ORIGINAL ARTICLE

Diagnostic Accuracy of Tc-99m-MIBI for Breast Carcinoma in Correlation with Mammography and Sonography

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ABSTRACT

Objective: To evaluate the accuracy of ^{99m}Tc-MIBI scintimammography (SMM) in differentiating malignant breast cancer from benign breast mass and in detecting axillary lymph node metastasis in comparison with mammography and ultrasonography.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: At the Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Karachi, from December 2006 to May 2007.

Methodology: A total of 28 patients (both with breast lumps or/and axillary masses) included were in the study. They underwent clinical examination, mammography and ultrasound imaging followed by planar SMM using a single head detector. All subjects received a 740-1110 MBq bolus injection of ^{99m}Tc-Sestamibi. 5-10 minutes and 1 hour delayed images were acquired after the injection. SMM scans were considered positive when there was focal area of increased radiotracer uptake. Qualitative (visual) as well as quantitative evaluation of scans was done and compared with ultrasound and mammography, taking histopathology as Gold standard. Sensitivity, specificity, negative and positive predictive values (NPV and PPV respectively) were determined.

Results: There were 22 patients presenting with breast lesions (20 palpable, 2 non-palpable) and 6 patients with axillary lump. Scintimammography accurately predicted malignant lesions in the breast (sensitivity 93.3%, specificity. 71.4%, PPV 87.5%, NPV 83.3%, overall accuracy 86.4%) as well as in patients with axillary metastasis (sensitivity 100%, specificity 66%, PPV 75%, NPV 100%, accuracy 83%). A combination of scintimammography with any other imaging modality provides better results than a single test to detect breast cancer.

Conclusion: SMM has good diagnostic accuracy in the detection of breast cancer as well as in axillary metastasis in association with mammography and ultrasound.

Key words: *Scintimammography. Mammography. Ultrasound. Breast lump. Axillary mass.*

INTRODUCTION

Breast cancer is one of the leading cause of cancer deaths in women today, second only to lung cancer.[1] Early detection is the best means of improving survival for beast cancer victims. Therefore, efforts have been directed towards the development of early detection tools that would lead to a better characterization of malignant lesions.

Today X-ray mammography (XMM) remains the modality of choice for screening, due to its high sensitivity. However, it has a low positive predictive value.[2] Ultrasonography (U/S) has proven to be of benefit in separating benign simple cysts, which are unlikely to be malignant, from complex masses, which may require tissue diagnosis.[3] But its specificity is reportedly not stable. Other modalities such as thermography, CT and MRI have also failed to demonstrate an advantage over mammography.[4]

Scintimammography imaging with tumour-avid tracers (most commonly Tc-99m-Sestamibi) can accurately diagnose primary breast cancer especially in dense breast, demonstrating sensitivities of 80-94% and specificities of 73-93%.[2,5,6] Evidence further suggests that this modality may also have a role in evaluating the axillary adenopathy.[2,7]

The study was carried out to assess the clinical value of Tc-99m-MIBI scintimammography by analyzing sensitivity, specificity, positive predictive value, negative predictive value and accuracy in differentiating breast cancer from benign breast mass and in detecting axillary lymph node metastasis in comparison with mammography and ultrasonography.

METHODOLOGY

It was a comparative cross-sectional study conducted at the Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Karachi, from December 2006 to May 2007.

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Received May 29, 2008; accepted June 12, 2009.

Those who presented with palpable mass or lump in either of the breasts and/or axilla or have positive or intermediate findings on a mammogram were included in the study. Medically unstable patients, lactating or pregnant women and patients with a history of recent surgery (within a week) were excluded from the study. Selected subjects were divided into two groups of A and B respectively.

After obtaining informed consent, all of them underwent clinical examination, conventional mammography and ultrasonography, followed by planar scintimammography (SMM). SMM images were acquired using a single headed gamma camera equipped with a Low-Energy All Purpose (LEAP) collimator, 10 minutes (early) and 60-90 minutes (delayed) after an intravenous injection of 740 MBq (20 mCi) Tc-99m-Sestamibi in the antecubital vein contralateral to the affected breast or in the dorsalis pedis vein of either foot. Images were obtained in prone lateral and supine anterior position with arms raised above the head to improve the visualization of the axilla. For prone lateral imaging, patients were laid in a prone position on a foam cushion designed for breast imaging overlying the imaging table, which permitted the breast to hang freely.

The images were analyzed visually as well as quantitatively. For visual analysis, assessment of scintimammograms was done by two independent, experienced nuclear medicine physicians, who were blinded to the clinical information of the patients. Disagreements between the two were resolved by consensus, with a third observer acting as a referee and evaluated for focal uptake in the tumour mass and axillary lymph node. Any focal high intense radiotracer activity greater than surrounding background activity, was accepted as a positive result (Figure 1).

Quantitative analysis of scans was performed using Regions Of Interest (ROIs) techniques and tumour to normal background ratio (T/B) was calculated for the early and delayed images.

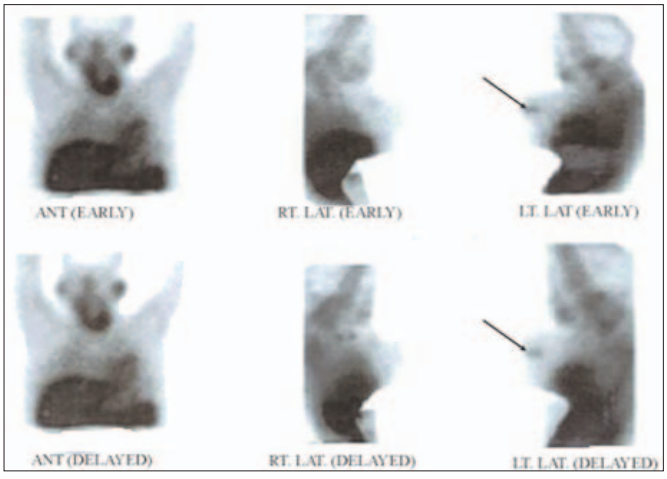

Figure 1: A 55-year-old female presented with mass in the upper outer quadrant of left breast.

Later on, all patients underwent core biopsy of the breast/axillary lesions. Comparison was done between imaging modalities and histopathology; the latter taken as a Gold standard.

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of scintimammography, mammography and ultrasound were calculated. Fischer's exact probability test was applied to compare the level of significance between the imaging modalities, used in the study with histopathological results. Student's t-test was applied to find the relationships between the quantifiable data (i.e. mean ± S.D of early and delayed counts). Correlation between scintimammography, mammography and ultrasonography was performed by using the Pearson correlation. A statistically significant difference was considered when p-values were < 0.05.

RESULTS

A total of 28 women (mean age, 36.5 years; median age, 40 years; ranging from 17-80 years) were included in the study. Twenty two women presented with primary breast lump (20 palpable, 2 impalpable), without axillary lymph node involvement, while 6 had at least one axillary palpable lymph node along with the primary breast tumour.

Out of the 20 patients with palpable breast lesions, 10 presented with masses on the left side while 9 patients had a mass on the right side and the remaining one patient had bilateral masses. Two patients had mass on left side on mammogram but impalpable clinically. Most of the lesions were characterized as infiltrating ductal carcinoma on histopathology.

Scintimammography was positive in 16 out of 22 patients. It was true positive in 14 patients (93.3%) and false positive in 2 patients (28.6%), one of them detected to have fibro adenoma and the other as chronic inflammatory disease. Five patients (71.4%) were found to be true negative and 1 patient (6.7%) was detected as false negative (Table I).

The sensitivity of ^{99m}Tc-MIBI scintimammography in detecting primary breast cancer is 93.3%, the specificity is 71.4%, positive predictive value is 87.5%, negative predictive value is 83.3%, and the accuracy is 86.4% (Table I).

The sensitivity, specificity, PPV, NPV and accuracy of mammography were found to be 73.3%, 80%, 91.7%, 50% and 75%. Similarly, the sensitivity, specificity, PPV, NPV and accuracy of ultrasonography were found to be 80%, 71.4%, 85.7%, 62.5% and 77.3%.

When comparison was done among different imaging modalities, the p-value obtained for SMM was 0.004 much more significant than other modalities (Table I).

Table I: Results of the imaging studies in group A.

	TP	FP	TN	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	P-value
SMM	14	2	5	1	93.3	71.43	87.5	83.3	86.4	0.004
XMM	11	1	4	4	73.33	80	91.7	50	75	0.05
U/S	12	2	5	3	80	71.43	85.7	62.5	77.3	0.02

TP=true-positives; FP=false-positives; TN=true-negatives; FN=false-negatives; PPV=positive predictive value; NPV=negative predictive value; SMM=$_{99m}$Tc-sestamibi scintimammography; XMM= Mammography; US=Ultrasonography; P-value=represents Fisher's probability test value.

Table II: Results of the imaging studies in group B.

	TP	FP	TN	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	P-value
SMM	3	1	2	0	100	66.67	75	100	83.33	0.20
XMM	2	1	2	1	66.67	66.67	66.67	66.67	66.67	0.45
U/S	2	1	2	1	66.67	66.67	66.67	66.67	66.67	0.45

TP=true-positives; FP=false-positives; TN=true-negatives; FN=false-negatives; PPV=positive predictive value; NPV=negative predictive value; SMM=$_{99m}$Tc-Sestamibi scintimammography; XMM= Mammography; US=Ultrasonography; P value=represents Fisher's probability test value.

Six patients were presented with single or multiple axillary lumps. Two patients had lumps in the right axilla and four on the left side. The most common malignancy found was infiltrating ductal carcinoma.

Scintimammography was positive in 4 out of 6 patients, and it was true positive in 3 patients (100%) and false positive in only 1 patient (33.3%), later on diagnosed as chronic inflammation on biopsy. Two patients (66.6%) were found to be true negative while there was no false negative case (Table II).

Sensitivity of ^{99m}Tc-MIBI scintimammography in diagnosing axillary lymph nodes metastasis was found to be 100%, the specificity was 66.6%, positive predictive value was 75%, negative predictive value was 100% and the accuracy was 83.33% (Table II).

The sensitivity, specificity, PPV, NPV and accuracy of mammography, all were found to be 66.7%. Similarly, the sensitivity, specificity, PPV, NPV and accuracy of ultrasonography were found to be 66.7%. The insignificant p-value i.e. > 0.05 was obtained for all the three modalities, when comparison was done among them (Table II).

To evaluate the importance of double phase SMM, student's t-test was applied for both groups. The results of t-test were found to be insignificant (p > 0.05), (Table III).

Table III: Statistical analysis of double phase T/B ratio.

Population	Number of patients	Early T/B Mean±SD	Delayed T/B Mean±SD	t-value	p-value
Group I	22	1.495 ± 0.460	1.447 ± 0.460	0.32	> 0.05
Group II	06	2.287 ± 1.194	2.013 ± 1.157	0.40	> 0.05

Correlation co-efficient between SMM and XMM in group A was found to be 0.97 with a p-value of 0.022. Therefore correlation co-efficient was highly significant between the two tests. But in group B it was found to be 0.89 with a p-value of 0.052. That was not significant in this group.

Correlation co-efficient between SMM and ultrasound in group A was found to be 0.99 with a p-value of 0.006. Therefore, correlation co-efficient is highly significant between the two tests. But in group B it was found to 0.89 with a p-value of 0.052. Hence, the correlation co-efficient in group B was not significant.

DISCUSSION

A total of 28 patients were included in the study. The mean age in this studied group is lower as compared to the United States but comparable with other studies in Pakistan.[8] This is probably due to the fact that the Pakistani population is younger and their life expectancy is lower than that of the United States.[9]

The exact mechanism of MIBI as a tumour-imaging agent is not very clear. It is reported that MIBI is accumulated within mitochondria (90% of tracer activity) and cytoplasm of cells on the basis of transmembrane electrical potentials.[10,7,11] Malignant tumours show increased transmembrane potentials due to increased metabolic requirements, which induce increased accumulation of MIBI in tumours.[12,13]

In this study, there was found a very high sensitivity 93% for the detection of primary breast cancer, which is comparable with the results of other studies. Taillefer and Khalkhali reported a sensitivity of 91.5% and 93.7% respectively.[14,15] The reason behind such good sensitivity is that typical diagnostic mammography uses X-rays with maximum energies of 20-40 Kev which can be highly attenuated by dense breast and mask certain tumours while in SMM the energy currently used is higher (140 Kev) which is unaffected by the dense fibro-landular breast.[14,3,16] Likewise, ultrasonography had the operator skill dependency, which is not in the case of scintimammography.[16] In addition, both mammography and ultrasound determine the nature of disease by the pattern of structural abnormalities in the breast,[17] while SMM exploits the functional differences of lesions from normal tissue to aid in detection.[4,18]

There was a relatively low specificity of ^{99m}Tc-MIBI scintimammography in detecting primary breast cancer; 70% as compared to Taillefer *et al.* and Khalkhali *et al.* i.e.; 94.4% and 98.8%.[14,15] That was because there were two false positive cases in the study i.e. fibro-adenoma and chronic inflammatory disease. This false

positive effect is caused by increased vascularity as well as cell metabolism in these diseases, as MIBI uptake is directly related to blood flow and mitochondrial transmembrane electronegativity and inversely related to necrosis and fibrosis.[18] In addition to this, there was one false negative case. It strongly correlated with the histological size of the lesion i.e., < 10 mm, as reported by other studies.[19,20]

In order to detect axillary lymph node metastasis, the role of Tc-99m-MIBI scintigraphy has been investigated.[21] Taillefer *et al.* reported the sensitivity of 79.2% and specificity of 84.6% of Tc-99m-Sestamibi breast scintigraphy in evaluating metastatic axillary lymph nodes.[22] In this study, we have sensitivity of 100% and specificity of 66.0%. The sensitivity is good when compared to other reports (i.e. Taillefer *et al.* and Lam *et al.* i.e. 90.9% and 90% respectively),[7] which are better than physical examination, axillary X-ray picture and ultrasound. The reason behind this is that in the present study a majority of the patients came to the hospital after they had found a mass in the breast or axilla and at the time of diagnosis they were all in an advanced stage or intermediate stage of breast cancer. But still there was one false positive case, which was not detected by mammography and ultrasound. That was the lymph node with chronic inflammation. Perhaps SMM reported this lesion as malignant because of the rich blood flow in this inflammatory tissue.[18]

The results of planar quantitative study demonstrate that Tc-99m-Sestamibi concentrates into malignant breast tumours with a contrast ratio of 1.47 ± 0.49, while in the case of axillary lump this ratio is 2.15 ± 1.17 when compared with normal surrounding tissue. Taillefer *et al.* showed in their study, that tumour to background ratio was 2.2 ± 0.7. Similarly another study by Khalkhali *et al.* found this ratio to be 2.13 ± 0.93.[15,22] Furthermore, when a comparison was done regarding the early and delayed imaging, no significant difference was obtained in the T/B ratio, implying the delayed imaging was ineffective. Le *et al.* also found that delayed-phase imaging did not enhance the diagnostic accuracy.[23,24]

We also used a combination of mammography and ultrasound with scintimammography. It is concluded that the use of any two complementary techniques along with SMM in the detection of breast cancer provides the most accurate diagnosis. Buscombe *et al.* reported a combined sensitivity, specificity; PPV and NPV of 93%, 72%, 80% and 90% respectively, while comparing the usefulness of mammography and scintimammography in identifying primary breast cancer.[17] However, for axillary metastasis detection, our study results rendered a combination of the tests as ineffective.

We recognize that there are a few limitations and possible biases in our study. First of all, our results were influenced by referral bias. In addition, a large proportion of insufficient samples reduced the usefulness of SMM for the evaluation of non-palpable breast lesions and axillary metastasis.

CONCLUSION

This study showed that Tc-99m-SestaMIBI scintigraphy improved the overall accuracy rate for breast cancer. It may provide additional information in differentiating malignant and benign lesions in patients with palpable breast masses. Detection capability also improved for non-palpable lesion and axillary lymph node metastasis.

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