

## **Assessment of Breast Carcinoma by <sup>99m</sup>Tc-Sestamibi Scintimammography: Effect of Lesion Site, Size and Histopathological Characteristics**

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### **ABSTRACT**

This study included 83 female patients with 94 breast lesions. All patients underwent clinical examination, X-ray mammography and <sup>99m</sup>Tc- MIBI scintimammography (SMM). Furthermore, fine needle aspiration biopsy (FNAB) was performed for 53 breast lesions prior to surgical excision. Complete agreement between histopathological diagnosis and SMM was observed in 66/80 (82.5%) malignant lesions, whereas 2/14 (14%) of benign lesions had false positive results and proved to be adenoma and granuloma. The overall sensitivity, specificity and accuracy were 83%, 85.5% and 83% respectively for SMM and 62.5%, 59.3% and 61.4% for x-ray mammography. This difference was statistically significant ( $p = 0.006$ ). On the other hand, sensitivity, specificity and accuracy of FNAB was 91.8%, 90% and 91% respectively. SMM and FNAB did not show much significant difference in their sensitivity, specificity and accuracy ( $p = 0.318$ ). The highest diagnostic sensitivity of SMM was 87% for the detection of invasive carcinoma measuring 1-2 cm. However, the sensitivity was only 29% for the detection of breast lesions less than 1 cm. On contrast, X-ray mammography had a higher diagnostic sensitivity of 75% for the detection of malignant breast lesions less than 1 cm. <sup>99m</sup>Tc-MIBI scintigraphy showed a higher sensitivity of 90% and 89% for the diagnosis of breast carcinoma grade 3 and 4 respectively. While, it had a lower sensitivity of 67% and 81% for the detection of malignant lesions grade 1 and 2 respectively. The sensitivity of <sup>99m</sup>Tc-MIBI scintimammography was not influenced by tumour pathology (invasive ductal carcinoma was 85% and invasive lobular carcinoma was 80%) ( $p = 0.22$ ). Presence of carcinoma in situ did not affect the diagnostic accuracy of <sup>99m</sup>Tc-MIBI. The sensitivity of SMM for the detection of invasive carcinoma with ER+ve was higher than that for the detection of invasive carcinoma with ER-ve (86% vs 70% respectively) ( $p < 0.05$ ). SMM had a significantly higher sensitivity (95%) for localizing breast lesions in the retroareolar region compared to that in the other sites (lower inner quadrant 50%, lower outer 70% and upper inner 82%).

**Key Words:** <sup>99m</sup>Tc-MIBI - Breast carcinoma - Scintimammography.

### **INTRODUCTION**

Breast cancer is the most common cancer-affecting women. With the current diagnostic procedures, including self examination and mammography, up to 80% of breast lesions are usually detected. The diagnosis of early disease could be of value for better defining the prognosis and probably in planning more appropriate treatment strategies [32]. Approximately 40-50% of early breast cancer are detected by mammography. About 35% of tumours detected by mammography and physical examination are invasive carcinomas smaller than 1 cm [28]. Technetium-99m methoxyisotrile (<sup>99m</sup>Tc-MIBI) is a lipophilic cation primarily used for myocardial perfusion imaging [3]. Since the late 1980s, an increasing number of reports have appeared describing <sup>99m</sup>Tc-MIBI uptake in several tumours including breast cancer [1,15,23,37]. <sup>99m</sup>Tc-MIBI has an intramitochondrial location [2]. It is also used as an indicator of breast invasiveness on the basis that radiotracer uptake is related to the degree of tumour angiogenesis and oxidative metabolism [33].

The aim of the present work was to study the influence of different histopathological parameters as tumour size, grading, presence or absence of carcinoma in situ and hormonal receptor status on the diagnostic validity of <sup>99m</sup>Tc-MIBI scintimammography for detection of invasive breast carcinoma.

### **PATIENTS AND METHODS**

This study included 83 female patients treated at Minia oncology center during the period

January to December 1999. Their age ranged between 37-89 year with a mean age of  $51 \pm 10.4$  years. Women of this study had suspicious and palpable breast lesions by clinical examination or X-ray mammography. All patients were evaluated by X-ray mammography and  $^{99m}\text{Tc}$ -MIBI scintigraphy. Furthermore, fine needle aspiration biopsy (FNAB) was performed in 53 breast lumps prior to surgical excision for all patients.

#### *Histopathology and scintimammography:*

The myocardial perfusion imaging agent hexakis-2-methoxyisobutylisonitrile (MIBI) was radiolabelled with 555-740 MBq technetium- $^{99m}$  and then injected intravenously in the contralateral arm of the affected breast. Patients were placed in the prone position parallel to a single headed gamma camera with a low energy, high resolution parallel hole collimator. The image matrix was 128 X 128 without zooming. After 5 minutes, planar images were performed with a posterior view. Thereafter, lateral and posterior oblique views were performed if the posterior view was not conclusive. Each image was acquired for 10 minutes. Scintimammography was considered to be positive when there was an increased radioactivity accumulation within the breast area.

After surgical excision, the tumour size was determined macroscopically. Thereafter, microscopic examination was done to determine histopathological type, grade, the presence of carcinoma in situ component in and around the invasive tumour were determined microscopically. Identification of estrogen and progesterone receptor status were performed using the immunohistochemistry. According to the histopathological results,  $^{99m}\text{Tc}$  scintimammography were considered as true positive, true negative, false positive and false negative.

## RESULTS

Eighty-three women with 94 breast tumours were surgically excised. Out of these 94 breast lesions, 14 proved to be benign. A final diagnosis of malignant lesions was established in 80 breast lesions (Table 1 and Fig. 1). For all pathological sites, agreement between histopathological diagnosis and scintimammography was observed in 66/80 (82.5%) malignant lesions. Whereas, scintimammography was true negative in 12/14 (86%) benign lesions except for 2

false positive cases. These benign lesions were fibroadenoma and granuloma. The overall sensitivity, specificity and accuracy of scintimammography were 83%, 85.5% and 83% respectively (Table 2). The sensitivity, specificity and accuracy of X-ray mammography was 62.5%, 59.3% and 61.4% respectively which were significantly lower than of SMM ( $p = 0.006$ ) (Table 2). On the other hand, fine needle aspiration biopsy (FNAB) of 53 breast lesions showed a higher overall sensitivity, specificity and accuracy of 91.8%, 90% and 91% respectively. However, the difference between FNAB and  $^{99m}\text{Tc}$ -MIBI scintigraphy was not statistically significant ( $p = 0.318$ ) (Table 2).

Table (3) and Fig. (2) gave the number of malignant lesions detected by scintimammography with respect to size of malignant breast lesions. Our data showed that the sensitivity of scintimammography was 87% for lesions 1-2 cm, 86 for lesions 2-5 cm, 81% for lesions larger than 5 cm and only 29% for lesions smaller than 1 cm. X-ray mammography had a significantly lower sensitivity than scintimammography for the detection of malignant lesions larger than 1 cm (63% for lesions 1-2 cm, 61% for lesions 2-5 cm and 55% for lesions larger than 5 cm), whereas lesions smaller than 1 cm, showed a higher sensitivity of 75% using X-ray mammography compared to that of SMM ( $p = 0.04$ ) (Table 3 and Fig. 2). The overall diagnostic sensitivity of X-ray mammography and  $^{99m}\text{Tc}$ -MIBI scintigraphy for diagnosis of breast carcinoma was 60% and 82.4%. This difference was statistically significant ( $p < 0.005$ ) (Table 3).

Twenty six out of 80 malignant lesions (32.5%) were located in the upper outer quadrant, 21/80 (26%) lesions in the retroareolar region, 12/80 (15%) lesions in the upper inner quadrant, 11/80 (14%) lesions in the lower outer quadrant while 10/80 (12.5%) tumours were discovered in the lower inner quadrant. The sensitivity of scintimammography for the detection of breast carcinoma in retroareolar region was 95%. This was significantly higher than the sensitivity in other sites [lower inner quadrant (50%) ( $p = 0.003$ ), lower outer quadrant (70%) ( $p = 0.023$ ) and upper inner quadrant (82%) ( $p = 0.041$ )] (Table 4).

$^{99m}\text{Tc}$ -MIBI scintigraphy detected 52 true positive (TP) results and 9 false negative (FN)

results within 61 invasive ductal carcinoma while 12 TP results and 3 FN results within 15 invasive lobular carcinoma were identified resulting in a sensitivity of 85% and 80% respectively with no statistical difference ( $p = 0.22$ ) (Table 5). For all types of breast carcinoma the positive predictive value was 100%.

Carcinoma in situ was detected in 22/61 (36%) cases with invasive ductal carcinoma and in 2/15 (13%) cases with invasive lobular carcinoma. Disregarding tumour size, site and histopathological types, the sensitivity of scintimammography for localizing invasive carcinoma in the presence of carcinoma in situ was higher than that for detecting invasive carcinoma in its absence (87% and 83% respectively). However, this was not statistically significant ( $p = 0.16$ ). Moreover, 2/4 cases of ductal carcinoma in situ, within our group of breast carcinoma, concentrated <sup>99m</sup>Tc-MIBI.

Eleven out of 76 (14%) lesions were grade one, 35/76 (46%) breast carcinomas were grade 2. However, 21/76 (28%) lesions were grade 3. Whereas, only 9 invasive carcinomas (12%) were grade 4. <sup>99m</sup>Tc-MIBI scintigraphy showed a sensitivity of 67% and 81% for the diagnosis of grade 1 and grade 2 respectively. However, the sensitivity of scintimammography for detecting grade 3 and grade 4 invasive carcinoma was much higher (90% and 89% respectively) (Table 6). There was a significant difference between the sensitivity of SMM for detecting low grade (grade 1-2) and high grade (grade 3-4) invasive carcinoma. This difference was statistically significant ( $p < 0.05$ ).

The overall sensitivity of <sup>99m</sup>Tc-MIBI scintimammography for localizing breast carcinoma in premenopausal and postmenopausal women was 86% and 79% respectively with no significant difference ( $p = 0.086$ ). Hormonal receptors assay were performed for 56 out of 80 malig-

nant breast lesions (70%). By using immunohistochemical staining, 64% (36/56) of malignant breast lesions expressed estrogen receptors (ER+ve) and/or progesterone receptors (PR+ve). Within these lesions, 23/36 (64%) were ER+ve and PR+ve, 9/36 (25%) breast carcinomas showed ER+ve but PR-ve whereas, 4/36 (11%) malignant tumours had ER-ve but PR+ve. On the other hand, 20/56 malignant breast lesions were not expressed both ER and PR. <sup>99m</sup>Tc-MIBI scintigraphy detected 95% (22/23) malignant lesions with both ER+ve and PR+ve, 89% (8/9) lesions with ER+ve but PR-ve, 25% (1/4) lesions with ER-ve but PR+ve. Fourteen out of 20 (70%) breast carcinomas with no expression for ER and PR concentrated radiotracer. There was a significant difference in comparison between lesions with ER+ve and ER-ve ( $p < 0.05$ ) (Table 7).

Table (1): Diagnostic value of <sup>99m</sup>Tc-MIBI scintimammography based on histopathological results from 4 breast lesions.

Histopathological types	No. of cases	TP	TN	FP	FN
Malignant breast lesions	80	66	-	-	14
Benign breast lesions	14	-	12	2	-
Total	94	66	12	2	14

TP = True +ve    TN = True -ve  
 FP = False +ve    FN = False -ve

Table (2): Diagnostic value of scintimammography in comparison with X-ray-mammography and FNAB.

Diagnostic method	Sensitivity	Specificity	Accuracy	p-value
Scintimammography	83%	85.5%	83%	
X-ray mammography	62.5%	59.3%	61.4%	0.006
FNAB	91.8%	90%	91%	0.318

FNAB = Fine needle aspiration biopsy.

Table (3): Sensitivity of TC-<sup>99m</sup> scintigraphy and X-ray mammography in relation to size of invasive breast carcinoma.

Size of lesion	Number of cases	% Sensitivity of scintimammography	% Sensitivity of X-ray mammography	p-value
< 1 cm	7	29	75	0.04
1-2 cm	24	87	63	0.019
2-5 cm	23	86	61	0.05
> 5 cm	26	81	55	0.027
Total	80	82.4	60	< 0.005

Table (4): Sensitivity of scintimammography for diagnosis of breast carcinoma in different breast sites.

Site of lesion	No. and % of lesions	TP	FN	Sensitivity %
Upper outer	26/80 (32.5%)	22	3	88
Retroareolar	21/80 (26%)	19	1	95
Upper inner	12/80 (15%)	9	2	82
Lower outer	11/80 (14%)	7	3	70
Lower inner	10/80 (12.5%)	4	4	50

Table (5): Sensitivity of  $^{99m}\text{Tc}$ -MIBI scintigraphy in relation to histopathological types of breast carcinoma.

Histopathological types	No.	TP	FN	% Sensitivity	p-value
Invasive ductal carcinoma	61	52	9	85%	
Invasive lobular carcinoma	15	12	3	80%	0.22

Table (6): Diagnostic value of scintimammography for detection of breast carcinoma in relation of tumour grade.

Grading	Number of lesions	Sensitivity %
Grade 1	11/76 (14%)	67
Grade 2	35/76 (46%)	81
Grade 3	21/76 (28%)	90
Grade 4	9/76 (12%)	89

ER = Estrogen receptor. PR = Progesteron receptor.

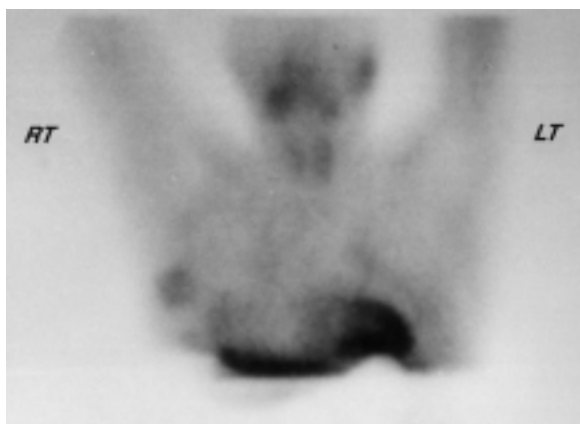


Fig. (1): Planar image of an invasive ductal carcinoma in the right breast of a 50 year-old patient.

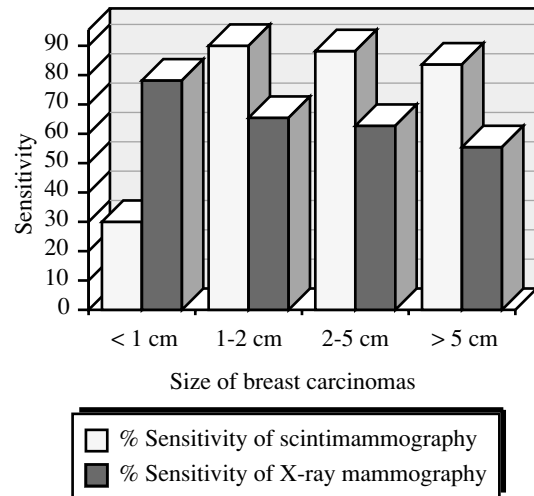


Fig. (2): Sensitivity of scintimammography and X-ray mammography in relation to size of breast carcinomas.

## DISCUSSION

Breast cancer is the commonest cause of cancer mortality in women. The majority of women with early stage cancer can be cured with appropriate treatment [8]. One of the diagnostic tools to confirm or exclude breast cancer is scintimammography. Recently technetium- $^{99m}$ -hexakis-2-methoxyisbutylisonitrile (MIBI) has been widely used for scintimammography [36]. Although the uptake mechanisms of technetium- $^{99m}$  sestamibi is not completely understood, it needs a viable tumour cells. The uptake of  $^{99m}\text{Tc}$ -MIBI depends on both membrane and mitochondrial potentials. The majority of  $^{99m}\text{Tc}$ -MIBI has an intramitochondrial location [2]. Additionally,  $^{99m}\text{Tc}$ -sestamibi is a substrate for Pgp, a multidrug resistance transporter [4,5,6]. The correlation of  $^{99m}\text{Tc}$ -sestamibi uptake and efflux characteristics with Pgp presence has been observed in vitro [10,11,12,29], as well as in several human tumours such as breast and lung cancer [18,19,21].  $^{99m}\text{Tc}$ -MIBI scintigraphy even proved its diagnostic value compared with magnetic resonance imaging [13,30].

In our group of patients,  $^{99m}\text{Tc}$ -MIBI scintimammography showed a high sensitivity of 82.4% for the diagnosis of breast carcinoma. In benign breast lesions, true negative results was evident in 86% with only 2 false positive patients (fibroadenoma and non-specific granuloma). Similar data was reported by Howarth et

al. [14], Moustafa et al. [22] and O'tuama et al. [25]. This finding is confirmed by the data of Deimon-Moirgeon et al. [9] that the high sestamibi uptake in malignant cells was due to high transmembrane potentials and high mitochondrial content.

In our planar study, the overall diagnostic sensitivity and specificity of scintimammography was 83% and 85.5% respectively (Table 2). This finding was confirmed by the data of Howarth et al. [14] that the overall sensitivity of scintimammography was 84% and the specificity was 80%. Also, the reported overall sensitivity and specificity of scintimammography were 84-94% and 72-94% respectively [35]. In contrast, two recent reports of Mekhmandarov et al. [20] and Tolmos et al. [31] showed a low sensitivity rate of 54.2% and 56% respectively in a comparable study of women with breast tumours. These variable data may be attributed to failure of scintimammography to visualize non palpable breast lesions less than 1 cm. On contrast to scintigraphy, X-ray mammography showed an overall low sensitivity, specificity and accuracy of 62.5%, 59.% and 61.4% respectively for evaluating palpable breast lesions with significant difference ( $p = 0.006$ ). This finding was reported by Howarth et al. [14] that the diagnostic accuracy of scintigraphy was shown to be significantly higher than that of X-ray mammography and breast ultrasound even when these modalities were used in combination in palpable breast lesions.

It is generally accepted that the sensitivity of scintimammography for the detection of malignant breast lesions less than 1 cm in size is reduced compared to its sensitivity with larger lesion [27]. In the present study, only 2/7 (29%) malignant lesions smaller than 1 cm were detected. Similar finding was confirmed by the study of Obwegeser et al. [24] that scintimammography detected 14% of small lesions below 1 cm in diameter. Data from a multicentre European study showed a sensitivity of 26-56% for lesions less than 1 cm [34]. On contrast to scintimammography, the sensitivity of X-ray mammography in our study was significantly higher (75%) than that of  $^{99m}\text{Tc}$ -MIBI scintigraphy (29%) for detecting such lesions smaller than 1 cm ( $p = 0.04$ ) (Table 3). Whereas, our study showed a higher sensitivity of 87% in larger lesions (1-2 cm). Then, there was a relative decrease in sensitivity for detection of larg-

er lesions (2-5 cm). Similar findings were reported by Howarth et al. [14] as large lesions may be confused with diffuse uptake in breast tissue. This may be exaggerated in-patients who had hormonal mastopathy or those who had previous history of breast surgery or radiotherapy [16].

SMM showed a significant higher sensitivity (95%) for localizing breast lesions in the retroareolar region compared to lesions in the lower inner quadrant as well as other sites. On contrast, other study showed that there was no significant difference in sensitivity of SMM as regard site of breast carcinoma [35].

The sensitivity of scintimammography for the detection of invasive ductal carcinoma (61 patients) and invasive lobular carcinoma (15 patients) were 85% and 80% respectively with no significant difference ( $p = 0.22$ ) (Table 5). Similar finding was reported by Howarth et al. [14] and Palmedo et al. [26] that the histopathological type of breast cancer does not influence the diagnostic accuracy of scintimammography. On the other hand, Buscombe et al. [7] reported that invasive ductal carcinoma showed significantly higher uptake of  $^{99m}\text{Tc}$ -MIBI than other types of breast cancer.

The sensitivity of  $^{99m}\text{Tc}$ -MIBI for diagnosis of invasive carcinoma in the presence of carcinoma in situ (CIS) (87%) was higher than that for detection of invasive carcinoma in absence of carcinoma in situ (83%). There was no significant difference between both groups. In a recent study, Howarth et al. [14] reported a higher MIBI uptake in breast cancer with CIS, which was attributed to the physical characteristics such as blood flow or intracellular mitochondrial density of carcinoma in situ. Also, Obwegeser et al. [24] reported that carcinoma in situ has a lower density of tumour cells per square unit than invasive carcinoma. Such light cells density might be one of the reasons for achieving a high target to background ratio that made a tumour visible.

The sensitivity of scintimammography for detection of grade 1 and grade 2 breast cancer was 67% and 81% respectively. However, in grade 3 and grade 4 the sensitivity of  $^{99m}\text{Tc}$ -MIBI scintigraphy was much higher (90% and 89% respectively) with a statistical significant difference compared to low grade tumours ( $p < 0.05$ ) (Table 6). On the another hand, other study

showed that tumour grade did not affect significantly the diagnostic accuracy of scintimammography [26].

In breast cancer, the hormone receptor status of the tumour greatly influences the choice of systemic therapy and is strongly linked to prognosis [8]. In this study, 31/36 (86%) lesions with hormonal receptor positive were detected by scintimammography whereas, 14/20 (70%) breast cancer with hormonal receptor negative concentrated  $^{99m}\text{Tc}$ -MIBI with a statistical difference ( $p < 0.05$ ) (Table 7). Other study showed that there were no correlation between tumour hormone receptor status and detection of breast cancer by scintimammography [14,17].

In conclusion, scintimammography is a useful tool for the detection of breast carcinoma. Also,  $^{99m}\text{Tc}$ -MIBI scintigraphy showed a good diagnostic accuracy for the detection of malignant breast lesions larger than 1 cm. Moreover, high grade breast carcinomas as well as tumours with ER+ve showed significant higher uptake of radiotracer. There was no significant difference in the diagnostic sensitivity of SMM for the detection of invasive carcinoma in relation to histopathological types and the presence or absence of CIS.

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