptake of ^{99m}Tc-MIBI and subsequent visualization[12]. It has been shown that tumor type may be as important as tumor size in determining whether a breast cancer is seen or not [4]. Small tumor size and a well-differentiated histotype characterize false negative cases [13].

As we expected, there is direct relation between detection of breast cancer and category of mammography. In our study there were 4 breast cancer with probably benign findings (category 3) in mammograms, which SMM detected one of them. There was only one false negative SMM for suspicious group (category 4) which was palpable, but one cm infiltrative ductal carcinoma.SMM detected all breast cancer in patients with highly suggestive of malignancy lesions (category 5). A hypothesis for non - visualization of breast cancer includes the lack of stromal reaction around tumor. ^{99m}Tc-MIBI may be accumulate in the desmoplastic or stromal reaction of the tumor as well as in the tumor. Tumor with minimal desmoplastic reaction may be difficult to be visualized. Another possibility

for non - visualization is over expression of the multidrug resistance gene.[99m] Tc-MIBI may enter into the tumor cell but be rapidly extruded [13].In spite of false negative results,SMM had high NPV in lesions suspicious of malignancy (low and intermediate).So when we have negative SMM in these groups ,which are1.5 cm or larger, we could refuse biopsy and follow the patient by routine physical exam and mammograms.

It's worth to say that, we had 2 normal mammograms which had positive SMM. one of them was medullary carcinoma of breast which was only seen in SMM.The other one was a case of adenoma of nipple. Of all false positve (11 cases) 3 were palpable fibroadenoma, 4 fibrocytic disease and one phylloides tumor. It is said that the causes of being active in SMM is the hypercellularity and adenosis in these lesions [2,4,14]. We found a leiomyoma of the breast that showed activity in SMM. It was not previously reported in literature.

Sensitivity, specificity, PPV and NPV in detection of axillary nodes involvement were as follow 45.5%, 93%, 83% and 70%. In some studies higher sensitivity for detection of axillary nodes involvement, upto 79.2% and 91.6% was reported [15,16]. The difference between our studies and previous results could be tumor size and number of lymph nodes involvement in each patient, as well as technical errors.

Conclusion

SMM has good specificity and sensitivity in detecting breast cancer, but it does not increase sensitivity of mammography. In lesions 1.5 cm or larger, and in palpable lesions the negative SMM is important, as the NPV are 91.6% and 81/8%, respectively. The most important role for SMM is in category 3 and category 4 patients, and it could reduce the rate of biopsy. SMM would be particularly useful among young women with dense breast with palpable mass because dense breast does not alter the result of SMM. SMM is not suggested for the detection of axillary lymph node involvement in patients with breast cancer, for low sensitivity. However positive axillary nodes in SMM is highly suggestive for lymph node involvement due to high specificity and high PPV.

Low sensitivity of SMM (50%) in lesions less than 1.5 cm, and low PPV(40%) in non-palpable lesions denote unusefullness of the test in these groups.

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