BREAST SCINTIGRAPHY EVALUATION WITH TECHNETIUM 99m SESTAMIBI

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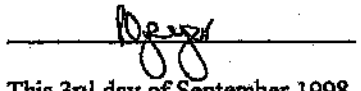
A research report submitted to the Faculty of Medicine, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Science in Medicine in Nuclear Medicine.

Johannesburg 1998

I, René Geyer, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in the branch of Nuclear Medicine in the University of the Witwatersrand, Johannesburg.



This 3rd day of September 1998.

This is dedicated to all the women who volunteered for this study.

ABSTRACT

Forty (40) female patients with breast masses underwent Technetium 99m Sestamibi scintigraphy in order to evaluate its usefulness in differentiating benign from malignant breast disease and to compare scintigraphy to mammography. Informed consent was obtained from each patient. Scintigraphy consisted of anterior chest and lateral and oblique breast planar images, obtained 5 minutes after intravenous injection of 20 mi. curies (740 MBq) Technetium 99m Sestamibi. Eleven (11) of the 40 patients also had Technetium 99m Methylene Diphosponate breast scintigraphy for comparison. Four nuclear medicine physicians of who three also graded the MDP images perfo.med grading of the Sestamibi scintigraphic images. The grading method, although focussing on the absence (0) or presence (>0) of uptake of isotope, was also designed for comparison of the Sestamibi and MDP images. Statistical analysis showed good correlation between observer grading. Breast scintigraphy was compared to mammography in 27 of the 40 patients.

Of the 26 malignant breast masses confirmed on histology, 19 were positively identified on Sestamibi scanning giving a sensitivity of 73%, 2 results were inconclusive (grading of 0-1) and 5 had a grading of 0. Of the 8 patients with confirmed lymph node metastases, only 2 were positive on the Sestamibi scans, with 1 inconclusive result. Of the 19 benign breast masses, 9 were visible on Sestamibi scans with additional 3 inconclusive results (grading of 0-1).

Statistical analysis showed no significant difference in the Sestamibi and MDP grading. In comparison to mammography, breast scintigraphy was less accurate in distinguishing benign from malignant breast masses. Mammography identified 85.7% of the malignant breast masses and 72.7% of the benign breast masses. Sestamibi scintigraphy identified 76.2% of the malignant breast masses and only 36.4% of the benign breast masses.

I would like to thank the following people for their assistance and support:

Dr. A. Mannell (Supervisor) Consultant, Department of Surgery, Johannesburg Hospital.

Prof. J.D. Esser Head of the Department of Nuclear Medicine, Johannesburg Hospital.

Ivan Boyd for designing and making the bed to fit the Helix scanner.

Dr. P. Jennings Nuclear Medicine Physician.

Dr. D. Rubin Nuclear Medicine Physician.

Dr. K. Milos Nuclear Medicine Physician.

Dr. A. Mc Knight Nuclear Medicine Physician.

The radiographers in the department of Nuclear Medicine who assisted me, especially Pat Gaede.

The staff of the Breast Clinic at the Johannesburg Hospital.

Dr. S. Lucas Department of Radiology, Johannesburg Hospital.

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1.0 INTRODUCTION

1.1 Breast Cancer - Overview

Breast cancer is an extremely common disease and causes significant cancer related mortality each year (1). The incidence rate for women aged 50 -64 is 160 per 100 000 as compared to 200 per 100 000 for women aged 65-74. (2) Follow up studies show that breast cancer is a devastating disease, with an annual death rate of around 8% among survivors' even 20 years after diagnosis (3).

Factors increasing the risk of breast cancer include family history, the presence of the BRCA1 gene, hormones (both endogenous and exogenous), diet, lifestyle (alcohol, smoking, exercise) and high dose ionizing radiation exposure to the chest (4).

The growth rate of breast cancers is highly variable, but in most cases the disease has been present for many years before it is detectable by any means. About 40 doublings of breast cancer cells create a lethal tumour burden, yet mammography cannot detect a mass until 25 - 30 doublings have already occurred (3). In view of the cytokinetics of the disease, it is not surprising that the eventual outcome (death due to breast cancer) for the majority of women is unaffected by screening mammography (3).

Breast cancer has an unusual age - incidence pattern; it is rare before the age of 25, the incidence increases with advancing age until the age of 45 when a leveling off occurs known as Clemmesen's hook. After 55, the incidence rate rises again, but more slowly until its apex at 75 years, after which the rate seems to decline (2).

Breast cancer is a chronic disease because the rising incidence, coupled with the improved survival rate after effective treatmem, has placed an increasing number of women at risk of developing cancer in the opposite breast (5,6).

Screening which refers to the "examination of asymptomatic people" for chronic disease therefore applies to breast cancer (7) and includes breast self-examination, education and diagnostic imaging.

1.2 Diagnostic Breast Cancer Imaging

1.2.1 Mammography

Mammography is certainly capable of identifying abnormalities that may be breast cancer at a clinically undetectable stage. (3) However, one major drawback to its widespread use is the financial and emotional cost of the large number of biopsies done for clinically occult benign lesions. (8)

Mammography's greatest limitation is its low specificity in distinguishing between malignant and benign lesions and even with the highest quality mammography, 5-10% of cancers may not be detected mammographically (9). These "missed" cancers are frequently caused by radiographically dense breast tissue (9) or interval cancers (10).

The current exposure from a mammogram is between 200-400 millirads (0.002-0.004 Gy). The estimated added lifetime risk of breast cancer mortality for a woman who has annual two-view mammography from age 50 is 3,9 per 100000 (4). Because of the low accuracy of mammography and the slightly lower incidence of breast cancer in younger women, the economic and clinical feasibility of screening in the 40-49 year age group remains controversial (9). Biannual mammography for women aged 50 and over is recommended at present.

1.2.2 Magnetic Resonance Imaging (MRI)

MRI provides multiplanar breast imaging and excellent soft tissue contrast without ionizing radiation. Dedicated breast surface coils improved the signal-to-noise ratio providing thin, contiguous imaging slices allowing detection of cancers as small as 3mm. The intravenous administration of gadolinium contrast agents has also improved cancer detection rates. The presence of dense fibroglandular tissue is not a limitation for MRI because the contrast enhancement pattern is reflective of the tissue blood supply and is not a function of differential tissue densities. However due to the high cost of contrast enhanced MRI and its limited availability, it cannot be viewed as a potential screening method. It is complementary to mammography and ultrasound (9). At present the rate of false-negative MRI reports are unknown and MRI alone should not be used to exclude the presence of breast cancer (11).

1.2.3 Ultrasound

Sonography is not useful for screening for breast cancer because its sensitivity and specificity are far lower than those of mammography. However, ultrasound examination of a palpable breast tumour is reliable in differentiating between benign and malignant (sensitivity of 96% and specificity of 94%) (12). It can differentiate cystic from solid masses with accuracy approaching 100% (9). Ultrasound of a palpable breast mass is useful in young women, pregnancy, after implantation of prosthesis, post-radiation to detect an abscess, to perform ultrasound-guided fine needle aspiration (12). Ultrasound has a definite complementary function in the management of palpable breast masses.

1.2.4 Radionuclide imaging

The differential diagnosis between benign and malignant breast lesions has long been a challenge for many researchers using radioisotope-based techniques. The various isotopes at present being studied include Technetium 99m Methylene Diphosphonate (MDP), Thallium-

201, Technetium 99m Tetrafosmin, Technetium 99m labeled synthetic peptides, the glucose analogue: 2-deoxy-2- F18-fluoro-D-glucose (FDG), Indium -111 octreotide (a somatostatin analogue) and Technetium 99m Sestamibi. The exact mechanism of cellular uptake of Tc99m Sestamibi by cancer cells is unknown. Recent data suggest that 90% of the tracer activity is concentrated in the mitochondria (13). Organ dosimetry of Tc99m Sestamibi demonstrates that a dose of 20 millicuries (740 MBq) delivers 3 rad (0.03 Gy) to the large intestine, which is the predominant target organ. The whole body dose is 300 millirads (0.003 Gy), which is comparable to mammography (13). The technique of prone breast imaging is more favorable than the supine position because of excellent separation of deep breast structures from the myocardium in the left breast and provides natural landmarks of the breast contour that are necessary for localization of lesions (14,13).

1.3 Literature Review of Scintigraphic Agents Used in Breast Imaging

1.3.1 Thallium 201 (Tl 201)

Tl 201 has chemical properties similar to those of potassium ion. As it is a potassium analogue, uptake of Tl 201 into tumour cells depends on the ATPase sodium potassium transport system. Breast cancers show higher concentrations of potassium than benign lesions of the breast (15). The concentration of thallium in breast cancers seems to be primarily dependent on vascularity and tumour size. Breast tumours of small size may negatively influence Tl 201scan because of low absolute Tl 201 uptake by the tumour (15). Thallium scintigraphy showed a low sensitivity for detecting lymph node metastases (15,16) Tl 201 appears to have a high sensitivity for the detection of malignancy in palpable breast masses. However, it cannot differentiate between malignancy and highly cellular fibroadenomas with accuracy. (17,16)

Tl 201 has a physical half-life of 73.1 hours and a biological half-life of 10 days. The kidney is the critical organ, receiving 3 rad (0.03 Gy) per 2-millicurie (74 MBq) dose. The long physical half-life, poor emission characteristics (80 kev) and restricted availability due to cyclotron production are definite disadvantages for using this agent.

1.3.2 Technetium labeled agents

Technetium 99m has a physical half-life of 6.02 hours and is available at any time.

1.3.2.1 Technetium 99m Methylene Diphosphonate (MDP)

This agent is used in the staging of breast cancer patients by detecting skeletal metastases. Extraskeletal accumulation of Tc99m MDP has been reported in some malignant tumours, possibly due to increased vascularization. In a study done by Piccolo, Lastoria et al (18) results similar to those of Tl 201 scintigraphy were found. A specific pattern of uptake of Tc99m MDP was however found in inflammatory carcinoma, i.e. well defined focus of increased uptake in early images that decreased in the late images. Infiltrated skin was well delineated. Conversely, acute inflammatory processes showed faint, non-homogenous uptake without signs of skin infiltration (18).

1.3.2.2 Technetium 99m Methoxyisobutylisonitrile (Sestamibi)

The use of Tc99m Sestamibi in tumour imaging was first reported in 1989 in lung tumours (19) and subsequently in thyroid, brain and bone tumours (20).

Preliminary studies have shown that a positive Tc99m Sestamibi breast image may indicate a possible malignancy. However, highly cellular fibroadenomas were found to exhibit Sestamibi uptake (21,22) and in one study, (21) two patients with invasive lobular carcinoma showed absent Sestamibi accumulation. The sensitivity of Sestamibi in detecting axillary metastases was low (57%) (21). However, fat necrosis, post-surgery scar formation, prostheses and dense breasts did not interfere with the interpretation of scans as compared to mammography.

Tumour size also affects sensitivity of Sestamibi. Lesions < 10mm were undetectable with Tc99m Sestamibi (23). Reports have varied from: "Tc99m Sestamibi breast scintigraphy is useful in distinguishing malignancies from benign breast masses" (20) to "mammography and ultrasound are the basic screening modalities for palpable breast masses and cannot be replaced by Sestamibi breast imaging" (21).

1.3.3 Indium 111 Octreotide

Octreotide is a somatostatin analogue. Somatostatin-receptor (SS-R) scintigraphy shows primary cancers and distant metastases in most patients with carcinoids, islet cell tumours and paragangliomas. Previous in-vitro studies indicated that somatostatin receptors are present in human breast cancers. By using SS-R scintigraphy those SS-R positive breast cancers could be demonstrated in vivo as well as any metastases present. Scintigraphy also showed the presence of metastases in symptom-free, initially SS-R positive, breast cancer patients on follow-up studies. These patients had normal CA15-3 and CEA serum levels (24).

The radioisotope used to label the somatostatin analogue, Indium-111, is cyclotron produced and therefore not readily available. It does however have a physical half-life of 2,81 days with photon energies of 172 kev and 247 kev, allowing delayed imaging of 24 to 48 hours.

2.0 OVERALL AIM OF THIS STUDY

Screening mammography, considered to be a vital defense against breast cancer, is fraught with controversy and lacks a high degree of diagnostic accuracy. Mammograms are insensitive to detecting some breast cancers, and can cause false alarms prompting unnecessary biopsies. These "false-positive" mammograms are physically as well as psychologically traumatic. All women experience some anxiety while having a mammogram and frequently suffer more distress while awaiting the study results. In addition, breast cancer in the elderly women is becoming a medical problem of increasing magnitude. Responding to the need for earlier, more accurate and cost-effective methods of cancer detection, researchers are investigating adjuvant and alternative methods to traditional screening (9). At present there is clinical interest, generated by published reports, in breast imaging using several radiopharmaceuticals such as Tc99m Sestamibi, Tc99m Tetrafosmin, Tl 201, Tc99m SM3 monclonal antibody and F18 FDG. Almost one in five presentations at the 1995 Annual Meeting of the European Association of Nuclear Medicine in Brussels dealt with oncology and one of the most prominent issues was breast cancer.

Preliminary results of breast scintigraphic studies are promising, but they generally concern small series of patients. Because the physical characteristics of Tc99m Sestamibi are more favorable for scintigraphic imaging than those of TL 201, the aim of this prospective study was to validate the use of Tc99m Sestamibi in the diagnostic work-up of patients with breast disease. Since the breast cancer patients were due to have a routine bone scan using Tc99m MDP, I initially intended to include a comparison of Tc99m Sestamibi and Tc99m MDP in this study. However, due to technical problems experienced during this study, at the conclusion of the study, only eleven completed studies were available for comparison. In this study, breast

scintigraphic imaging was compared to the histological diagnosis obtained via fine needle biopsy or post surgical excision.

3.0 METHOD

The study protocol was reviewed by the Postgraduate Committee, the Faculty of Health Sciences of the University of the Witwatersrand. Ethical clearance to perform this study was obtained from the Department of Human Ethics (Appendix B).

3.1 Study Sample

25 patients with breast carcinoma (Group A) and 15 patients with benign breast masses (Group B) gave informed consent to participate in this study (Appendix C). In Group B, three patients (numbers 1, 10 and 14) had bilateral breast masses. In Group A, one patient had a benign mass in one breast (included in the results of the benign group) and a malignant mass in the other breast.

All the patients had either fine needle biopsy or excision biopsy/mastectomy.

Eleven patients in Group A had both a Tc99m MDP scan and a Tc99m Sestamibi scan.

3.2 Imaging Method

Each patient received 20 millicuries (740MBq) Tc99m Sestamibi, injected intravenously in the arm opposite to the breast with the abnormality. If both breasts had abnormalities, the arm opposite to the breast with the larger abnormality was used. Imaging was commenced five minutes postinjection.

An anterior chest image was obtained in the upright position with the arm raised in order to view the axillae. The patient was then positioned prone with the breast pending and a lateral and posterior oblique image was obtained of the breast/s with an abnormality. A lateral image only was performed of the opposite breast if there was no known abnormality.

Scintimammography was performed using a gamma camera equipped with a high-resolution collimator. Acquisition parameters included: 1) a 10% window centred on a 140 kev photopeak and 2) static imaging for 1 million counts for the anterior view and 2 million counts for the prone views 3) zoom factor of 1.5 for the lateral views.

This procedure required approximately 40 - 50 minutes.

The patients who also had a Tc99m MDP scan, were having a routine bone scan as part of their metastatic work-up. The breast imaging was performed fifteen to twenty minutes postinjection using the same technique as for Tc99m Sestamibi. Due to difficulties experienced trying to coordinate timing and gamma camera availability, only eleven completed Tc99m MDP studies were obtained.

4.0 RESULTS

Four nuclear physicians, independently, without prior knowledge of the clinical or histological data, performed the interpretation and grading of the scintigraphic scans (Appendix D). Observers were allowed to discuss the scintigraphic grading method prior to being given the study material, thereby trying to minimize variation between observer grading. All four observers used a modem (grey scale) and not X-rays to interpret the results, so as to produce a uniform standard of grading. The scintigraphic grading of the scans was performed as defined in Table 1. This grading method was decided on after discussions with various nuclear physicians and breast surgeons. Initially I looked at using a region of interest (ROI) and calculating a target-to-background ratio, however after testing this method using the departmental registrars, lack of consistency in the results led to favoring the selected method (breast size variation also made it difficult to standardize a ROI). Although the focus is on the presence or absence of uptake of the isotope, the 0 to 3 grading was used with the intention of

comparing the uptake of Tc99m Sestamibi with Tc99m MDP and (for interest only) to assess whether the size of the lesion had any effect on the intensity of uptake.

TABLE 1 - SCINTIGRAPHIC GRADING

0	NO FOCAL UPTAKE OF ISOTOPE
1	PRESENCE OF SLIGHTLY INCREASED UPTAKE OF ISOTOPE
2	DEFINITE INCREASED UPTAKE OF ISOTOPE
3	INTENSE INCREASED UPTAKE OF ISOTOPE

Most patients presented with breast masses with the exception of the following patients in Group A:

- Patient number 4 presented with a persistent nipple discharge. Cytology smears were repeatedly negative. A mastectomy was performed at the patient's request. Histology showed Paget's disease with an underlying duct cell carcinoma-in-situ behind the nipple.

Although Paget's disease of the breast is uncommon, it accounts for 1-4 % of all breast cancers and was found to be associated with an underlying carcinoma in situ which is often not evident prior to surgery (8). Both Sestamibi and MDP gradings were positive (>0).

- Patient number 6 had had bilateral mastectomies followed by prosthetic breast implants, because of a strong family history of breast cancer. Now she presented with a painful palpable lymph node in the left axilla, which on biopsy was found to be malignant. She subsequently had surgical removal of all remaining breast tissue and axillary clearances. Only the left axillary node was found to be malignant on histology.

The Sestamibi scan was negative for lymph node detection in this patient.

- Patient number 23 presented with enlarged left axillary nodes and an inflamed swollen left breast. FNA of the axillary nodes showed duct cell carcinoma but the breast biopsy was negative for malignancy. Both the Sestamibi and the MDP grading for breast masses are inconclusive, since they vary from a grading of 0 to 2. Two observers rated the Sestamibi scans positive for lymph nodes. The MDP gradings were all negative for lymph nodes.
- Patient number 24 had previously had a left mastectomy and now presented with a mass in the right breast. Duct cell carcinoma was diagnosed on fine needle aspiration, but only proliferative breast tissue was found on histology post mastectomy. She has been included in the malignant group of patients. The Sestamibi scan of the right breast showed only slightly increased uptake of isotope (Grade 1).

Interobserver reliability test results:

The statistical analysis (Appendix E) shows a good correlation between observers (Z-value significantly greater than 1.96) for breast mass grading. Lymph node grading was less consistent (Z-value of less than 1.96).

Of interest, was that all four the observers found uptake of isotope in the opposite breast tissue of two of the patients in the benign group, neither of whom had palpable masses in these breasts. One patient had mammography which was negative.

TABLE 2 - GROUP A (CARCINOMA)

Patts.		AGE	BREAST	TUMOUR	MAMMOG.	MIBI		MDP		HISTOLOGY	NODES
		Yrs		Size		Lesion	Nodes	Lesion	Nodes		Histology
1	S.C	58	LEFT	2,4 X 2,4 cm	Suspicious	0	Negative			Malignant	
			RIGHT	5 X 4,5 cm	Suspicious	3	Negative			Malignant	
2	C de B	50	RIGHT	2,5 X 2 cm		3	Positive			Malignant	Positive
3	A D	51	LEFT	3 X 3 cm		0-1	Negative			Malignant	
4	E A D	28	RIGHT	nipple disc	Not suspic.	1-2	Negative	2	neg	Malignant	
5	M F	60	RIGHT	6 X 6 cm	Def. Malig.	1-2	Negative	2	Pos/ neg	Malignant	Positive
6	V F	53	LEFT AXIL	NODE		0	Negative			Malignant	Positive
7	M C G	70	LEFT	under 1 cm	Suspicious	0	Negative			Malignant	
			RIGHT	2,4 cm	Benign	0	Negative			Benign	
8	H H	66	LEFT	8 cm	Def. malig.	3	Pos/ neg			Malignant	
9	Z K	55	LEFT	app. 1 cm	Suspicious	0	Negative	0	neg	Malignant	
10	C M	36	LEFT	3,3 X 1,7 cm	Suspicious	1-2	Pos/ neg			Malignant	
11	J R M	78	RIGHT	2,5 X 2 cm	Suspicious	1-2	Negative	1-2	neg	Malignant	Positive
12	M M	59	LEFT	pseudoran	Suspicious	2-3	Pos/neg	2	neg	Malignant	
13	E M	54	LEFT	2,1 X 2,5 cm	Suspicious	2	Negative	2	neg	Malignant	
14	B M	71	LEFT	6cm		3	Positive			Malignant	
15	E N	35	LEFT	2 X 2,5 cm	Def malig	2-3	Positive	1	neg	Malignant	Positive
16	W P	46	LEFT		Suspicious	0	Negative			Malignant	
17	M P	32	LEFT	5 X 4 cm	Suspicious	2	Negative			Malignant	Positive
18	A R	39	LEFT	more 10 cm	Suspicious	2	Positive			Malignant	
19	A J S	68	LEFT	2,4 X 1, 8 cm	Suspicious	1-2	Negative			Malignant	
20	S S	53	RIGHT	3,5 X 2,5 cm	Suspicious	1-2	Negative	0-2	neg	Malignant	
21	M T	47	LEFT	4 X 4 cm		3	Positive			Malignant	
22	C v H	54	RIGHT	2,0 X 1, 7 cm	Benign	1	Negative	2	neg	Malignant	Positive
23	R V	59	LEFT		Not suspic	0-1	Pos/neg	0-1	neg	Malignant	Positive
24	M v Z	79	RIGHT		Suspicious	1	Negative			Malignant	
25	B G Z	35	LEFT	3 X 3 cm	Suspicious	2	Negative	0-1	neg	Malignant	

TABLE 3 - GROUP B (BENIGN)

PATIENT		AGE	BREAST	TUM SIZE	MAMISON	MIBI GRAD	MIBI GRAD	HISTOLOGY
		Yrs		Cms		Lesion	Nodes	
1	J M B	33	LEFT X 2	0,5X0,3X0,7	Probable cyst	0	Negative	Cyst
				3,3x1,4x1,5	Fibroadenoma	1-2	Negative	Fibroadenoma
2	H d S	39	RIGHT	4 X 2,5	Suspicious	2	Negative	Fibroadenoma
3	G K	48	RIGHT	3 X 4,5	Def malignant	3	Negative	Chron abscess
4	S M	20	LEFT	4 x 2	Suspicious	0-1	Negative	Fibroadenoma
5	G M	53	RIGHT		Benign	0	Negative	Benign
6	C M	36	RIGHTX2		Benign	0	Negative	Benign
7	E M	28	LEFT			0	Negative	Fibroadenoma
8	T M	18	LEFT			1-2	Negative	Fibroadenoma
9	E M	48	RIGHT			0-1	Negative	Fibroadenoma
10	D M	20	LEFT			0-1	Negative	Benign
			RIGHT			2	Negative	Fibroadenoma
11	V M	24	RIGHT			0	Negative	Fibroadenoma
12	N M	35	RIGHT	1,5X1,2X0,5	Benign	1	Negative	Fibroadenoma
13	K R	41	LEFT			1	Negative	Cyst
14	D S	41	LEFT	1,8X1	Prob benign	1-2	Negative	Benign
			RIGHT		Prob benign	1	Negative	Fibroadenoma
15	H v A	53	RIGHT			0	Negative	Fibroadenoma

4.1 Tc99m Sestamibi Vs Pathology

Of the 26 malignant breast masses confirmed on histology, 19 were positively identified on Sestamibi scanning giving a sensitivity of 73%, 2 results were inconclusive (grading of 0-1) and 5 had a grading of 0. No correlation was found between the size of the lesion and the degree of uptake of isotope.

Of the 8 patients with confirmed lymph node metastases, only 2 were positive on the Sestamibi scans, with 1 inconclusive result.

Additional 3 patients, who did not have surgery, (i.e. lymph node metastases not confirmed) showed lymph node involvement on Sestamibi scans. All 3 patients had palpable lymph nodes.

Of the 19 benign breast masses, 9 were visible on Sestamibi scans with additional 3 inconclusive results (grading of 0-1). Interestingly, the patient with the chronic breast abscess had a grading of 3, suggesting that inflammation could be a cause of increased uptake of isotope. This gives a false positive value of 47.4%-61%. This high false positive value is in contrast to previous studies. In the study done by Khalkhali et al (13) only 5 out of 33 benign breast lesions were false positives; of these 2 were fibroadenomas. The study by Kao et al (20) showed all 6 benign masses as true negatives; all 6 were fibrocystic disease. In the study by Burak et al (21) 2 of 14 benign masses were false positives; both were fibroadenomas. Again in the study by Lu, Shih et al, (22) 4 of 7 fibroadenomas were false positives and this led them to conclude that fibroadenomas with hypercellularity may cause false positive Sestamibi scans. In the study by Tabuenca (26) 10 of 13 benign masses were positive on Sestamibi scans, but they concentrated on the 3 becoming true positives.

In this study, the statistical analysis (Appendix E) clearly demonstrates that Sestamibi imaging cannot differentiate between benign and malignant breast masses with accuracy. Although the statistical analysis of lymph node detection by Sestamibi imaging compared to histology correlated, the numbers are small (only 8 confirmed) and should be interpreted with caution, since the interobserver grading of lymph nodes showed poor correlation.

Thus, although the sensitivity of Sestamibi for detecting palpable breast masses is good, the specificity is very low. Lymph node detection is also poor and only positive in quite advanced breast carcinoma.

Breast scintigraphy, however, is unaffected by breast density or the presence of scar or fibrous tissue as these did not influence or interfere with the interpretation of these scans.

TABLE 4 - SESTAMIBI vs. MDP

PATIENT		AGE YRS	BREAST	MIBI-lesion	MIBI-nodes	MDP-lesion	MDP-nodes	HISTOLOGY	NODES
1	EAD	28	RIGHT	2	Negative	1-2	Negative	Malignant	
2	MF	60	RIGHT	2	Negative	1-2	2neg/1pos	Malignant	Positive
3	ZK	55	LEFT	0	Negative	0	Negative	Malignant	
4	JRM	78	RIGHT	1-2	Negative	1-2	Negative	Malignant	Positive
5	MM	59	LEFT	2-3	Negative	1-3	Negative	Malignant	
6	EM	54	LEFT	2-3	Negative	1-3	Negative	Malignant	
7	EN	35	LEFT	2-3	2pos/1neg	1	Negative	Malignant	Positive
8	SS	53	RIGHT	1-2	Negative	0-2	Negative	Malignant	
9	CvH	54	RIGHT	1-2	Negative	1-3	Negative	Malignant	Positive
10	RV	59	LEFT	0-2	2pos/1neg	0-1	Negative	Malignant	Positive
11	BGZ	35	LEFT	1-2	Negative	0-1	Negative	Malignant	

4.2 Tc99m Sestamibi Vs MDP

Only the results of 3 of the observers were used (1 did not receive the MDP images and therefore did not grade them).

The statistical analysis showed a good correlation between the Sestamibi and MDP grading. Due to the small sample size, this would have to be confirmed by a larger study.

The hypothesis that the mechanism of uptake of Tc99m MDP may be due to increased vascularisation or inflammatory change (18) may account for the slight difference in grading in Paget's disease (however, it would have been interesting to compare the uptake in the chronic abscess).

Sestamibi showed a slightly better detection of lymph nodes than MDP. This is consistent with the study done by S. Lastoria et al (27), which concluded that Sestamibi better depicts lymph nodal infiltration.

4.3 Scintigraphy Vs Mammography

Mammography was performed in 27 patients who also had scintigraphy. There were 32 breast masses as 5 patients had bilateral masses.

Of the 21 histologically confirmed malignant breast masses, 16 were detected by Sestamibi (plus1 inconclusive result) compared to the 18 found to be either suspicious or malignant on mammography.

Of the 11 histologically confirmed benign breast masses, 8 were benign on mammography compared to only 4 (grading of 0) on Sestamibi imaging.

In the study by Burak et al (21), comparing Sestamibi scanning to mammography and ultrasonography, all the malignant breast masses were detected by mammography with ultrasonography. Sestamibi scanning detected 25 of 27 malignant masses. The differential diagnosis of fibroadenomas was however, still more accurate on mammography compared to Sestamibi scanning. This correlates with the findings in this study.

5.0 DISCUSSION AND CONCLUSION

5.1 Value and Usefulness of Scintimammography

The results of this study shows clearly that scintigraphy is not accurate in distinguishing benign from malignant breast masses, nor in detecting lymph node metastases.

Scintigraphy can, however, play a complementary role to mammography, especially in the patients with dense breast tissue, the post surgical patient with a suspicious breast mass, the patient who has had radiation therapy and in the patient with breast prosthesis. As observed in this study, these did not interfere with the interpretation of the scans. Scintigraphy cannot be used to diagnose or exclude malignancy, but can therefore be more useful in localizing the mass in the presence of dense breast tissue, scar tissue or prosthesis.

Due to the high false positive results, the objective to determine the extent of the disease was abandoned as this would only have been relevant if scintigraphy showed a high sensitivity and specificity in detecting breast malignancy.

At present, mammography is the most effective method of detecting breast abnormalities and in conjunction with sonography, (especially ultrasound guided fine needle aspiration) the most accurate cost-effective method for differentiating benign from malignant masses.

Ultimately the definitive diagnosis is still made on cytology or histology.

5.2 Future of Breast Imaging

At present, interesting research is being done on the feasibility of imaging using monoclonal antibodies and labeled receptors. If, for example, somatostatin receptor scintigraphy is effective in the early detection of somatostatin- receptor- positive breast cancer, it may have future use in the selection of patients who can be treated with somatostatin analogues or

radiotherapy using an alpha-emitting or beta-emitting radionuclide coupled to a somatostatin analogue (24). Positron emission tomography (PET) using the glucose analogue: F18-2-fluoro-2-deoxy-D-glucose (FDG) or C11-methionine in breast cancer scintigraphy could be useful in providing early information on the efficacy of chemotherapy, allowing earlier adaptation of therapeutic strategies. PET using FDG or C11-methionine has been effective in identifying primary breast tumours, axillary lymph node metastases, pleural and hepatic metastases (28,29). Another possible application of PET, is to study dynamic changes over time, including metabolic changes in the tumour (29).

Digital mammography, although still in the developmental stage, uses the direct digital capture of the mammographic image with an electronic detector (vs. film); this allows more flexible mapping and display of radiographic densities (30). It has several advantages and disadvantages.

Advantages include: a) improved image quality especially of those patients with dense breast tissue. b) computer-aided diagnoses. c) digital images that can be transmitted via telephone or internet for rapid expert interpretation.

The main disadvantage is that the digital technique can cover only a small area of the breast at a time and has limited spatial resolution (31,30).

Colour-coded as well as spectral doppler ultrasound is also being evaluated as a possible supplementary diagnostic tool for differentiating benign from malignant breast masses, especially as a means of reducing the number of unnecessary exploratory biopsies (32). Colour-coded doppler sonography visualises the vascularity of breast masses. Tumours as small as 3mm rely on the formation of capillary vessels for further growth which can be imaged by highly sensitive colour-coded doppler units (32). Colour-coded doppler ultrasound is also being assessed as a potential technique for detecting axillary lymph node metastases (1).

Hopefully, with the integration of all these new technologies, and continued research, the detection and diagnoses of early breast cancer will become more accurate.

APPENDIX

A. Examples of Scintigraphic Images

B. Clearance certificate

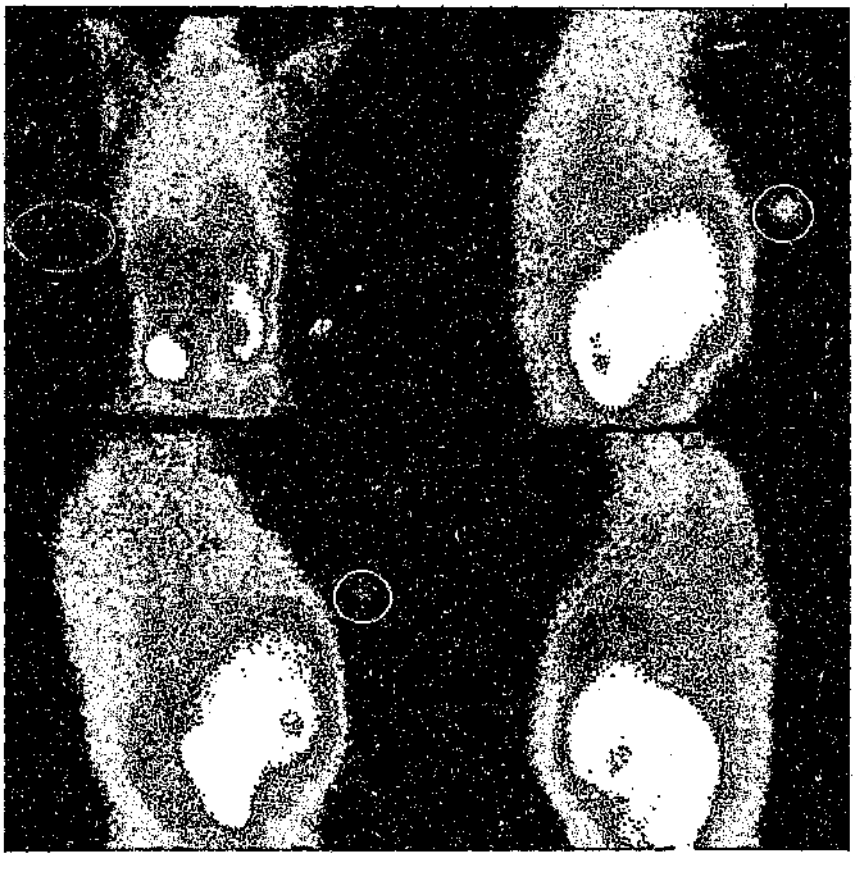
C. Consent forms

D. Observer results

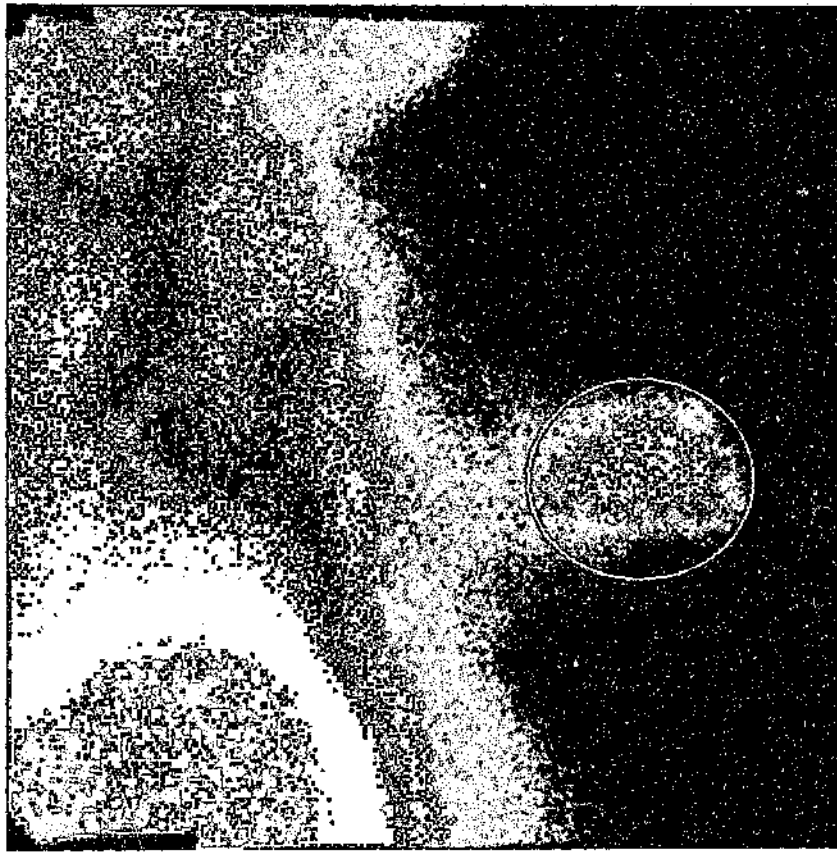
E. Statistical analysis performed by DMSA CC, University of the Witwatersrand.

APPENDIX A

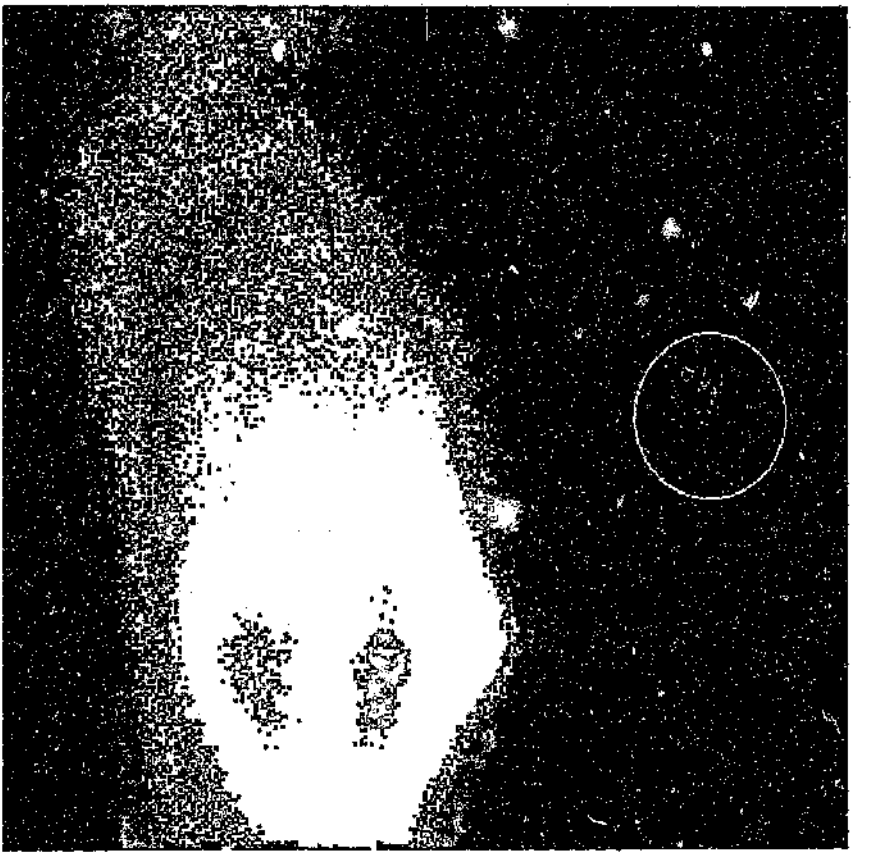
EXAMPLES OF SCINTIGRAPHIC IMAGES



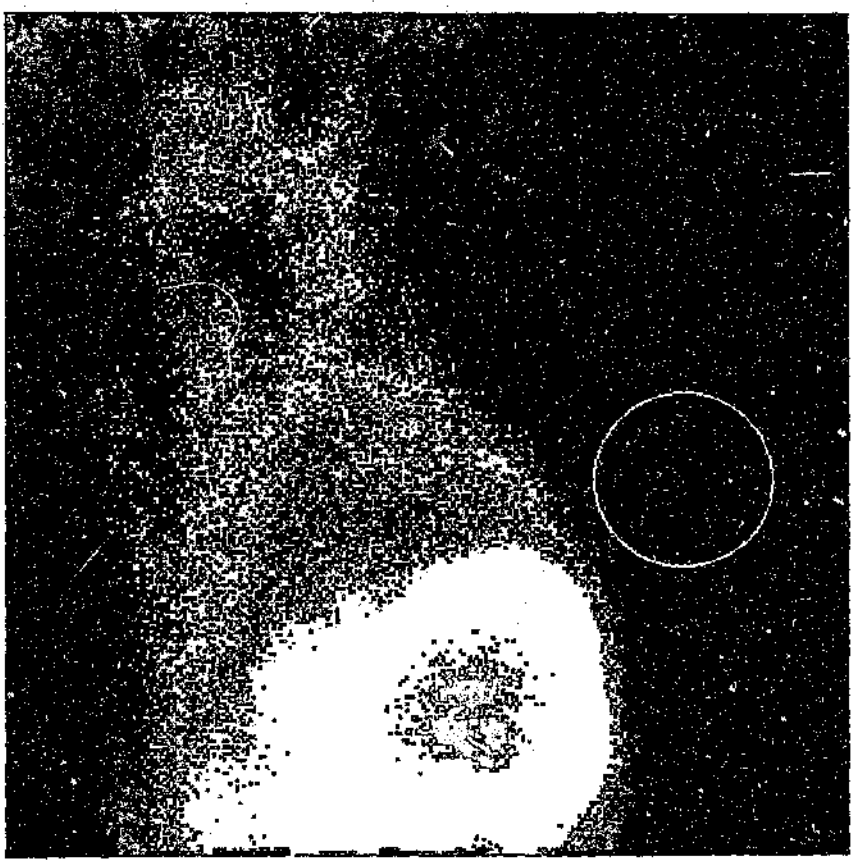
Fibroadenoma (four views) – Sestamibi Grading 2



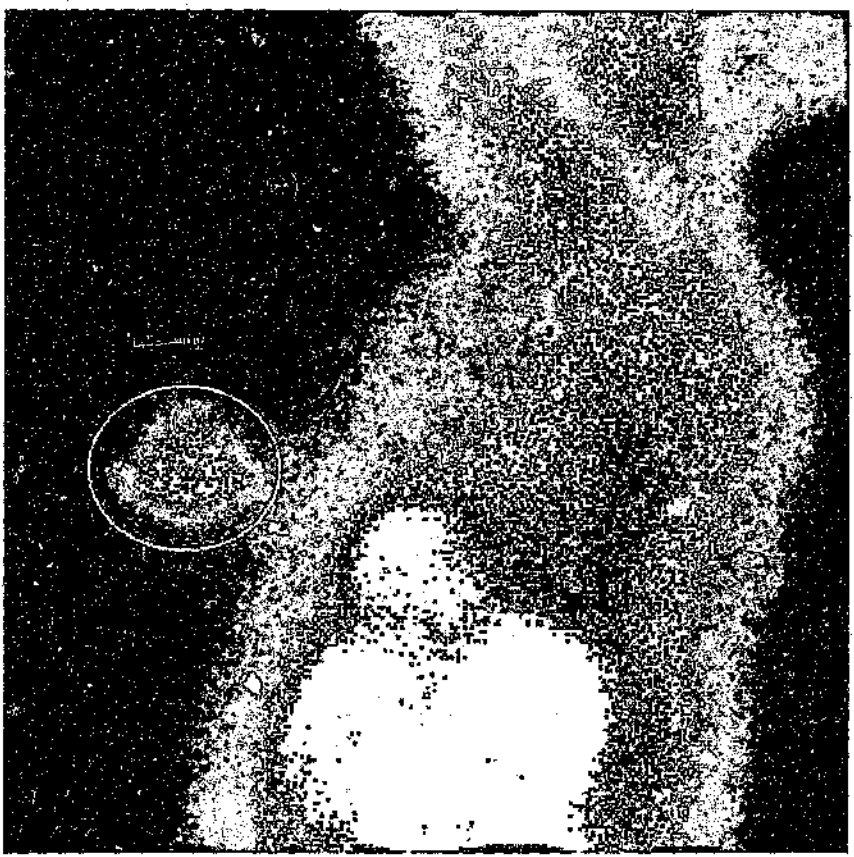
Chronic breast abscess – Sestamibi Grading 3



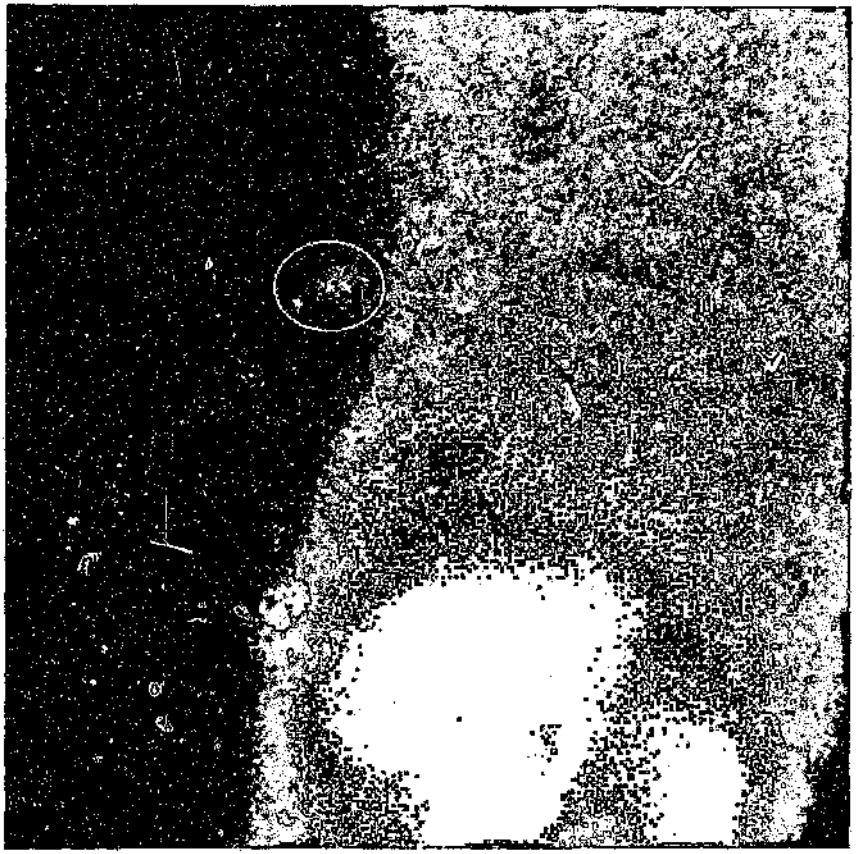
Fibroadenoma – Sestamibi Grading 2



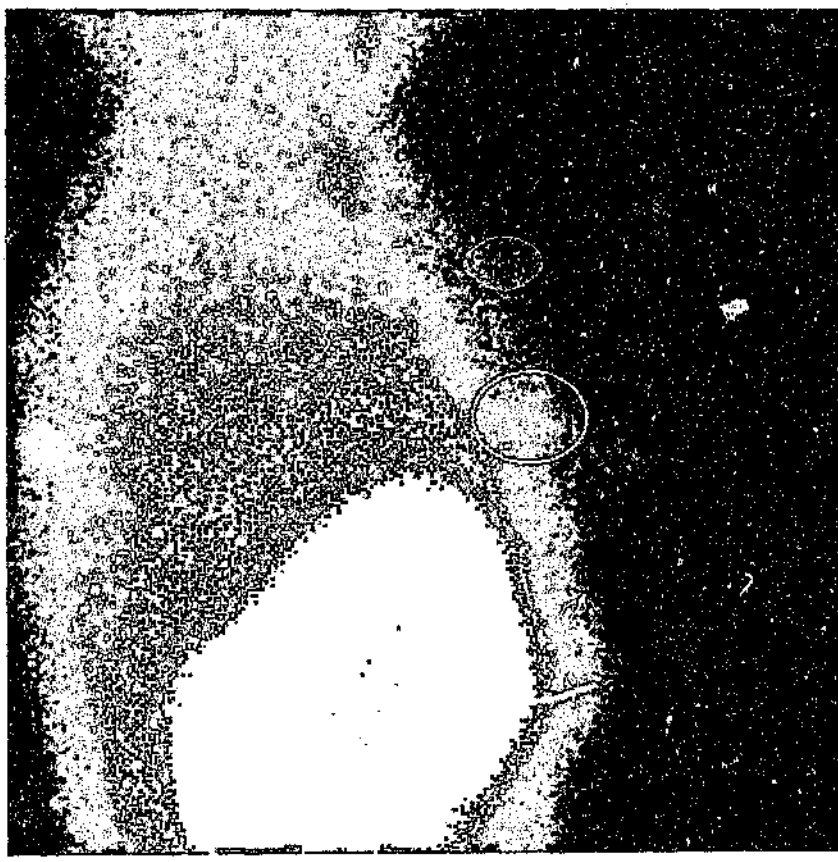
Fibroadenoma – Sestamibi Grading 1



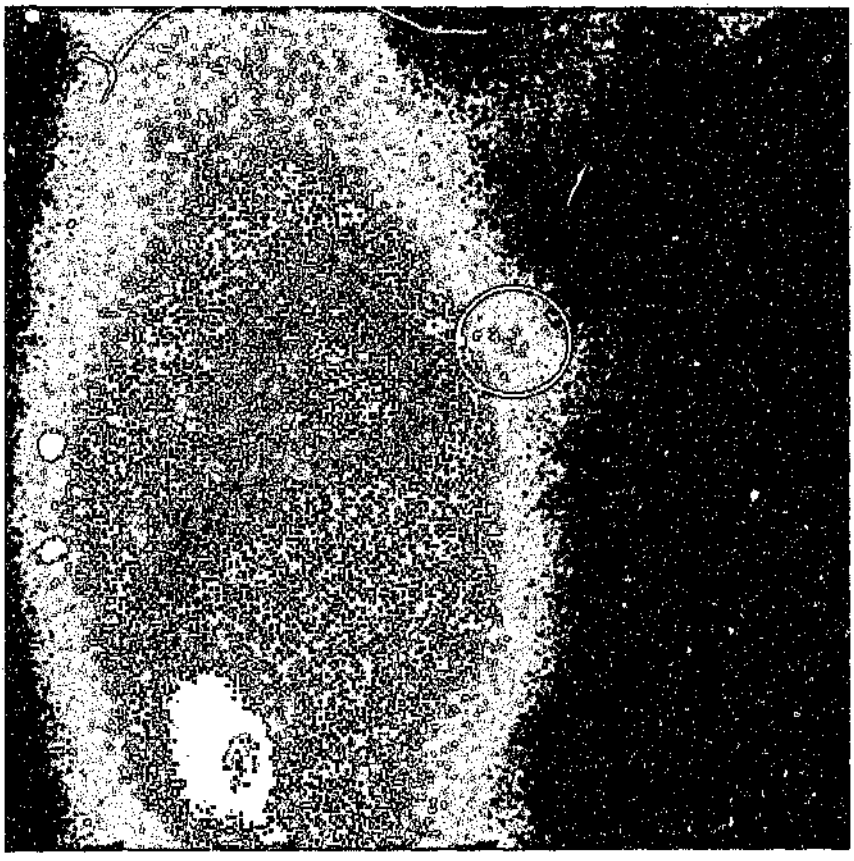
Carcinoma – Sestamibi Grading 3



Carcinoma – Sestamibi Grading 2-3



Carcinoma - Sestamibi - Grading 1-2



Carcinoma - MDP - Grading 1-3

APPENDIX B

CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 Geyer

CLEARANCE CERTIFICATE — PROTOCOL NUMBER M 950629

PROJECT	To establish the sensitivity,specificity and accuracy of Tc 99m Sestamibi in palpable breast masses in comparison to mammography and magnetic resonance imaging (Reported in literature: references attached)
INVESTIGATORS	Dr R Geyer
DEPARTMENT	Nuclear Medicine, Johannesburg Hospital
DATE CONSIDERED	950630

DECISION OF THE COMMITTEE *

Approved unconditionally

DATE 950829

CHAIRMAN. .....(Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

c c Supervisor: Dr A Mannel
Dept of Breast Clinic, Johannesburg Hospital

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 10th Floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee.

DATE....31.8.95.....SIGNATURE ....R Geyer.....

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C

CONSENT FORMS

ROLE OF BREAST SCINTIGRAPHY IN CANCER

Patient Information and Consent (Breast Cancer)

Because you have diagnosed breast cancer, I am asking you to participate in this research study to determine if radioisotopes can be useful to detect breast cancer. As your diagnosis has already been established, it will not be useful to you but may be of future benefit to other patients.

If you participate you will have a 20mCi Tcc99m Sestamibi injection followed by a scan of both breasts. This will involve lying face down for approximately twenty minutes and standing with arms raised for five minutes. Your privacy will be ensured by means of closed doors, adequate clothing and female staff only. Tc99m Sestamibi is a radioactive isotope but the lowest possible dosage is used to ensure minimal exposure to radiation (Tc99m Sestamibi has been safely used in many studies).

We are unable to use radioisotopes during pregnancy or if you are breastfeeding

Possible adverse effects include:

1) Short-lived metallic or bitter taste after injection.
2) Short-lived headache, flushing or non-itching rash.

Other rare adverse effects include possible seizures, short-lived arthritis of the wrists and allergic reactions.

We shall need to do a routine bone scan which is not part of this research, but is necessary as part of the investigations into your condition.

Participation in this study is voluntary and you are free to refuse to participate or to withdraw your consent and to discontinue participation at any time. If you decline or withdraw from this study it will not affect your treatment or medical care in any way. A signed copy of this consent form will be made available to you.

ROLE OF BREAST SCINTIGRAPHY IN BREAST CANCER

Patient Information and Consent (Benign Condition)

Because you **do not** have breast cancer, but do have a breast mass, I am asking you to participate in this research study, so that I can compare benign breast conditions to breast cancer using radioisotopes. This will enable me to establish the usefulness of radioisotopes in detecting breast cancer. Therefore, it may not be of use to you now, but hopefully will be of future benefit to other patients.

If you participate you will have a 20mCi Tc99m Sestamibi injection followed by a scan of both breasts. This will involve lying face down for approximately twenty minutes and standing with arms raised for five minutes. Your privacy will be ensured by means of closed doors, adequate clothing and female staff only. Tc99m Sestamibi is a radioactive isotope but the lowest possible dosage is used to ensure minimal exposure to radiation (Tc99m Sestamibi has been safely used in many studies).

The scan results will be discussed with you.

We are unable to use radioisotopes during pregnancy or if you are breastfeeding.

Possible adverse effects include:

1) Short-lived metallic or bitter taste after injection.
2) Short-lived headache, flushing or non-itching rash.

Other rare adverse effects include possible seizures, short-lived arthritis of the wrists and allergic reactions.

Participation in this study is voluntary and you are free to refuse to participate or to withdraw your consent and to discontinue participation at any time. If you decline or withdraw from this study it will not affect your treatment or medical care in any way. A signed copy of this consent form will be made available to you.

ROLE OF BREAST SCINTIGRAPHY IN BREAST CANCER

Patient Information and Consent (Possible Recurrence)

Because you have had breast cancer and this method may be useful in detecting a recurrence, I am asking you to participate in this research study. At present I am trying to establish the usefulness of radioisotopes in detecting breast cancer. Therefore, it may not be of use to you now, but hopefully will be of future benefit to other patients.

If you participate you will have a 20mCi Tc99m Sestamibi injection followed by a scan of both breasts. This will involve lying face down for approximately twenty minutes and standing with arms raised for five minutes. Your privacy will be ensured by means of closed doors, adequate clothing and female staff only. Tc99m Sestamibi is a radioactive isotope but the lowest possible dosage is used to ensure minimal exposure to radiation (Tc99m Sestamibi has been safely used in many studies).

We are unable to use radioisotopes during pregnancy or if you are breastfeeding

Possible adverse effects include:

1) Short-lived metallic or bitter taste after injection.
2) Short-lived headache, flushing or non-itching rash.

Other rare adverse effects include possible seizures, short-lived arthritis of the wrists and allergic reactions.

We shall need to do a routine bone scan which is not part of this research, but is necessary as part of the investigations into your condition.

Participation in this study is voluntary and you are free to refuse to participate or to withdraw your consent and to discontinue participation at any time. If you decline or withdraw, from this study it will not affect your treatment or medical care in any way. A signed copy of this consent form will be made available to you.

I have fully explained the procedures, identifying them as investigational and have explained their purpose. I have asked whether or not any questions have arisen regarding the procedures and have answered the questions to the best of my ability.

Date: .....

Doctor: .....

I have been fully informed as to the procedures to be followed and have been given a description of the attendant discomforts and risks to be expected. In signing this consent form I agree to participate in this method of investigation and I understand that I am free to refuse to participate or to withdraw my consent and discontinue my participation in the study at any time. I understand also that if I have any questions at any time they will be answered.

Date: .....

Patient: .....

Witness: .....

APPENDIX D

OBSERVER RESULTS

Observer Grading Comparison for Tc99m Sestamibi and MDP (Group A)

Patient		AGE	BREAST	MIBI Observers(4)	Observers	MDP Observers(3)	Observers	HISTOLOGY	HISTOLOGY
		Yrs		Lesion	Nodes	Lesion	Nodes	Lesion	Nodes
1	S.C	58	LEFT	0000	Negative			Malignant	
			RIGHT	3333	Negative			Malignant	
2	C de B	50	RIGHT	3333	4positive			Malignant	Positive
3	A D	51	LEFT	0101	Negative			Malignant	
4	E A D	28	RIGHT	1221	Negative	222	Negative	Malignant	
5	M F	60	RIGHT	1221	Negative	222	2Neg/1pos	Malignant	Positive
6	V F	53	LEFT AXIL	0000	Negative			Malignant	Positive
7	M C G	70	LEFT	0000	Negative			Malignant	
			RIGHT	0000	Negative			benign	
8	H H	66	LEFT	3333	3neg/1pos			Malignant	
9	Z K	55	LEFT	0000	Negative	000	Negative	Malignant	
10	C M	36	LEFT	1222	3Neg/1pos			Malignant	
11	J R M	78	RIGHT	1221	Negative	112	Negative	Malignant	Positive
12	M M	59	LEFT	3321	Negative	232	Negative	Malignant	
13	E M	54	LEFT	2232	Negative	123	Negative	Malignant	
14	B M	71	LEFT	3333	4positive			Malignant	
15	E N	35	LEFT	3322	3pos/1neg	111	Negative	Malignant	Positive
16	W P	48	LEFT	0000	Negative			Malignant	
17	M P	32	LEFT	2232	Negative			Malignant	Positive
18	A R	39	LEFT	2232	4positive			Malignant	
19	A J S	68	LEFT	1122	Negative			Malignant	
20	S S	53	RIGHT	1221	Negative	022	Negative	Malignant	
21	M T	47	LEFT	3332	4positive			Malignant	
22	C v H	54	RIGHT	1211	Negative	132	Negative	Malignant	Positive
23	R V	59	LEFT	0210	1pos/3neg	011	Negative	Malignant	Positive
24	M v Z	79	RIGHT	1111	Negative			Malignant	
25	B G Z	35	LEFT	1222	Negative	011	Negative	Malignant	

Observer Grading Comparison for Tc99m Sestamibi (Group B):

PATIENT		AGE	BREAST	MIBI GRAD Observers(4)	MIBI GRAD Observers(4)	HISTOLOGY
		Yrs		Lesion	Nodes	
1	JMB	33	LEFT X2	0000	negative	cyst
				1221	negative	fibroadenoma
2	HdS	39	RIGHT	2222	negative	fibroadenoma
3	GK	48	RIGHT	3333	negative	chron abscess
4	SM	20	LEFT	0110	negative	fibroadenoma
5	GM	53	RIGHT	0000	negative	benign
6	CM	36	RIGHTX2	0000	negative	benign
7	EM	28	LEFT	0000	negative	fibroadenoma
8	TM	18	LEFT	1121	negative	fibroadenoma
9	EM	48	RIGHT	1110	negative	fibroadenoma
10	DM	20	LEFT	1001	negative	benign
			RIGHT	2227	negative	fibroadenoma
11	VM	24	RIGHT	0000	negative	fibroadenoma
12	NM	35	RIGHT	1111	negative	fibroadenoma
13	KR	41	LEFT	1112	negative	cyst
14	DS	41	LEFT	2121	negative	benign
			RIGHT	1111	negative	fibroadenoma
15	HvA	53	RIGHT	0000	negative	fibroadenoma

APPENDIX E

STATISTICAL ANALYSIS

1. Inter-rater r ability tests:

Right side:

Category	PROP.	Kappa	St Dev	Z-value
0	0.60	0.89	0.2601	3.43
1	0.19	0.61	0.1598	3.85
2	0.12	0.46	0.1556	2.96
3	0.08	0.92	0.1589	5.76

Overall results:

Kappa	St Dev	Z-value
0.74	0.0754	9.83

Left side:

Category	PROP.	Kappa	St Dev	Z-value
0	0.56	0.75	0.2425	3.09
1	0.17	0.23	0.1574	1.47
2	0.17	0.26	0.1574	1.66
3	0.11	0.49	0.1560	3.17

Overall result:

Kappa	St Dev	Z-value
0.48	0.0664	7.30

Nodes:

Category	PROP.	Kappa	St Dev	Z-value
Present	0.85	0.75	0.4650	1.60
Absent	0.15	0.75	0.1562	4.77

Comment:

The Z-value is greater than 1.96 for breast masses, therefore there is a strong correlation between observer results. The Z-value for node detection is <1.96.The correlation between observers for node detection is poor.

2. Comparison of Sestamibi with histology:

Sample size is adequate to perform binomial distribution test approximating the normal distribution.

Results:

Condition	Grading	Frequency	Prop	Z-value	P-value
Benign	0	34	0.45333	39.4576	0
Benign	>0	41	0.54667	47.5812	0**
Malignant	0	32	0.23881	27.7831	0**
Malignant	>0	102	0.76119	88.5585	0

**Note: The Z-values are large and the P-values are small. This means that the given proportions are significantly greater than zero, meaning that there is no significant difference between benign and malignant in the grading.

Node detection analysis:

Frequency Percent	Histology-Positive	Histology-Negative	Total
Grading-Positive	4.81	8.56	13.37
Grading-Negative	20.86	65.78	86.63
Total	25.67	74.33	100.00

Statistic	DF	Value	Probability
Chi-Square	1	1.614	0.204
Likelihood Ratio Chi-Square	1	1.519	0.218
Continuity Adj. Chi-Square	1	1.050	0.306
Mantel-Haenszel Chi-Square	1	1.606	0.205

The results show no significant difference between histology and the rater's scores on nodes.

3. Sestamibi vs MDP:

Frequency Cell Chi-Square	0	1	2	3	Total
MDP	6	12	12	3	33
SESTAMIBI	4	8	17	4	33
Total	10	20	29	7	66

Statistic	DF	Value	Prob
Chi-Square	3	2.205	0.531
Likelihood Ratio Chi-Square	3	2.218	0.528
Mantel-Haenszel Chi-Square	1	1.580	0.209

The results show no significant difference between Sestamibi and MDP at the 5% level.

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