DIAGNOSTIC ACCURACY OF 99mTc METHOXYISOBUTYLISONITRILE (MIBI) SCINTIMAMMOGRAPHY IN DETECTION OF BREAST CANCER

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ABSTRACT

Objective: To evaluate the diagnostic accuracy of Scintimammography as a reliable diagnostic modality for detecting carcinoma breast keeping histopathology as a gold standard for final diagnosis.

Study Design: Cross sectional validation study.

Place and Duration of Study: Nuclear Medical Centre (NMC), Armed Forces Institute of Pathology (AFIP) Rawalpindi, from Oct 2016 to Apr 2017.

Methodology: 738-1100 MBq (20-30 mCi) of 99mTc methoxyisobutylisonitrile (MIBI) was injected intravenously in the contralateral arm to the affected breast, in case of bilateral breast lumps tracer was injected in foot. Planar Images were acquired in prone and supine positions at 20 and 60 min. Gamma camera was equipped with low energy all-purpose collimator. Photopeak centered at 140 Kev (Kiloelectron volt) with 20% window, and matrix size of 256X256 pixels.

Results: Total 96 patients were included in the study. After scintimammography each patient underwent FNAC/ TRUCUT for histopathological diagnosis. The age of patients ranged from 20-74 years. The mean age of presentation was 43.22 ± 12.59 years. Diagnostic accuracy was calculated for 96 patients. Fifty three had true positive (TP) while 37 had true negative (TN) results. The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of the study was 98.1, 88.1, 91.4, 97.4% respectively and an accuracy of 93.75%.

Conclusion: This study has shown an excellent sensitivity, specificity in detection of malignant mitotic lesions of breast, although any test with <100% negative predictive values is not reliable but a negative predictive value >85% is worth trying for especially in patients where Mammography may not be of much benefit. The patient will benefit from non-invasive, non-painful modality with less need for biopsy.

Keywords: Breast cancer, Breast imaging, Scintimammography, 99mTc MIBI.

INTRODUCTION

Breast cancer (Ca) is the most common and feared cancer among females. In Pakistan breast cancer carries the overall prevalence of 31%. However, the epidemiology of any cancer is difficult to describe because of lack of a proper national tumor registry process in Pakistan[1]. The risk factors for developing breast cancer are lack of breast feeding, obesity, unmarried marital state, smoking, postmenopausal state and lack of physical activity[2].

The important causes of advanced presentation include majority of people living in rural areas, lack of education and awareness, low socioeconomic status, lack of access to medical facilities and non-availability of screening tools[3]. Early diagnosis and management have a profound role in the 5-year survival of patient. Screening contributes a lot in early recognition of disease among high risk ladies. Triple assessment, a combination of self-examination, imaging and pathology carries an accuracy of 99% for correct diagnosis of breast lumps[4]. The imaging modalities available are Ultrasound Breast (Sonomammography), Mammography, MRI Breast, Computed Tomography (CT) Breast, scintimammography and histopathological diagnosis both Fine needle aspiration cytology (FNAC) and core needle biopsy. European Society for Medical Oncology (ESMO) has given the guidelines for diagnostic workup of Primary Breast Cancer (table-I)[5]. Breast Imaging Reporting & Data System (BIRADS) assessment criteria was developed in 1993 by American College of Radiology (ACR) the BIRADs mammographic report gave information about breast density, imaging findings, assessment and management[6]. Study has shown that increased breast density increases the risk of having breast cancer and reduces the ability of mammography to pick up breast cancer[7]. In a study carried out on 936 participants Mammography gave a diagnostic yield of 3.2/1000 while Gamma Imaging gave a diagnostic yield of 9/100. Gamma Imaging significantly increased the detection rate of Ca breast in mammographically dense breasts[8]. 99mTc MIBI a tumor imaging agent, accumulates in lesions having increased number of

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Received: 31 Jan 2019; revised received: 21 Aug 2019; accepted: 26 Aug 2019

mitochondria, vascularity and mitosis. Scintimammography is a noninvasive, non-painful technique with lesser radiation exposure. Mammography has two and a half times higher benefit to risk ratio as compared to low dose scintimammography when it comes to screening[9]. FNAC is considered the first choice for diagnosis of Ca breast with a sensitivity and specificity of >90% [10]. Few of the limitations of FNAC include borderline lesions, sampling error and inexperience of cytopathlogist. In our study, we would evaluate the diagnostic accuracy of Scintimammography by 99mTc MIBI in diagnosis of Ca breast with histopathology as a gold standard.

METHODOLOGY

The study was conducted at Nuclear Medical Centre, Armed Forces Institute of Pathology from Oct 2016 to Apr 2017. Non-pregnant, non-lactating patients having suspicious single or multiple BIRADs III, IV, V lesions, age ranging from 20-80 years, unilateral/bilateral breast involvement through non-probability consecutive sampling were included while already diagnosed cases of Ca breast, those having accessory breasts, in those patients where histopathology is not possible metastatic lesion to breast from other cancers and those having indeterminate study results were excluded from the study. Subjects fulfilling the inclusion criteria were elaborately apprised about the study to obtain their informed consent. Patients were interviewed, and previous clinical records were evaluated prior to Scintimammography. 738-1100 MBq (20-30 mCi) of 99mTc labelled MIBI was injected intravenously in the contralateral arm to the affected breast. Planar images were acquired in prone (lateral images of both breasts) and supine (anterior images) with arms raised during imaging. The static images were acquired for 10 minutes duration each at 20-60 min. Camera parameters included low energy all-purpose collimator. Photopeak centredat 140 KeV with 20% window, and matrix size of 256 × 256 pixels. Distance was kept minimum between the breast and the detector.

The images were analysed by two observers after performing clinical examination. In cases of different opinions, advice by a third observer (unaware of previous results two results) was sought and then it was considered final. Reporting was done as positive and negative. Patients were then referred for Trucut/ FNAC.

The image analysis was done according to SNM guidelines:

Suspicious of Malignancy: Focal increased uptake of the radiopharmaceutical with well delineated margin in the breast or axilla (in the absence of radiopharmaceutical infiltration).

Normal: Mild homogenous uptake of radiopharmaceutical in breast or axilla.

Indeterminate: Patchy or diffuse mild to moderate intensity uptake, often bilateral, with blurred edges in breasts.

Data was entered and analysed by SPSS-21. Mean and SD was calculated for quantitative Variables i.e. tumor size and age; while qualitative variables i.e. family history of Cabreast, history of breastfeeding and intake of hormonal contraception were analysed throughdiagnostic accuracy tests and chi square, a *p*-value <0.05 was considered statistically significant.

A 2x2 table was used to calculate sensitivity, specificity, accuracy, PPV and NPV based on the findings of Scintigraphy in comparison with histopathology results. ROC was also calculated.

RESULTS

Sample size of 96 was calculated by using WHO calculator with 95% confidence interval, 5% error and 41% prevalence[12]. Diagnostic accuracy was calculated for 96 cases. The mean age of the patients was 43.22 ± 12.59 years (20-74 years). The mean age of those with true positive results was 48.11±11.4 years (28-74 years).

Table-I: ESMO diagnostic work up for the Ca breast.

Assessment of General Health Status	History Physical examination Full Blood Count Liver Renal & Cardiac Function Tests
Assessment of Tumor	Physical Examination Mammography Breast Ultrasound Breast MRI Core Biopsy with Pathological Determination of histology, grade, ER, PgR, HER-2 and Ki67
Assessment of Regional Lymph Nodes	Physical Examination Ultrasound Ultrasound Guided Biopsy, if suspicious
Assessment of Metastatic Lesions	Physical Examination Other tests are routinely not recommended unless locally advanced or when symptoms suggestive of metastasis is present

ER : Estrogen Receptor, PgR: Progesterone Receptor, HER2: Human Epidermal Growth Factor Receptor 2

The sample characteristics have been shown in (table-II). The mean size of positive lesion was 3.2 cm (1.2-8 cm). Various operating characteristics including sensitivity, specificity, PPV, NPV and *p*-values of scintimammography and effect modifiers when compared with gold standard i.e. histopathologyis given in table-III (a, b). There were only two cases which showed tracer uptake in the axilla along with that in the breast. Histopathology of the breast lesions was positive for Ca breast; histopathology of axillary lesions was not done (out of the study domain). All the breast lesions underwent histopathology either FNAC/Trucut. Scintimammography was positive in 4 benign and negative in 1 malignant case. The most common malignant lesion detected on histopathology was invasive ductal carcinoma. Accuracy as measured by Area under curve (AUC) is 0.931 which represented a highly accurate test (figure).

Table-II: Sample characteristics.

Characteristics	Options	
Cases Studied	96	
Sampling technique	Non-probability consecutive sampling	
Mean age of TP cases	48.11 ± 11.4 years	
True Positive	53	
Breast Involved in Positive Cases	Right	Left
	24 (45%)	29 (55%)
No of Lesions	104	
Mean size of lesions in positive cases	3.2cm ± 1.41	
Marital Status	**Unmarried**	**Married**
	2 (22%)	94 (98%)
Breastfeeding	Yes	No
	74 (77%)	22 (23%)
Family History	Positive	Negative
	17 (18%)	79 (82%)
History of Hormone Replacement Therapy	Yes	No
	7 (7%)	89 (93%)
Parity	Nulliparous	Parous
	5 (5%)	91 (95%)

Table-III(a): Two-by-two contingency table comparing the gold standard with scintimammography.

		Histopathology		*p*-value
		Positive	**Negative**	
Scintimam-mography	Positive	53 (55%)	5 (5.2%)	<0.05
	Negative	1(1.04%)	37 (38%)	

Table-III(b): Diagnostic accuracy parameters.

Diagnostic accuracy parameters	Gold standard vs Scintimammography
Sensitivity	98.1%
Specificity	88.1%
PPV	91.4%
NPV	97.4%

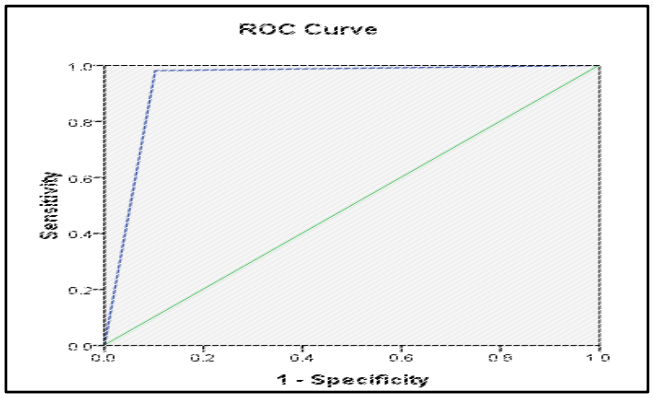

Figure: ROC curve analysis of scintimammography.

DISCUSSION

All over the world breast Cancer is considered a major health risk for women. On top of that, Pakistan has the highest rate of Breast Cancer among Asian countries[11-13]. Mammography although considered a screening/diagnostic tool for Ca breast carries low sensitivity in young females with dense breasts. A test with high NPV such as Scintimammography can prove helpful in diagnosis and therapeutic management of Ca breast. Scintimammography has proved to be beneficial mostly in palpable lumps. We used 99m Tc-MIBI because of it being Cost effective and utilized as a myocardial perfusion imaging agent which is a routine procedure in our department. The only FDA approved radiotracer for breast imaging, localizes itself in the tumor tissue relative to blood flow, and mitochondrial activity[14] nine times more as compared to normal cells [15]. It was approved by FDA as a breast imaging agent in 1997[16]. We used the technique of prone breast imaging using lateral planar views. It assisted in the demarcation of breast lesions by providing natural landmarks i.e. separating liver and myocardium from right and left breast respectively. The prone position of the patient with the assistance of specially designed table helped in relaxation of the pectoralis muscle which demarcates it from the chest wall and to some extent improvement of the resolution (to visualize small lesions)[17]. Few of the recognized risk factors for developing Ca breast according to National Comprehensive Cancer Network (NCCN) are inherited genes e.g. BRACA1 and BRACA2, increasing age, absence of breastfeeding, use of hormonal contraceptives and nulliparity[18]. In a local study on 105 cases of Ca breast, risk factors were analyzed, among which 10.5% patients were using hormonal contraceptives, 21.9% had no history of breastfeeding, 9.5% patients had history of Breast Cancer in their families; while 16.2% patients

were nulliparous. The mean age of presentation was 48.8 ± 2.4 years[19]. This study had a comparable age of presentation with our study i.e. 48.11 years ± 10.9 years. This mean age of presentation was lower as compared to west[20]. Risk factor analysis of our study showed 17 patients with positive family history of Ca breast. Among them, 8 were true positive for Ca breast (p=0.282), 74 patients had a history of breastfeeding among which 44 were TP for Ca breast (p=0.179), 7 patients had a history of usage of hormonal contraception, among which 3 were TP for Ca breast (p=0.361). The results showed that family history, history of hormonal contraception and breast feeding had insignificant relationship to development of Ca breast (p-value calculated between the risk factor and gold standard). This was in contrast to a meta-analysis carried out on 27 studies which concluded that a positive family history of Ca breast and no breastfeeding were among other risk factors for developing Ca breast[21]. However, Ahmed *et al*[22] in his study carried out in Islamabad, Pakistan concluded that these and many other recognized risk factors are rarely observed in our part of the world and more studies are required to look for the risk factors for Ca breast in our country.

Another study carried out in Karachi by Habib *et al*[23] on 28 patients among which 22 patients had breast lumps (both palpable and non-palpable) Planar Scintimammography carried a sensitivity and specificity of 93.3 and 71.4% respectively, they concluded by saying that Scintimammography had a good diagnostic accuracy in breast cancer detection when done with Mammography and Sonomammography.

The false positive cases of Scintimammography included fibroadenoma, fibrocystic disease and papillary. Moriguchi *et al*[24] studied the results of Scintimammography in both palpable and non-palpable lesions and described the causes of false positive results which included fibroadenoma (3/11 cases) and fibrocystic disease (1/10 cases), giving both a sensitivity and specificity of 89%. In our study there was only one 45 years old lady with positive family history of Ca breast presented with heaviness of right breast and a BIRADs III lesion on Mammography with normal Sestamibi who was subsequently diagnosed as having invasive ductal carcinoma (False Negative Scintimammography), the reason for this false negative result could be size less than 1 cm because of low resolving power of standard gamma camera, SPECT was not done on this patient. We evaluated a total of a total of 104 breast lesions on 96 patients the positive lesions had a size range from 1.2-8 cm. The size was measured in largest diameter. Tolmos *et al*[25] in his study on evaluation of non-palpable lesions by Scintimammography, concluded by giving a sensitivity of 56% and specificity of 87%, there by giving a closing remark that Scintimammography is not an appropriate modality for screening /diagnosis of non-palpable lesions. Thus, it can be said that sensitivity of Scintimammography is limited by size of lesion.

CONCLUSION

This study has shown an excellent sensitivity, specificity in detection of malignant mitotic lesions of breast, although any test with less than 100% NPV is not reliable but a negative predictive value above 85% is worth trying for especially in patients where Mammography may not be of much benefit. The patient will benefit from non-invasive, non-painful modality with less need for biopsy.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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