

ORIGINAL ARTICLE

Advantages of ROC analysis in the diagnosis of breast tumours using combined x-ray mammography and scintimammography

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Abstract

Aims To evaluate the postulate that a combination of x-ray mammography (XMM) and scintimammography (SMM) using receiver operating characteristic (ROC) statistical technique is better than either imaging used alone in the diagnosis of early breast cancer.

Methods A cohort of 27 patients with 30 breast tumours was studied prospectively. The patients underwent a clinical examination, XMM and SMM, followed by fine needle biopsy/excision biopsy. The findings on XMM and SMM were divided into five grades: (1) probably normal, (2) probably benign, (3) equivocal, (4) probably malignant and (5) definitely malignant. Sensitivity and specificity were determined and ROC curves were drawn for XMM and SMM and compared against combined XMM and SMM.

Results The overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for XMM were calculated at 77%, 82%, 77% and 82% respectively; 85%, 94%, 92% and 89% for SMM; and for combined XMM and SMM, the values were 92%, 94%, 92% and 94% respectively. ROC curves were drawn and analysis of areas under ROC curves yielded values for XMM, SMM and combined imaging (XMM+SMM) at 0.85, 0.90 and 0.93 respectively. Wilcoxon signed ranked test showed that *p* value for XMM and result of combination images (XMM+SMM) was close to significant at 95% confidence level (i.e. 0.06) and the *p* value for SMM and combination images (XMM+SMM) was also close to significant at 95% confidence level (i.e. 0.062). The *p* value for XMM and SMM was not significant.

Conclusion The study shows that a combination of XMM and SMM, is more accurate in the diagnosis of early breast cancer than XMM or SMM alone. The study further suggests a role for SMM in equivocal breast lesions documented on XMM.

***Key words**: X-ray mammography, scintimammography, Receiver Operating Characteristic analysis*

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Introduction

Breast cancer, has been a challenge for physicians throughout the ages. Despite centuries of theoretical studies and scientific inquiry, breast cancer remains one of the most dreaded of human diseases. However, progress has recently been made to counter the physical and psychological aspects of the disease [1]. It is the most common cancer affecting women today and the incidence of breast carcinoma is increasing with an age-adjusted reported incidence rate of 106 to 110 per 100,000 women [2, 3]. Current statistics show that approximately 1 in 9 women will develop invasive breast cancer during her lifetime [4].

In Pakistan, breast carcinoma accounts for almost 26.6% of all female cancers [5 ,6]. The incidence is higher in younger age [7, 8]. The reasons for a higher breast cancer mortality and morbidity in Pakistani population as compared to those reported in international literature are the socioeconomic factors and the fact that most patients have advanced disease at presentation [9].

Regular breast self-examination, physical examination by experienced medical professionals and screening mammography after age of 50 years, are effective in reducing the morbidity and mortality. Several studies have shown the efficacy of screening mammography in the detection of early breast cancer [10-12]. Easy access to medical care, advancement in medical imaging technologies, better guidelines and better trained technologists, have all resulted in 25-30% reduction in the relative risk of dying from breast cancer in western women older than 50 years [13].

Other complementary imaging techniques, such as breast ultrasonography, color Doppler ultrasound, CT, MRI, and digitalization of mammograms with artificial neural network analysis, have been developed to improve the sensitivity and specificity of mammography in the diagnosis of breast cancer [14]. These complementary procedures are only useful as problem solving techniques but the search for more reliable methods to complement the existing diagnostic modalities in breast cancer continues [4].

Functional imaging can complement structural imaging and can help significantly increase the sensitivity and specificity in breast cancer diagnosis. Many radionuclide imaging techniques have been evaluated [15-17] using different radiopharmaceuticals including ^{201}Tl, ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin, ^{18}F-fluoro deoxyglucose and ^{99m}Tc-methylenediphosphonate [18-20].

In the present study, a combination of functional and structural imaging was performed in patients with breast cancers and the postulate that a combination of X-ray mammography (XMM) and scintimammography (SMM) using receiver operating characteristic (ROC) statistical technique, is better than either imaging used alone was tested.

Materials and Methods

A prospective study of 27 female patients (aged 25-80 years) with 30 breast tumours, was performed at the Institute of Radiotherapy and Nuclear Medicine, Peshawar. All patients were subjected to XMM and SMM followed by surgical or needle biopsy of the tumour. Histopathological findings were considered as gold standard. XMM were read by two experienced breast radiologists and SMM were read by two experienced nuclear medicine physicians independently. The Society of Nuclear Medicine Guidelines for SMM were followed and consulted for interpretation [21-29].

Inclusion criteria included: palpable breast mass, positive or equivocal XMM or discrepancy between physical examination and the XMM findings. Exclusion criteria included: recurrent breast cancer or previous mastectomy/chemotherapy, recent surgery (within 2 weeks), FNA (one week) or core biopsy (one month).

XMM was carried out with a Metaltronica FLAT SE, dedicated mammography unit. SMM was carried out using 740-1,110 MBq (20-30 mCi) of intravenous ^{99m}Tc-MIBI and the imaging was performed with a Siemens E.CAM gamma camera.

XMM and SMM image Interpretation

Mammographic images were graded from 1-5 as: *Grade 1*: definitely normal or benign: no dominant masses, architectural disturbance or suspicious microcalcifications present or benign finding like lipoma, secretory calcifications or calcified fibroadenoma; *Grade 2*: probably benign or a high probability of being benign; *Grade 3*: equivocal or indeterminate when images were not clear because of high density of the breasts or did not match the physical examination; *Grade 4*: probably malignant with a very high probability of malignancy although appearance not characteristic of malignancy. Appearances highly suspicious with indirect signs of breast cancer on imaging (i.e. focal architectural distortion, asymmetric breasts, ductal asymmetry and microcalcifications without mass); and *Grade 5*: definitely malignant with the images showing a high probability of malignancy (e.g. speculated opacity with or without microcalcifications, irregular border of the opacity in the fatty breasts, etc.).

Scintimammography images were graded as: *Grade 1*: definitely normal or benign with homogeneous uptake in both breasts; *Grade 2*: probably benign or a high probability of being benign; *Grade 3*: equivocal with diffuse homogenous or nonhomogenous diffuse activity without focal accumulation; *Grade 4*: probably malignant or a high probability of being malignant; and *Grade 5*: definitely malignant with focal uptake of ^{99m}Tc-MIBI.

Statistical Analysis using ROC curves

Receiver Operating Characteristic (ROC) curves were drawn for XMM and SMM images scored on a five point grading system. ROC curves were drawn for XMM, SMM and combination image (XMM + SMM). XMM and SMM image interpretation grading was done as: definitely normal (grade 1), probably normal (grade 2), equivocal (grade 3), probably abnormal (grade 4) and definitely abnormal (grade 5). Combination image was defined as highest score obtained with either study, i.e. if XMM was scored 1 and SMM scored 2, the combination image was scored 2. True negatives were defined as histopathologicaly benign and image scoring of 1 and 2 (definitely and probably benign). True positives were defined as histopathologically malignant and image scoring of 4 and 5 (probably and definitely malignant). False-negatives were defined as histopathologically malignant and image scoring of grade 1, 2 or 3 (definitely benign, probably benign or equivocal). False-positives were defined as histopathologicaly benign and image scoring of 3, 4 and 5 (equivocal, probably malignant or definitely malignant). Sensitivity and specificity were calculated and receiver operating characteristic curves were drawn with sensitivity on the Y-axis and 1-specificity on the X-axis for XMM, SMM and the result of combination imaging. Area under the receiver operating characteristic curves for all the three modalities was determined by trapezoidal rule. Wilcoxon signed ranked test was used to calculate *p* values for the results of XMM and SMM, XMM and combination imaging, and SMM and combination imaging.

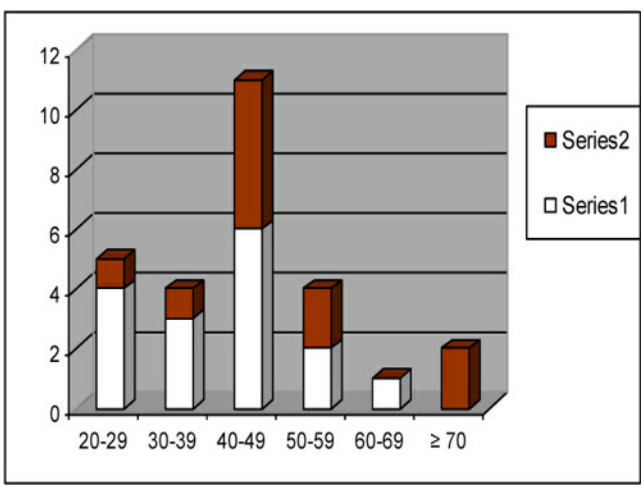

Figure 1 *Bar chart shows study population of benign (series 1) and malignant (series 2) lesions according to age*

Table 1 *Data showing results of histopathology, XMM and SMM**

Case	Age (yr)	Clinical exam	Tumour size (mm)	Histopathology	XMM Grade	SMM Grade	XMM+ SMM Grade
1	80	Left breast nodule	11x10	IDC	2	5	5
2	60	Left breast lump	13x11	FCD	3	1	3
3	45	Left breast lump	22x12	FCD	1	1	1
4	35	Left breast lump	11x08	CNM	2	1	2
5	40	Left breast lump	30x25	FD	1	4	4
6	50	Left breast lump	25x22	IDC	5	5	5
			10x08	IDC	1	1	1
7	42	Left breast lump	22x12	PDC	3	4	4
8	42	Left breast lump	11x10	IDP	1	1	1
9	28	Right breast lump	22x12	BMD	3	3	3
10	28	Left breast lump	10x10	FCD	1	1	1
11	50	Left breast nodule	12x10	mastitis	1	1	1
12	50	Left breast lump	8x8	FCD	1	1	1
13	20	Right breast lump	15x13	galactocoele	2	3	3
14	50	x2 lumps right breast	14x12	IDC	5	5	5
			15x10	IDC	5	5	5
15	40	Right breast lump	55x52	IDC	5	5	5
16	35	Left breast lump	12x10	LC	1	4	4
17	36	Left breast lump	20x15	FCD	1	1	1
18	22	Left breast lump	15x10	FD	2	1	2
19	48	Right breast nodule	10x10	FD	1	1	1
20	40	Left breast lump	10x09	FD	1	1	1
21	70	Left breast lump	35x30	IDC	5	5	5
			12x11	IDC	5	1	5
22	44	Right breast + axillary mass	11x10	FD	2	1	2
23	45	Right breast lump	20x18	IDC	3	4	4
24	40	Right breast lump	12x12	IDC	3	4	4
25	35	Left breast lump	07x06	Mastitis	1	1	1
26	26	Left breast lump	35x21	IDC	5	5	5
27	42	Left breast lump	10x10	Mastitis	3	1	3

** XMM = mammography, SMM = scintimammography, XMM+SMM = combined mammography & scintimammography, IDC = Invasive ductal carcinoma, FCD = fibrocystic disease, CNM = chronic non-specific mastitis, PDC = poorly differentiating carcinoma, LC = Lobular carcinoma, IDP = Intraductal papilloma, BMD = Benign mammary dysplasia, FD = Fibroadenoma.*

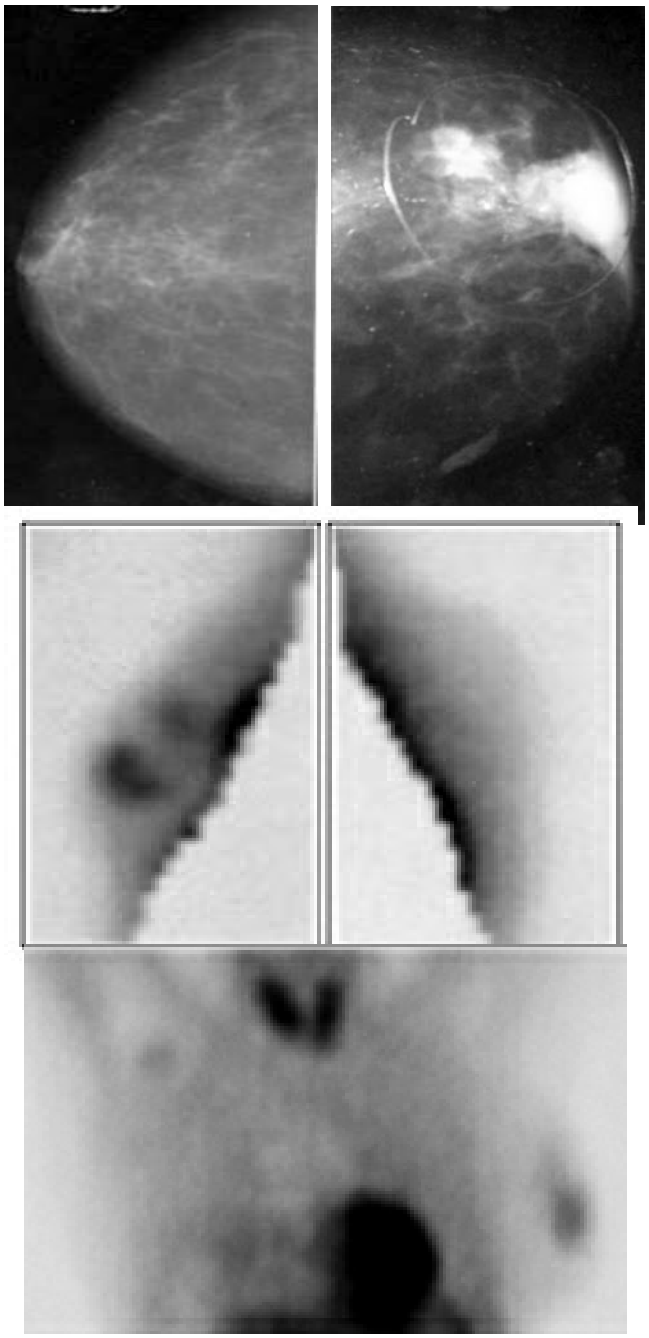

Figure 2 *(Top) XMM CC view of right & left breasts showing two grade 5 XMM radiodense lesions in left breast; (Middle) SMM left lateral & right lateral and (Bottom) anterior view of same patient showing two SMM Grade 5 malignant lesions in left breast. High activity in the thorax is masked. Biopsy showed IDC. Note: focal area of activity in the right axilla is suspicious for a malignant lymph node*

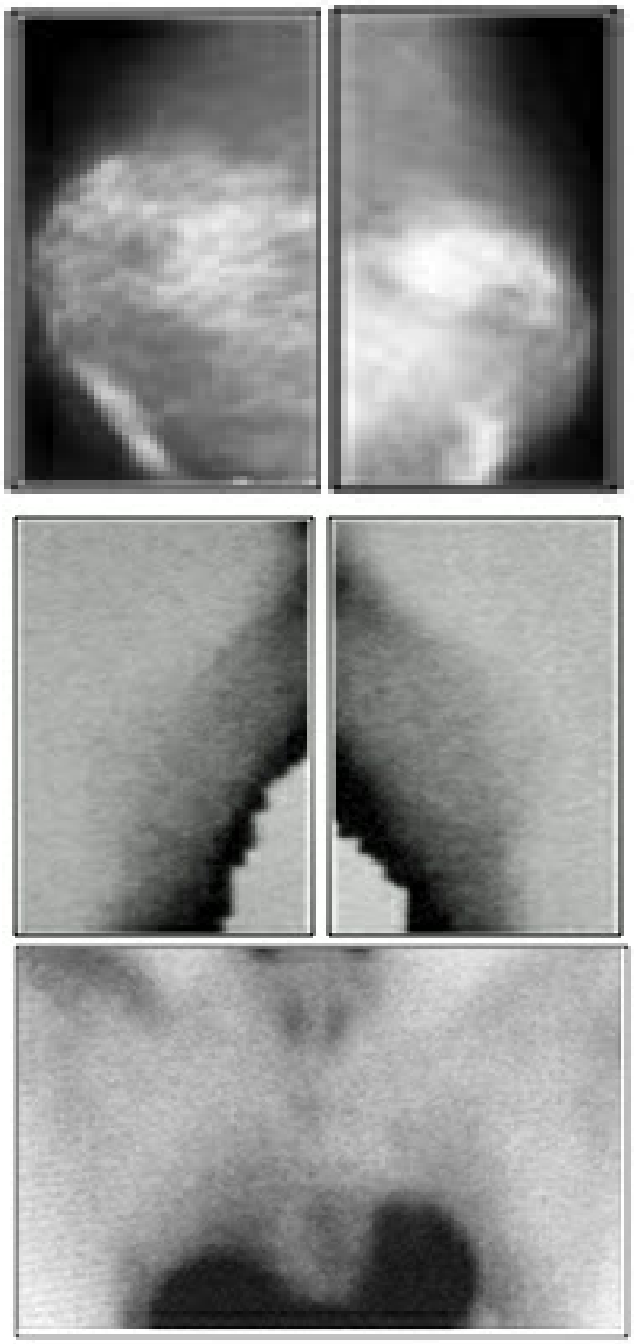

Figure 3 *42-year-old with left breast nodularity. (Top) XMM MLO view right and left breast showing glandulofatty pattern in both breasts with an opacity in the left breast retracting the parenchymal tissue. Findings are equivocal for benign/ malignancy left breast (XMM grade: 3); left & right lateral (Middle) and anterior view (Bottom) of SMM shows homogeneous tracer uptake of left breast consistent with normal SMM. Biopsy showed mastitis*

Results

Total of 27 patients with 30 breast tumours were included. Thirteen tumours were malignant and 17 benign confirmed by histology. The distribution of the population according to age is shown in Figure 1. The individual tumour sizes and histopathology results are detailed in Table 1.

Histopathology results Of the 13 malignant lesions, 11 were invasive ductal carcinomas (Figure 2), one was poorly differentiated carcinoma and one was invasive lobular carcinoma. Seventeen lesions were benign. In the benign group, 5 were fibroadenomas, 5 fibrocystic disease, 4 mastitis (Figure 3) one ductal papilloma, one benign mammary dysplasia and one galactocoele.

Image evaluation XMM, SMM and combination (XMM+SMM) images were categorized into 5 grades separately and sensitivity and specificity was calculated. ROC curves constructed for XMM, SMM and combined (XMM+SMM) images (Figure 4).

To determine the accuracy of the studies, area under the ROC curve was calculated by trapezoidal rule. Table 2 below shows the area under ROC curves calculated by trapezoidal rule. As shown in the Table 2, area under the ROC curve for combined XMM+SMM came out to be 0.93, whereas for SMM it was 0.90 and for XMM it was 0.85.

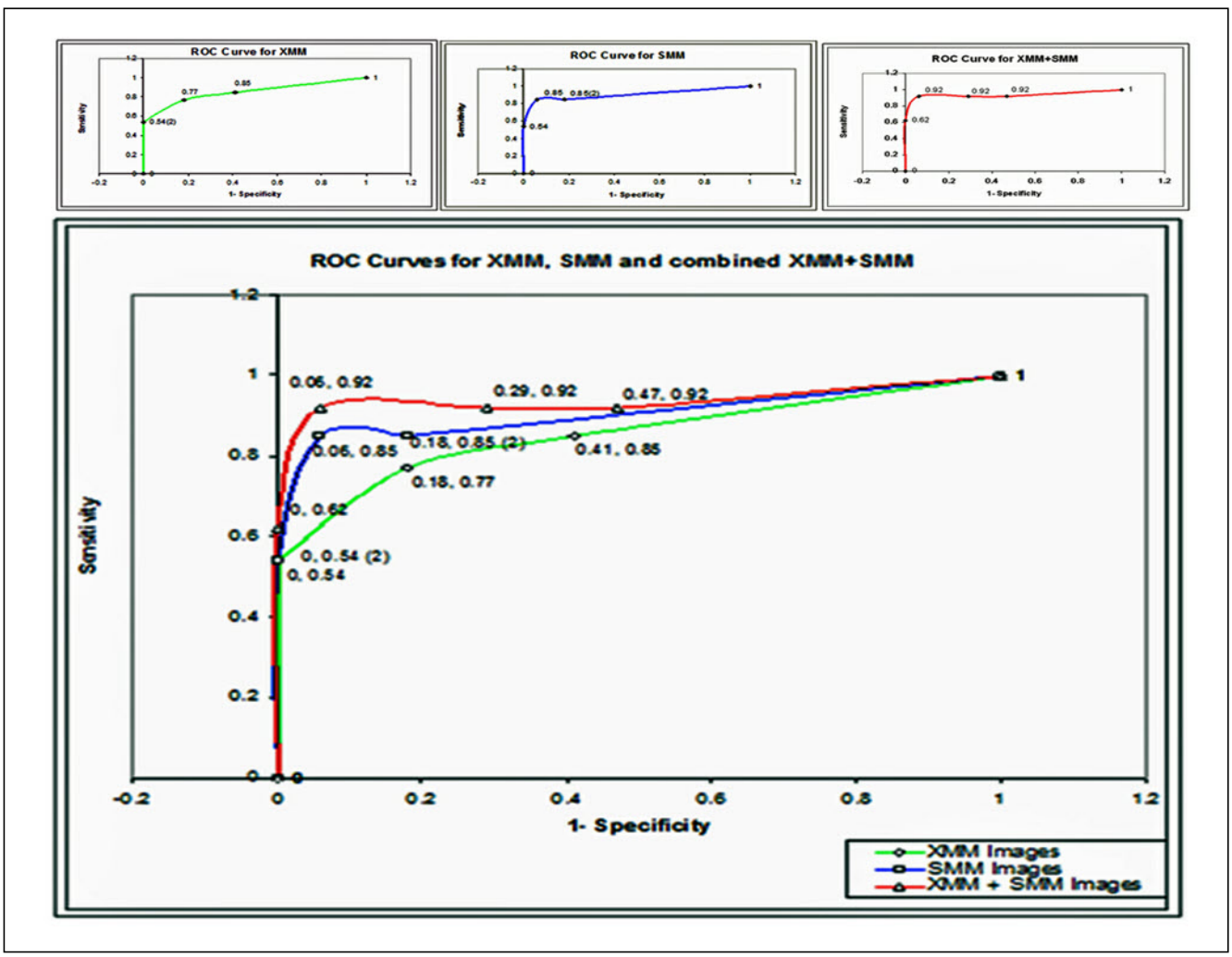

Figure 4 *Top row showing ROC curves for XMM (left), SMM (middle) and XMM+SMM (right); bottom row showing all the three ROC curves in one graph*

Table 2 Area under ROC curves

Imaging modality	Area under ROC curve
XMM	0.85
SMM	0.90
XMM+SMM	0.93

The results show 85% probability of correctly distinguishing a normal from an abnormal subject based on the relative ordering of the mammographic reading. There is a 90% probability of correctly distinguishing a normal from an abnormal subject on the basis of SMM. The probability of accurate diagnosis of breast cancer is increased to 93% when XMM and SMM are combined. Wilcoxon signed ranked test showed that *p* value for XMM and result of combined imaging (XMM+SMM) was close to significant at 5% level of significance ($p = 0.06$). The *p* value for SMM and combined imaging (XMM+SMM) was also close to significant at 5% level of significance ($p = 0.062$). The *p* value for XMM and SMM was however not significant.

The overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined. Mammography correctly diagnosed 10 out of 13 malignant lesions. Of the 3 false-negatives, two were 11mm and 10mm invasive ductal carcinomas and one was 12mm lobular carcinoma. In benign lesions, 3 were reported as false-positive and included fibrocystic disease, benign mammary dysplasia and mastitis. Therefore the sensitivity, specificity, PPV and NPV for XMM were calculated at 77%, 82%, 77 % and 82% respectively.

SMM correctly diagnosed 11 out of 13 malignant lesions. The two false-negatives included a 10mm and 12mm invasive ductal carcinoma. The 3 false-positives were a fibroadenoma, a benign mammary dysplasia and a galactocoele. The sensitivity, specificity, PPV and NPV for SMM came out to be 85%, 94%, 92% and 89% respectively.

For combined XMM and SMM the sensitivity, specificity, PPV and NPV were calculated at 92%, 94%, 92% and 94% respectively. There was one 10mm invasive ductal carcinoma that could not be seen with either modality.

Discussion

Functional imaging complements XMM and significantly increases the sensitivity and specificity of the test. SMM detects abnormal tumour uptake of ^{99m}Tc-sestamibi, which is the only radiopharmaceutical currently approved by the US Food and Drug Administration for SMM [30]. It is a lipophilic cationic complex and its uptake correlates with perfusion, high intracellular levels of mitochondria and cell viability. Strong electrostatic attraction occurs between the positive charge of the lipophilic ^{99m}Tc-sestamibi and the negatively charged mitochondria. This is the main reason given by most researchers for the higher sensitivity and specificity of SMM compared with XMM. Unlike XMM, the result of SMM is dependent upon increased uptake rather than the structural appearance of the lesion. Increased density of normal breast or altered density resulting from previous surgery or radiotherapy negatively affects the specificity of XMM, which however is not the case with SMM [27, 31-34].

Our research hypothesises that there is a significant difference between the accuracy of combined XMM and SMM when compared with XMM or SMM performed as a single test. Our study reconfirms the higher accuracy of combined conventional XMM and SMM when compared with XMM or SMM alone in a cohort of local subjects. This result is comparable to results from similar studies in a European population [30, 35]. The present study however shows a higher sensitivity and specificity for both XMM and SMM in comparison with statistics quoted in literature. Since women in our population usually present with comparatively larger breast masses, the sensitivity and specificity were respectively 77% and 82% for XMM and 85% and 94% for

for SMM. These figures are in the upper ranges in literature from other countries [30, 35]. We assume that breast cancer awareness and availability of medical care in those countries is significantly higher compared with Pakistan.

ROC curve analysis is one of the most reliable and elegant methods for determining the accuracy of a diagnostic test. It measures sensitivities and specificities over a wide range of data, both qualitatively and quantitatively. Test results are placed in several pre-determined categories of response rather than simply positive or negative. The benefit of this method of result interpretation is that the test under investigation can be scrutinized more intensively over a wide range of possible results and disease presentations.

Comparing the results of this study to similar studies in the literature, Fenlon *et al* reported the sensitivity of XMM at 81%, specificity at 82%, PPV at 85% and NPV at 87.5% for palpable masses [36]. A 5-year period retrospective study of 353 consecutive patients with 374 suspicious lesions imaged with XMM and SMM for suspected breast cancer by Buscombe *et al* reported the results of XMM, SMM and sequence imaging (combination of XMM and SMM); the sensitivity, specificity, PPV and NPV for XMM were reported as 70%, 69%, 73% and 66% respectively [35]. For SMM the values were 89%, 71%, 79% and 84% respectively. For combined XMM and SMM the values were reported as 93%, 72%, 80% and 90% respectively. A large multi-centre trial of SMM, with 673 patients from 30 institutions showed an overall sensitivity of 85% and specificity of 81% for diagnosis of breast cancer. These patients had palpable masses or mammographically detected lesions. For palpable masses, the sensitivity was better with a reported sensitivity and specificity of 95% and 74% respectively. The sensitivity and specificity for non-palpable masses were reported as 72% and 86% respectively. The sensitivity was lower for non-palpable masses. Another large multi-centric study recruited 530 patients with palpable breast masses with a reported sensitivity and specificity of 90% and 87.5% respectively; NPV value was reported as 99% whereas PPV was 50.8% [30].

p-values were computed and applied to the research hypothesis. We were successful in detecting a "close to significant " difference with a *p* value of 0.06. After analysis of areas under the ROC curves, the values for conventional XMM, SMM and combined imaging (XMM+SMM) were 0.85, 0.90 and 0.93 respectively. This study shows no significant difference between XMM and SMM. Close to significant difference ($p = 0.06$) was observed between XMM and combined imaging (XMM+SMM). Similarly, close to significant difference was observed for SMM and combined imaging ($p = 0.062$). Comparing this result to similar studies in literature, area under the ROC curves was reported as 0.79, 0.85 and 0.93 for XMM, SMM and combined imaging (XMM+SMM) respectively. In a similar work, analysis of areas under the ROC curves showed no significant differences between SMM and XMM but significant differences ($p < 0.05$) were found between SMM and combined imaging and between XMM and combined imaging [35]. The present study showed close to significant difference between XMM and combined imaging and SMM and combined imaging, in spite of the fact that the sample size was small.

This study confirms that a combination of XMM and SMM provides a better evaluation of breast masses than any single test alone and that the methods can be used as effectively in our local population as in the reported European studies.

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