THE ROLE OF TECHNETIUM-99m SESTAMIBI SCINTIMAMMOGRAPHY TO EVALUATE PALPABLE BREAST LESIONS: A COMPARISON WITH MAMMOGRAPHY AND HISTOLOGICAL RESULTS

BY

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DEDICATED TO

MY PARENTS

for leading their children into intellectual pursuits

MY WIFE TAHMEED

for her magnificent devotion to her family

MY DAUGHTERS FAARIA & EMAN

for making everything worthwhile

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PREFACE

This study was conducted with the support of the Combined Breast Clinic at our institution which consists of the Departments of Surgery, Radiology and Radiation Oncology.

The work was done in three parts.

The literature showed somewhat lengthy imaging procedure for scintimammography which were not whole suitable to the setting of the Combined Breast Clinic. Initially a *Pilot Study* was conducted to determine the practicality of the imaging procedure. The results of this study were promising but the imaging procedure was time consuming. Certain modifications were subsequently done in the imaging method of the *Formal Study* to accommodate more number of patients into the study without jeopardizing the quality of the images. This study, however, had a shortcoming in that the way this study was structured one could not demonstrate *lesion by lesion* analysis of each breast lesion detected on clinical examination, mammography and scintimammography with their respective biopsy results. Our *Formal Study* and the literature suggested that scintimammography is of value in patients with *indeterminate mammograms* due to its high negative predictive value.

Therefore, a separate *Additional Study,* with the same scintigraphic method, was conducted on patients with clinical breast lumps with *indeterminate* mammographic lesions. Special emphasis was placed on *lesion by lesion* comparison of each breast lesion detected by clinical examination or scintimammography or both with the biopsy results of that particular lesion.

CONTENTS

CHAPTER ONE

INTRODUCTION

1.1. BACKGROUND

Breast cancer is the most common and probably the most feared malignancy of women today. It is the leading cause of cancer related deaths in women in the United States after lung cancer, with 46,000 deaths from the disease and 183,400 new breast cancer cases reported in 1995. The incidence of breast cancer has been reported to be rising at an annual rate of 3% in US [1]. In South Africa during 1992, 4084 new breast cancer cases were recorded by the National Cancer Registry. The overall lifetime risk of developing cancer in the female population in South Afica is 1 in 31 [2].

The primary purpose of screening women for breast cancer is to diagnose breast cancer at an early stage and thus reduce mortality. Traditionally, clinical breast examination, mammography and ultrasonography have been the mainstay of breast cancer detection. Mammography has been shown to have certain limitations [3-6]. Ultrasonography results in improved specificity when used in combination with mammography and is used in most breast centres to direct patient management. The sensitivity and specificity of ultrasound is variable and depends upon multiple factors. However, newer transducers seem to be more sensitive [7]. At the same time, newer imaging modalities, including several nuclear imaging techniques, have become important role players in breast cancer detection [8].

Scintimammography (SMM) is a relatively recent development in clinical nuclear medicine. Thallium 201 (Tl-201) and recently Technetium-99m methoxyisobutylisonitrile (Tc-99m MIBI) have been suggested as radiopharmaceuticals with a great deal of promise in imaging breast cancer. Recent medical literature contains several reports regarding the efficacy of these agents [9-21]. Tc-99m MIBI has been at the forefront of radiopharmaceuticals used for breast cancer evaluation. The United States Food and Drug Administration has recently approved the clinical use of Tc-99m MIBI for breast imaging as it has been found to be a potentially important radiopharmaceutical for the evaluation of primary breast cancer.

1.2. AIMS

The aims of the study were:

Firstly, to determine if Tc-99m MIBI scintimammography differentiates benign from malignant breast lesions and secondly, to compare the sensitivity and specificity of Tc-99m MIBI scintimammography with that of mammography in the detection of primary breast cancer.

1.3. SCOPE AND LIMITATIONS OF RESEARCH

The results of numerous recent trials, using Tc-99m MIBI, have shown high sensitivity, specificity and predictive values for the detection of palpable breast cancer [22]. The reasons for this study were to validate the results of others with respect to sensitivity and specificity, using an optimal imaging method. Therefore, for the first time at our institution, we have tested the value of this relatively new non-invasive diagnostic modality for the detection of breast cancer, in addition to already well established procedures like x-ray mammography and biopsy.

1.4. STRUCTURE OF THE THESIS

The next chapter (2) covers the relevent literature review pertinent to the diagnosis of breast cancer. The role of mammography, its limitations and those of nuclear medicine imaging, with special emphasis on Tc-99m MIBI in the diagnosis of breast cancer, have been reviewed.

Chapter 3 deals with the methodology, and describes the sample selection criteria, method of fractionating sestamibi including its quality control and the actual scintimammography (SMM) imaging procedure.

Chapter 4 describes the results of SMM, mammography and biopsy findings and

their comparative analysis.

Chapter 5 contains an additional study, conducted on patients with clinically palpable breast lumps and with indeterminate mammography findings, in order to determine the value of Tc-99m MIBI SMM in diagnosing breast cancer in those patients.

Chapter 6 includes discussion on the findings of the research and relating them to published studies and reporting both the importance and the limitations of the research.

Chapter 7 describes the conclusions drawn from this study. Also included are the recommendations arising from the research.

CHAPTER TWO

LITERATURE REVIEW

In this chapter, the literature pertinent to the diagnosis of breast cancer in general and the use of nuclear medicine in particular, is reviewed. Special emphasis is laid on the use of Tc-99m MIBI, the reagent of interest in the present study.

2.1. IMPORTANCE OF BREAST CARCINOMA AND ITS DIAGNOSIS

Breast cancer is the leading cause of death among women between the ages of 40 and 55 years. The best line of defence against it is early detection. The three early detection methods currently used are *breast-self examination, clinical breast examination* and *screening mammography*. As 9 out of 10 breast cancers can be discovered by women themselves, regular and correct *breast self-examination* must be taught to all women, regarding what symptoms and signs to look for and which changes are significant enough to merit further examination.

The doctor may detect a breast problem in a patient with a specific symptom or in an asymptomatic patient, as part of a routine medical examination. The earlier the doctor is presented with a problem, the sooner treatment can be started. A suspicious feature detected on *clinical examination* will require further investigation and treatment. The detection of early breast tumours on *screening mammography* can significantly contribute to the early diagnosis of breast cancer. Neither breast examination nor mammography, however, can accurately differentiate breast cancer from the myriad of benign breast abnormalities.

The diagnosis of breast cancer in patients presenting with breast masses is difficult when using non-invasive techniques because of their limitations in distinguishing between cancerous and non-cancerous lesions. This causes a great reliance on invasive procedures such as biopsy for confirming the nature of a breast lesion. Thus thousands of women are subjected to a potentially unnecessary biopsy procedure with associated risk, discomfort and expense. According to Kunni [23], breast biopsy results are negative for breast cancer in 68-87% of women, varying from one institution to another. Therefore, it has been suggested that a better diagnostic imaging tool is needed that can reduce the number of unnecessary biopsies [24].

2.2. ROLE OF MAMMOGRAPHY IN THE DIAGNOSIS OF BREAST CARCINOMA AND ITS LIMITATIONS

Athough mammography is used routinely and is considered as a non-invasive diagnostic tool of high standard, it is actually of limited value in the evaluation of clinically evident breast abnormalities as it can potentially "overdiagnose" the number of breast cancers. Mammography depends on the differential attenuation of x-rays passing through compressed breast tissue. Breast malignancies are detected due to spiculation and calcifications within or around neoplasms or the increased density of the neoplastic tissue relative to adjacent normal breast tissue. According to Sickles [6], calcifications may sometimes be the only evidence for malignancy within the breast. However, many benign conditions also result in calcifications, which will result in false positive mammograms.

Kopans [25] has suggested that the primary value of mammography is the earlier detection of breast cancer through the screening of asymptomatic women. However, there is value in mammography for symptomatic women, but it should not be overestimated. He further states that mammography is used routinely to assess an individual who has a lump, thickening, discharge or other sign or symptom that might indicate a possible malignancy. Mann et al. [26] have reported that in women with fatty breasts the mammographic interpretation is known to be very accurate but it has certain limitations, particularly in young women with dense breasts, because radiographically dense glandular breast tissue may obscure an underlying tumour.

Some mammographic screening studies have shown that early detection of breast cancer allows a 30% reduction in mortality in patients older than 50 years [27-30]. The *screening mammography* method has the potential to detect lesions well before they are palpable. The threshold for screening mammography to detect a breast lesion may be as low as 2 mm [31]. Shapiro [32] has reported that mammography with current film screen technique is sensitive in detecting breast cancer. According to Lannin et al. [33], however, there are still significant limitations to the use of mammography in the detection of breast cancer, and these limitations persist in spite of technical improvements that facilitate diagnosis, especially in women with dense breasts. Kopans [25] has suggested that, as mammography fails to demonstrate between 5% and 15% of cancers, it cannot be relied on to exclude a malignancy.

The purpose of breast imaging is the detection of lesions and differentiation of benign from malignant lesions. According to Hermann and Winsberg, "Each new modality must be compared to x-ray mammography to determine whether it can supplement or replace mammography in detecting and characterising breast abnormalities. If an imaging modality complements plain mammography in detection of lesions or differentiation of benign from malignant lesions, then it should be used" [34]. Several recent articles have emphasised the role of nuclear medicine techniques in the detection of breast carcinoma [7,8,22].

2.3. ROLE OF NUCLEAR MEDICINE IMAGING IN THE DIAGNOSIS OF BREAST CANCER

Nuclear medicine techniques rely on biological and physiological characteristics of tumours and have been used to evaluate breast cancer.

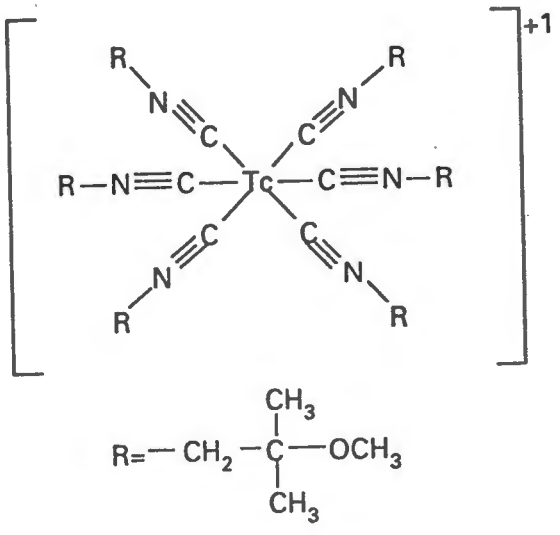
2.3.1. Radiopharmaceuticals

A wide variety of radiopaharmaceuticals have been used for breast imaging.[22]. These include nonspecific tumour imaging agents like thallium-201 (Tl-201) [9,35-37] and technetium-99m (Tc-99m) labelled agents, which include methoxyisobutylisonitrile (MIBI) [10,12-21,38,40-42] and tetrofosmin [42-46], the bone imaging agent Tc-99m methylene diphosphonate (MDP) [20,47], and specific agents such as indium labelled (In-111) somatostatin analogs [48-50] and monoclonal antibodies.

Breast tumour scintigraphy was first performed with thallium chloride (Tl-201) [51] but thallium has largely been replaced by technetium-99m labelled MIBI because of its superior imaging characteristics. Originally developed as a myocardial imaging agent, Tc-99m MIBI has been found to concentrate in a number of different tumours [52,53]. The first use of Tc-99m MIBI in tumour imaging was reported by Muller et al. [54].

2.4. TECHNETIUM-99m HEXAKIS-2-METHOXY-2-ISOBUTYLISONITRILE (Tc-99m SESTAMIBI): A VALID BREAST TUMOUR IMAGING AGENT

2.4.1. Structure of Sestamibi



Tc-99m sestamibi (MIBI) is a positively charged lipophilic complex belonging to a new class of Tc-99m labelled isonitrile compounds, formed with technetium in a +1 oxidation state [Tc (I)]. The ligand tetra (2-methoxyisobutyl isocyanide) copper (I) chloride is synthesized by heating 2-methoxyisobutyl isocyanide with anhydrous cuprous chloride in anhydrous ethanol at 90°C for 1 hour.The compound is purified and prepared in a kit form for labelling with Tc-99m pertechnetate. After labeling the six monodentate methoxyisobutyl isocyanide (MIBI) ligands are symmetrically attached to the central Tc-99m atom [55].

2.4.2. Clinical role of Sestamibi

Tc-99m MIBI has been effectively used in tumour imaging of patients with lung cancer [13,56], recurrent brain gliomas [57], bone tumours [58], carcinoma of the thyroid gland [59], parathyroid adenomas [60], and more recently, breast carcinoma [10,12,14,21].

In published research series, sestamibi breast imaging has demonstrated high sensitivity and specificity in differentiating benign from malignant breast lesions when compared to histopathological results. Several studies demonstrate overall sensitivity of 84%-96% for the detection of breast carcinoma using Tc-99m MIBI [12,14,16,18,61].

2.4.3. Experimental Evidence

Most breast cancers have increased blood flow and many tumours induce neovascularity strictly to facilitate tumour growth. Scopinaro et al. [62] have shown a close relationship between neoangiogenesis and Tc-99m MIBI uptake. Their study suggested that Tc-99m MIBI is a marker of breast cancer invasiveness: its uptake is related to angiogenesis and; possibly, to oxidative metabolism of the tumour.

Experimental studies on cultured normal cells and carcinoma lines using Tc-99m MIBI have shown that neoplastic cells have a metabolic rate of 4-10 times that of normal cells [11]. These experimental studies with cultured cells emphasize the role Tc-99m MIBI can play for *in vivo* tumour imaging in humans. The experimental results of De Jong et al. [44] showed that, among the Tc-99m labelled compounds tested, Tc-99m MIBI has the highest cellular uptake in 60 minutes, in both normal and human breast tumour cells, theoretically making it the most suitable compound for imaging. Delmon-Moigeon et al. in 1990 demonstrated in their experiments, uptake of Tc-99m MIBI in nine tumour cell lines [63]. Preliminary reports have suggested *in vivo* localization of MIBI in primary cancers and metastatic deposits from thyroid, lung and bronchial carcinoma [64]. Stimulation of metabolism by some growth factors [65] or changes in neoplastic plasma membranes may also play a role [63,66].

2.4.4. Advantages of Tc-99m MIBI over Tl-201

Tc-99m MIBI has some properties similar to those of Tl-201 chloride (e.g. myocardial accumulation) as well as some dissimilar characteristics (notably lack of redistribution). It has been successfully evaluated for myocardial imaging [67,68]. Labelling with Tc-99m has several advantages over Tl-201. These advantages are related to its continuous availability for use, freedom in patient scheduling, smaller radiation dose

to the patient, larger injected dose and better physical characteristics for both dynamic, static and tomographic studies [56].

2.4.5. Mechanism of Uptake of Tc-99m MIBI

Many studies have shown that Tc-99m MIBI is often, but not always, taken up by breast cancer cells [10,14,18,41]. Crane et al. [69] recently performed an experimental study using Tc-99m MIBI imaging in the c-neu Onco Mouse TM (transgenic mouse that spontaneously develops mammary tumours). Results showed that tumour retention of Tc-99m MIBI was highest at the periphery of the tumour, while the centre of the tumour (often acellular and filled with blood and necrotic debris) showed less retention. These data support the use of Tc-99m MIBI as a marker of active cellular tumour tissue. Recent data suggest that 90% of the Tc-99m MIBI activity is concentrated in the mitochondria [70]. The exact mechanism of uptake of Tc-99m MIBI by tumour cells is not yet clearly understood. It has been shown that Tc-99m MIBI is taken up by mitochondria using some form of active transport, but is passively transferred across the cell membrane [18].It accumulates within the mitochondria and cytoplasm of cells on the basis of trans-membrane electrical potentials [71].

2.4.6. Pharmacokinetics of Tc-99m MIBI

After intravenous injection at rest, the highest Tc-99m MIBI concentration is found in the gall bladder and liver, followed by the heart, spleen and lungs. As hepatic activity decreases in the first hour because of excretion via the biliary tract, maximum accumulation occurs in the gall bladder at 60 minutes [67]. Twenty percent of the injected dose is cleared through renal elimination in 24 hours. The agent is excreted without any evidence of metabolism [72].

2.4.7. Dosimetry

Organ dosimetry of Tc-99m MIBI demonstrates that a dose of 740 MBq (20 mCi) delivers 0.03 Gy (3 rads) to the large intestine, which is the predominant target organ. The whole body dose is 0.003 Gy (0.3 rad) [67].

2.5. FACTORS AFFECTING UPTAKE OF TECHNETIUM-99m MIBI

There are many factors which can affect the uptake of Tc-99m MIBI in SMM imaging and therefore influence the detection. The nature, size and location of the breast lesion are among the important factors. These effects are discussed in detail in Chapter 6. Chemotherapy and/or radiotherapy prior to surgery can also have an effect. This factor did not play an important role in the present study because coincidentally none of the patients we selected had had chemo and/or radiotherapy prior to surgery. Therefore this is not discussed in Chapter 6, but a brief review of the pertinent literature follows here.

2.5.1. Effects of Chemotherapy and Radiotherapy

It is assumed that as breast conserving surgery continues to become more prevalent [73], the ability of MIBI breast imaging to noninvasively investigate the primary breast cancer will become very important. Chemotherapy administered prior to surgery allows breast conservation in a far greater number of women and may improve survival from breast cancer even in advanced stages [74]. Mankoff et al. [75] performed Tc-99m MIBI SMM in 14 patients with locally advanced breast cancers, who underwent chemotherapy before surgery. The SMM was done before and after chemotherapy and then followed by surgery. These authors suggested that this reduced uptake of Tc-99m MIBI may have been related to pleiotropic (multiple) drug resistance (MDR).

According to Kabasakal et al., multiple drug resistance (MDR) is a problematic form of resistance in which tumour cells that become refractory to chemotherapy develop cross-resistance to a variety of other agents [76]. This resistance to a broad range of structurally unrelated drugs, due to enhanced outward transport of drugs, is mediated by p-glycoprotein that is encoded by multiple drug resistance gene (MDR1). This specific protein functions as an energy-dependent extrusion pump that efficiently transports cationic and lipophilic chemotherapeutic agents as well as some toxins, causing decreased accumulation and decreased retention of these agents. The same mechanism for the outward transport of all drugs was found to be responsible for the rapid efflux of MIBI from cells resulting in its suboptimal intracellular accumulation [77].

Recently, Piwnica-Worms et al. [78] have shown that decreased accumulation of MIBI in MDR cells can be reversed by administration of MDR-modulating agents such as verapamil. Varrella et al. [79] and Khalkhali [22] have also reported similar results, which suggest that decrease in MIBI uptake after chemotherapy could be used to detect p-glycoprotein-dependent MDR and so aid in tailoring chemotherapy protocols and developing new drugs targeted to inhibit p-glycoprotein expression.

On the other hand, Cwikla et al. [80] showed that infact reduced uptake of Tc-99m MIBI after chemotherapy might be a non-specific change i.e. not related to MDR and therefore not predictive of the clinical response to treatment. They demonstrated that the reduction in the uptake of Tc-99m MIBI in patients receiving chemotherapy as initial treatment, before surgery, was independent of the tumour size. Reduced uptake was seen not only in those patients in whom tumour size was reduced but also in patients in whom tumour size increased during treatment. This is because the size of the lesion is influenced by other factors, such as oedema and inflammatory cell infiltrate.

Cwikla et al.[80] also suggested that the reduction in uptake of Tc-99m MIBI did not bear any relationship to clinical response. The proportion of *viable* malignant cells present is important rather than the size of the lesion. They showed that exposure of the tumour to cytotoxic chemotherapy results in reduced uptake of Tc-99m MIBI, and assumed that these changes in uptake were due to expression of the MDR-1 gene or interference in the mitochondrial uptake of Tc-99m MIBI.

The effect of radiotherapy on Tc-99m MIBI uptake in tumours was first shown by Hassan et al. [56]. They demonstrated reduced MIBI uptake in patients with lung carcinoma after radiotherapy (2000 rads). They reported that the mechanism of the radiation effect seemed to be related to interference with the binding of MIBI to intracellular protein (lysosome protein to which MIBI is attached in a viable cell). Presumably, similar effects could be implicated in breast cancer which shows decreased MIBI uptake.

2.5.2 Technical Aspects to be considered in SMM

Careful patient positioning is critical to SMM interpretation. Protocols used for SMM have included supine, upright and prone imaging [12,20,40]. Diggles and co-

workers [40] described prone dependent-breast imaging, which has several advantages over the supine or upright position. The prone position allows relaxation of anterior chest muscles, which helps in evaluating deep breast tissue adjacent to the chest wall. This position also allows improved separation of breast tissue from liver and myocardium, allowing improved lesion detection.

CHAPTER THREE

METHODOLOGY

3.1. PURPOSE

As stated in Chapter 1, the objectives of the study were firstly, to determine if Tc-99m sestamibi (MIBI) scintimammography differentiates benign from malignant breast lesions and secondly, to compare the sensitivity and specificity of Tc-99m MIBI scintimammography (SMM) with that of mammography in the detection of primary breast cancer.

3.2. SAMPLE SELECTION

The study population consisted of 51 women between the ages of 33 and 81 years with a mean age of 50 years. This formal study followed a pilot study on a sample of 11 patients chosen according to the same criteria (see Appendix A).

Women selected for this trial were chosen by an experienced surgeon at the Breast Clinic at Groote Schuur Hospital, Cape Town and represent patients with clinically ***palpable breast lumps***. Some of these selected patients also had a high risk of breast cancer and therefore a higher prior probability of the breast lumps being malignant, due to:

a) A family history of breast cancer;
b) Previous occurrence of breast cancer;
c) Previous breast surgery.

The Combined Breast Clinic (CBC) is held once every week at Groote Schuur Hospital in its out-patient department. The concept of *CBC* is well known in many developed countries [81]. In our institution it is jointly run by the multidisciplinary teams of breast specialists from departments of *Surgery, Radiotherapy, Anatomical Pathology (Cytopathology) and Radiology*. Only patients with breast diseases are referred to the clinic

for screening and follow-up purposes. All patients are seen as out-patients. For patients with breast lumps, combined assessment (aspiration cytology and mammography) of clinically suspicious breast masses is performed. The patients who need further evaluation and treatment are referred to the respective departments. This routine is practised at the *CBC,* firstly to improve efficiency and secondly, as a cost and time saving measure for the patient and the hospital. *Mammography* and *Fine Needle Aspiration Biopsy (FNAB)* are performed as part of the normal screening process on all patients with clinically palpable breast lumps.

The patients selected for nuclear medicine breast imaging, *Scintimammography (SMM)*, along with routine *Mammography* and *FNAB*, usually underwent all these investigations on the same day. They always underwent *SMM* before the *FNAB*, because *FNAB* is a minor surgical (invasive) procedure and therefore can potentially interfere with the results of *SMM*. All these patients were asked for their informed consent and the research was explained to them.

The *FNAB* was performed at the *Combined Breast Clinic*. The *mammography* and *SMM* scans were done in the Departments of Radiology and Nuclear Medicine respectively.

The following patients with palpable breast lumps were ***excluded*** from selection for SMM:

1. Patients who had undergone any *invasive procedure* on the involved breast during the past month (e.g biopsy) or had any *inflammatory lesion* (e.g. mastitis, ulceration), as these may cause false evidence of increased activity in the breast to appear on the scan.

2. Pregnant patients, to avoid any radiation effects on the foetus.

3. Patients who were physically or mentally handicapped and could not comprehend the prerequisites of the scanning procedure or give informed consent.

As there was no definitive imaging protocol available at the time the trial was started, a pilot study was conducted in order to determine an appropriate imaging

procedure (see Appendix A).

3.3. PROCEDURE

All the patients underwent scintimammography scans using locally produced sestamibi (methoxyisobutylisonitrile- *Myotek*) produced by the Atomic Energy Corporation (AEC) of South Africa.

Each vial contained:

$[Cu(DM1)_4]BF_4$	*1.00 mg*
Cysteine	*1.00 mg*
Sodium dihydrogen citrate	*2.50 mg*
Mannitol	*20.00 mg*
Tin dichloride($SnCl_2.2H_2O$)	*0.08 mg*

(DM1: one deuterium atom)

Sestamibi is produced in lypholysed form and not as liquid.

3.3.1. Use of Fractionated Sestamibi

Cost-effective preparation of various Tc-99m radiopharmaceuticals by splitting kits has been explored in recent years. Use of *fractionated* MIBI is economically advantageous and may enable many additional patients to be diagnosed [82].

In order to make the radiopharmaceutical economically affordable, each vial of MIBI was divided into multiple fractions (fractionated) before use. Each sestamibi vial was reconstituted with sterile saline, and divided into *10 fractions*. *Quality control* was performed on each fractionated dose to ensure the purity and efficacy of the product.

3.3.2. Fractionation Procedure

Items required:

1. A vial of *sestamibi* from the refrigerator which was allowed to equilibrate to reach room temperature.
2. Ten "elu"/10ml vials from the hot laboratory, to store the fractionated *sestamibi*. These vials were labelled with the radiopharmaceutical name, lot number and date of fractionation.
3. A 10ml vial of nitrogen-purged saline from the hot laboratory. This was used to reconstitute the *sestamibi*.

Method

Fractionation was performed in a *Laminar Flow Cabinet (LFC)* as the fractionated sestamibi might be stored for extended periods and it is essential to maintain sterility.

1. The *LFC* was switched on and the stainless steel tray wiped with alcohol.
2. Anything not removed from sterile packaging was sprayed with alcohol before it was introduced into the *LFC*.
3. The vials were purged with nitrogen, in order to provide an oxygen-free storage

units were attached to the green tubing connected to the nitrogen cylinder and 21-gauge needles to the other end of the filters. All the tubing was wiped with alcohol before being put into the *LFC*.

4. 5ml of nitrogen-purged saline was withdrawn into a 5ml syringe using a 21-gauge needle. It was necessary to ensure that there were no air bubbles in the syringe, as any air introduced into the sestamibi will adversely affect the labelling efficiency.
5. 5ml of saline was added to the sestamibi vial, an equal amount of air being withdrawn to equalise the pressure. The vial was shaken gently several times.
6. The entire contents of the vial of reconstituted sestamibi vial were withdrawn into a 5ml syringe, fitted with a 26-gauge needle. Again all air bubbles were eliminated.
7. 0.5ml of the reconstituted sestamibi was introduced into each elu vial, with exclusion of air.
8. All elu vials were purged with nitrogen in the following manner:
   A small 26-gauge needle was inserted into the elu vial. The 21gauge needle attached to the filter was then pushed into the elu vial, and the nitrogen cylinder was turned on to a pressure of 60kPa. After one minute of purging both needles were removed simultaneously.
9. The reconstituted sestamibi was stored in the freezer compartment of a refrigerator at -4 to -8°C.

In order to compensate for oxidation of tin during the storage of sestamibi, additional tin was added to the fractionated sestamibi. The tin was obtained from invivo *Red Blood Cell Labelling Agent*, manufactured by *AEC of South Africa.* Each vial of invivo *Red Blood Cell Labelling Agent* contains 2504g of tin.

When required, the individual dose was thawed at room temperature and mixed with Tc-99m pertechnetate.

Each dose was prepared as follows:

1. A vial of fractionated sestamibi was removed from the freezer and allowed to stand on a bench top to thaw and reach room temperature (approx. 5 minutes).
2. A vial of invivo *Red Blood Cell Labelling Agent* was diluted with 5ml of normal saline. Then 0.1ml of the diluted solution (containing 50.08μg of tin) was added to the thawed sestamibi as described, followed by approximately 1000 MBq of Tc-99m pertechnetate.
3. The vial was then placed in boiling water for 10 minutes after which it was cooled in cold water for 2 minutes.

3.3.3. Quality Control of Fractionated Tc-99m Sestamibi

Each reconstituted dose was tested, before use, to ensure that the labelling efficiency was satisfactory. Miniaturized rapid ascending paper radiochromatography technique, developed by Owunwanne et al. [83], was performed as illustrated in Figure 3.1.

Mobile Phase: Ethyl acetate

Stationary Phase: Schleicher & Schüll paper No. 2040 A

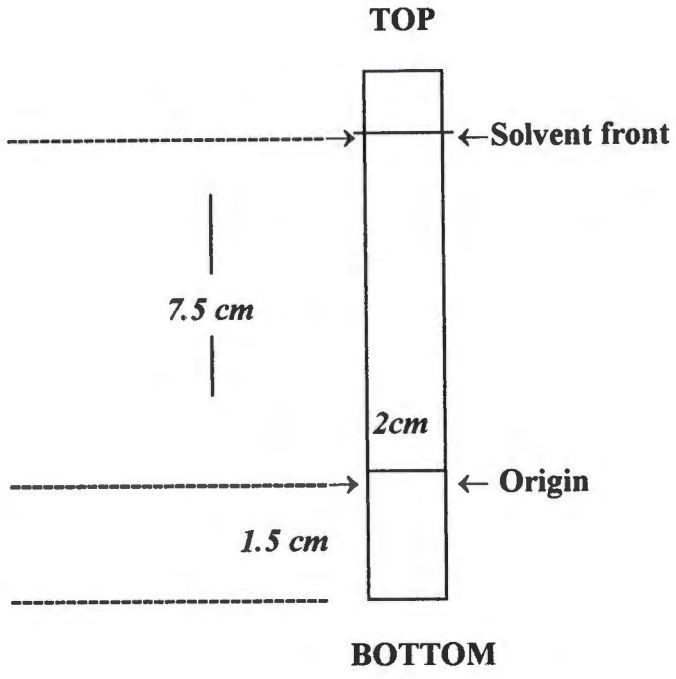


Figure 3.1. Illustrating the dimensions of the *Scheicher & Schüll paper* and the levels of solvent movement.

Method:

1. Ethyl acetate was added to a 100 ml beaker to a depth of approximately 1cm.
2. The upper end of the paper strip (10 x 2cm) was pierced with an orange needle.
3. The strip was placed on 2 supports.
4. With a 1ml syringe, a small amount of the radiopharmaceutical was spotted at the origin. A copper wire holder was threaded through the hole in the strip and the strip was suspended in the beaker containing the ethyl acetate. The bottom of the strip was immersed in the ethyl acetate but its level was well below the radiopharmaceutical spot.

5. The chromatogram was developed until the *solvent front* reached the upper line (approximately 7 minutes).
6. When the *solvent front* reached the upper line (1cm from the top of the paper) the strip was removed and dried. The dried strip was then fixed to a glass plate.
7. The protocol *QC Pharm*, available on all GE cameras, was used for acquisition and analysis of the radiochromatogram. A parallel hole collimator was used.
8. The strip was positioned on the collimator in such a way that the origin was on the left side of the image. This was checked with a radioactive *source.*
9. The following R_F (mobility relative to front) values apply for MIBI:
   Impurities: R_F: *0.0*
   Labelled product: R_F: *1.0*
10. The data analysis may be done automatically or manually. The automatic analysis will work correctly if MIBI is the most intense dot on the image. If it is not, the manual analysis should be used.

The *radiochemical purity* of the Tc-99m labelled sestamibi, injected into the patients, was 89% or more for all but one sample in which labelling efficiency was 80% (see Figure 3.2).

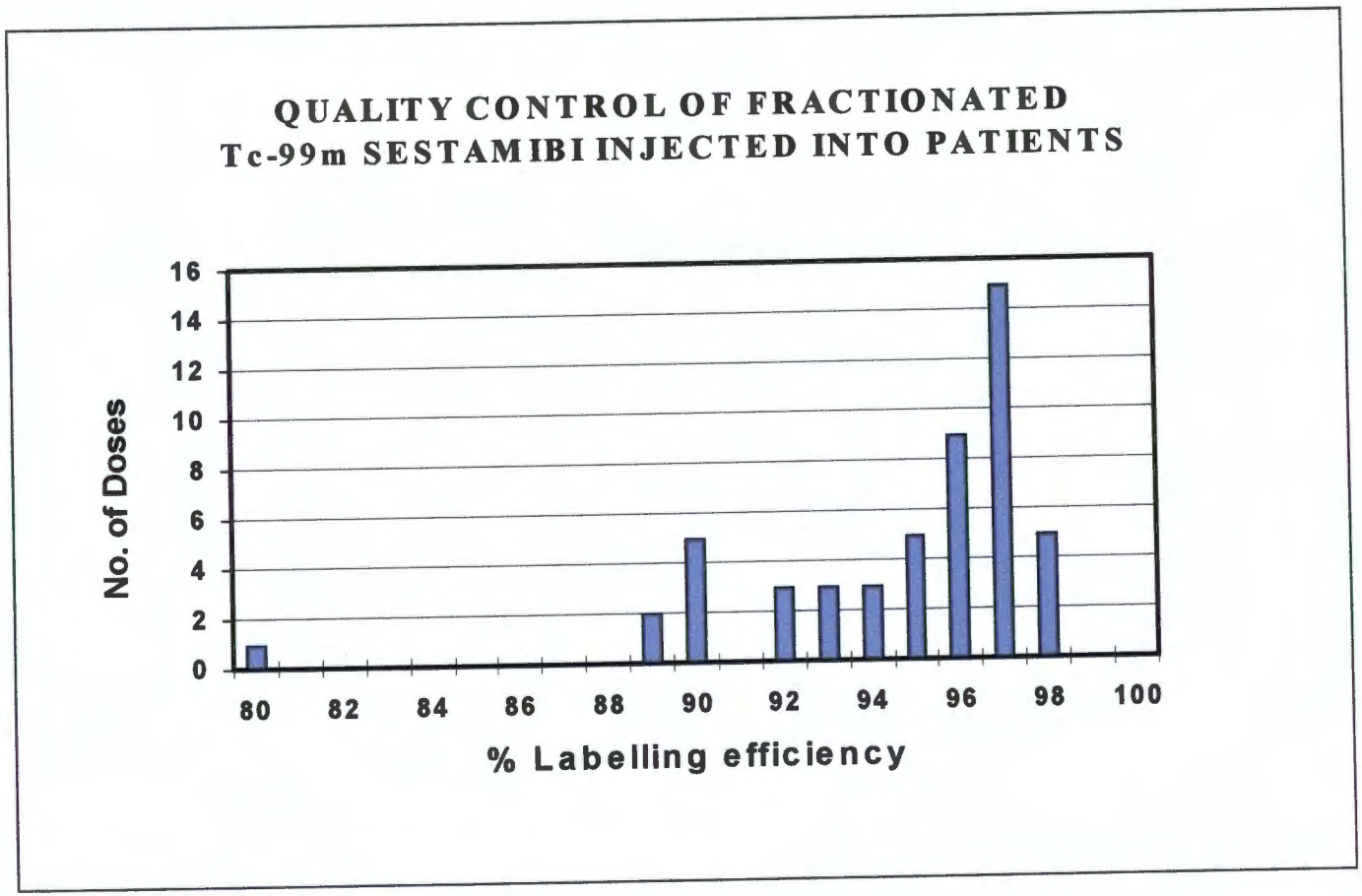
3.3.4. Scintimammography Procedure

The procedure used for scintimammography (SMM) is described below:

A gamma camera *(GE 400 AC Starcam)* equipped with a low-energy, high-resolution collimator was used for imaging. A brief description of the gamma camera and imaging procedure was given to each patient before scanning.

Privacy was provided in the camera room by putting a curtain screen in front of the entrance and by restricting entry strictly to necessary staff members only (the researcher and radiographer). The patient was requested to undress down to the waist and was provided with a surgical gown to wear with the opening in front; the gown was

Figure 3.2.


QUALITY CONTROL OF FRACTIONATED
Tc-99m SESTAMIBI INJECTED INTO PATIENTS
No. of Doses
16
14
12
10
8
6
4
2
0
80
82
84
86
88
90
92
94
96
98
100
% Labelling efficiency

kept loose so that proper prone positioning could be achieved. Both breasts and axillae were examined for palpable lesions before the tracer was injected.

The patient's breast was divided into four anatomical quadrants and the nipple used as an *anatomical landmark* in order to describe the position of the breast lesion. We developed an *adhesive radioactive marker* to mark the position of the nipple. This was based on an *ECG chest electrode*. A minute amount of Tc-99m pertechnetate was spotted on a small cotton plug, which was then carefully sealed with cellophane tape and securely stuck to the metallic tip of the electrode. The adhesive side of the electrode was used to stick the marker on the nipple of the breast.

An intravenous dose of 740 Mbq of Tc-99m MIBI was given in the arm *contralateral* to the affected side. In patients who had clinically bilateral breast lesions, the injection was given in either of the arms.The breast on the side of the injection was scanned last.

3.3.4.1. Patient and camera position

Planar views of both breasts were acquired in the following projections and sequence:

1. Lateral view.
2. Posterior oblique view at 25 degrees
3. Anterior chest/axillary view

The affected breast was imaged first.

The patient lay in the prone position for *lateral* and *posterior oblique* views in exactly the same way as in the pilot study (Appendix A). For the *lateral view*, the surface of the detector was positioned vertically parallel and close to the breast. For the *posterior oblique view*, the patient remained in the same position and the detector was tilted to 25°, keeping the breast in the centre of the field of view. The ipsilateral axilla and adjacent

anterior chest wall were included in the field of view to detect any lymph node involvement and deep-seated lesions in the breast or chest wall, respectively.

Just before each image acquisition was started, the nipple was marked by using the *radioactive marker* described above. After the marker had been stuck over the nipple, its position was indicated on the screen with a "+", using the marking facility of the gamma camera. The marker was removed from the nipple before the acquisition was started.

For the *anterior chest/axillary view*, the patient lay in a supine position in the same way as in the pilot study (Appendix A). The detector was positioned above the anterior chest, parallel and close to the breast. The entire breast and axilla were included in the field of view.

Other acquisition parameters included an *image zoom* of factor 2 for *lateral and posterior oblique views,* in order to magnify the breast image and to exclude heart and liver activity. No image magnification was used for the *anterior chest / axillary view*. Images were acquired in a 256x256 matrix covering an area of 400 mm in diameter when the zoom factor was 1. The photopeak was centered at 140 keV with a 10% symmetric energy window.

Only *one* set of images was acquired on each breast. Imaging started 5 minutes after the injection of the tracer. The affected breast was always imaged first. The injection site was always kept out of the field of view. All images were acquired for a preset time of 5 minutes. The patient was allowed to rest for a few minutes after the images of the first breast were completed.

After acquisition had been completed, the study was transferred to another computer terminal to make *hard copies* of all the images. All images were interpreted *visually* both on the computer screen and on the hard copies, to detect any abnormal increased activity of the tracer in the breast or axilla. The *objective assessment* was performed by semiquantitative analysis using *target to background (T/B)* ratio, as described below.

The intensity of MIBI uptake within the visually detected breast lesion was evaluated by determining the *T/B ratio*. Either the *lateral* or *posterior oblique* view of the breast was selected to draw the region of interest, depending upon which view better illustrated the lesion.

The total counts obtained in each view were recorded. In addition on lateral view, *irregular region of interest* were drawn around each breast, excluding the chest wall. The total counts in each irregular ROI and area in pixels, were used to calculate counts per pixel for each breast. These recorded data can be seen in Table 5 of Appendix B.

A square region of interest was drawn within the outline of the breast lesion. Another region of the same dimensions was drawn over the apparently normal breast tissue of the same breast. The background region was drawn at a variable distance, ranging from 0.5 to 1.5 cm from the target region, in different patients. In breasts with more than one target lesion, a common background region was drawn in the same breast, at approximately the same distance from the target regions. *T/B ratios* were the ratios of the total counts for each region of interest.

The *T/B ratio* was used as a quantitative measure to determine whether it could help to distinguish between true malignant and benign breast lesions.

3.3.5. Scan Interpretation

From visual assessment of the scintimammographic scans the breast lesions were classified as *positive, negative* or *indeterminate.* The following criteria were used:

POSITIVE:	A clearly defined area of increased uptake with an intensity greater than the normal surrounding breast tissue.

NEGATIVE:	No focal increased uptake in the breast.
INDETERMINATE:	An ill-defined area of low-grade increased uptake which is unclassifiable as benign or malignant; as there is increased uptake, it cannot not be termed normal, but the uptake is not intense or well enough defined to be classified as malignant.

All studies were evaluated by the researcher and another experienced nuclear medicine physician. A third observer, another nuclear medicine physician, was referred to in cases of disagreement.

CHAPTER FOUR

RESULTS

4.1. CLINICAL EXAMINATION

A total of 54 palpable breast lumps in 53 breasts of 51 patients were found on clinical examination. Twenty four patients presented with solitary breast lumps in their right breast and 24 patients with lumps in their left breast. Another patient had two palpable lumps in her left breast, while 2 more patients presented with one lump in each breast.

Three of the patients presented with possible tumour recurrence after surgery and radio and chemotherapy. Ten had a positive family history of breast cancer.

Six were nulliparous and 3 of these were among those with a positive family history of breast cancer.

The distribution of 54 breast lesions palpated on clinical examination are shown in Table 4.1.

Patient details are enlisted in Table 2 in Appendix B.

Table 4.1: Number And Distribution Of Lesions In Each Breast On Clinical Examination.

RIGHT BREAST	LESIONS
Upper Outer Quadrant:	8
Upper Inner Quadrant:	7
Lower Outer Quadrant:	7
Lower Inner Quadrant:	1
Other (periareolar):	3
TOTAL	**26**

LEFT BREAST:	LESIONS
Upper Outer Quadrant	16
Upper Inner Quadrant:	2
Lower Outer Quadrant:	8
Lower Inner Quadrant:	1
Other (periareolar):	1
TOTAL	**28**

4.2. BIOPSY RESULTS

All 51 patients had biopsies done. These include 54 palpable lesions in 53 breasts. Biopsies were also performed on 3 clinically impalpable lesions. Of these, 2 were situated close to the palpable lesions, seen on mammography and SMM; and another lesion was seen only on mammography, in a clinically normal breast. These make a total of 57 lesions in 54 breasts which were biopsied (54 palpable and 3 impalpable). Further 2 impalpable lesions in one of these breasts were seen only on SMM and were not biopsied.

Three of the patients with palpable lumps had clinical suspicion of tumour recurrence after treatment. Two of these showed normal breast tissue with some sclerosis on histological examination. One patient had a recurrent infiltrating ductal carcinoma at the site of previous cancer.

In the 10 patients with positive family history of breast cancer, 4 were found to have malignant lesions while the other 6 patients had benign breast lesions. Two of the 6 nulliparous patients had malignant breast lesions, while 4 had benign breast lesions. Two patients with mammographically dense breasts were found to have fibroadenomas on histology.

In total, there were 22 malignant lesions in 21 breasts of 21 patients, including 2 patients who had bilateral breast masses, with malignant lesions in one and benign lesions in the other breast. One of these patients (patient 25) had a ductal carcinoma in her left and fibrocystic disease in her right breast, confirmed on histology. The other patient (patient 44) had clinically palpable lumps in the left breast showed bilateral involvement on mammography, with 2 cystic lesions in her left and a small 1x1 cm solid lesion, an adenocarcinoma in situ, in her right breast which was clinically impalpable.

A total of 35 benign lesions in 33 breasts of 32 patients were biopsied. These included a patient with bilateral breast lesions (bilateral fibroadipose tissue masses) and 4 patients with biopsy confirmed normal breast tissue. The histopathological results are listed in Table 4.2.

Table 4. 2: Histopathological Results of 57 lesions in 54 breasts.

HISTOPATHOLOGICAL FINDINGS	LESIONS	BREASTS
Malignant Tumours :		
Infiltrative Duct Ca.	15	15
Lobular Ca.	4	3
Colloid Ca.	1	1
Adeno Ca.	1	1
Phylloides Tumour	1	1
Benign Tumours :		
Fibroadenoma	7	7
Lipoma	1	1
Other Benign Lesions :		
Fibrocystic Disease	5	4
Fat Necrosis	4	4
Fibrosis/Sclerosis	1	1
Inflammatory Lesions	5	5
Cyst	5	4
Fibroadipose Tissue	3	3
Normal Adipose tissue	4	4
Total	**57**	**54**

4.3. MAMMOGRAPHY RESULTS

A total of 57 lesions in 54 breasts of 51 patients were noted on mammography.

Of the 3 patients referred with clinically palpable breast masses for suspected tumour recurrence, one was found to have a recurrent infiltrating ductal carcinoma on histology, but the mammography showed no definite mass besides scarring (false negative mamogram). In the other 2 patients, one had features of benign pathology, while the other had a normal mammogram. Both these results corresponded with the biopsy results.

Table 4.3: Summary of Histopathological and Mammography Results.

		HISTOLOGY	
		Malignant	**Benign**
MAMMO	**Positive**	**16**	**0**
	Negative	**4**	**32**
	Indeterminate	**2**	**3**

Of the 22 malignant lesions in 21 breasts, mammography was positive in 16 lesions in 16 breasts (including 3 patients with positive family history of breast cancer) while 4 malignant lesions in 3 breasts showed mammographic features of benign pathology (including a nulliparous woman with positive family history of breast cancer). Two breasts had solitary lesions with indeterminate mammography results.

Thirty two benign breasts lesions (including lesions with normal breast tissue) in 30 breasts showed concordant results on mammography, while 3 lesions in 3 breasts showed indeterminate mammographic findings. There were no false positives in this category.

Also included among these patients was a case (patient 44) in whom mammography detected
a small spiculated mass with microcalcification, consistent with malignancy, in the clinically normal breast during the routine investigation. Excision biopsy showed a 1x1 cm solid lesion with a central focus of invasion approximately 2 mm in diameter. Histology results confirmed an apocrine tumour (adenocarcinoma) in situ. It was clinically nonpalpable.

Of the 35 benign breast lesions in 33 breasts, mammography was negative in 32 breasts lesions including 4 lesions with normal tissue, while 3 breast lesions showed indeterminate mammographic features including a nulliparous patient.

There were 20 patients with mammographically dense breasts. Of these, 3 had indeterminate mammographic masses (2 had fibroadenomas and one had invasive ductal carcinoma). Three patients with malignant breast lesions (phylloides tumour, infiltrating ductal and lobular carcinomas) demonstrated mammographic features suggestive of benign pathology (false negative mammograms). The rest of 5 patients with malignant and 9 with benign breast lesions showed congruent mammographic results.

4.4. TECHNETIUM-99M MIBI SCINTIMAMMOGRAPHY RESULTS

All 51 patients had SMM scans.

Out of a total of 59 lesions in 54 breasts, abnormal increased MIBI uptake was noted in 41 lesions in 37 breasts. Of these 41 lesions, 28 were regarded as positive and 13 as indeterminate on SMM. This also includes a patient in whom further 2 lesions were detected in one breast on SMM. Rest of the 18 lesions did not show abnormal MIBI uptake and were regarded as negative on SMM.

Table 4.4 shows the number and distribution of lesions in each breast as detected on SMM.

Table 4.4 Total Number Of Lesions And Their Distribution In Each Breast Quadrant as Detected on Tc-99m MIBI Scintimammography.

RIGHT BREAST	LESIONS
Upper Outer Quadrant	6
Upper Inner Quadrant	7
Lower Outer Quadrant	4
Lower Inner Quadrant	1
Other (retroareolar)	1
TOTAL	**19**

LEFT BREAST:	LESIONS
Upper Outer Quadrant	9
Upper Inner Quadrant:	3
Lower Outer Quadrant:	6
Lower Inner Quadrant:	4
Other:	0
TOTAL	**22**

Of the 3 patients referred with clinically palpable breast masses for suspected tumour recurrence, one had a recurrent infiltrating ductal carcinoma and the other 2 had benign pathology. All these patients showed negative SMM scans.

The results are illustrated in Table 4.5.

Table 4.5: Summary of Histopathological and Tc-99m MIBI Scintimammography Results.

		HISTOLOGY	
		Malignant	**Benign**
SMM	**Positive**	**17**	**9**
	Negative	**2**	**16**
	Indeterminate	**3**	**10**

Of the 22 histologically confirmed malignant lesions in 21 breasts, 17 lesions showed true positive MIBI uptake, 2 lesions showed negative MIBI uptake and 3 lesions in 2 breasts showed indeterminate SMM result.

From a total of 35 benign lesions in 33 breasts, 16 lesions showed negative SMM results i.e no MIBI uptake. Nine lesions showed positive MIBI uptake. In one of these patients (patient 24) further 2 lesions were detected in one breast on SMM which were not biopsied as they were clinically impalpable and not seen mammographically. Ten lesions in 9 breasts showed indeterminate SMM features. This includes a patient (patient 58) who showed a single fibrocystic lesion in a breast on histology but SMM showed 2 separate lesions (one scintimammographically positive i.e false positive and the other indeterminate).

Details of scintigraphic findings for each pathological diagnosis are given in Table 4.6.

Examples of typical cases with breast lesions as seen on SMM are shown in Figures 4.1, 4.2 and 4.3 in the following pages.

Table 4.6. Scintigraphic Findings Correlating With Histopathological Results

Histological Diagnosis	*Number of Lesions*	*Tc99m MIBI Uptake*		
		Positive	*Negative*	*Indeterminate*
Infiltrative Duct Ca	**15**	**14**	**1**	**0**
Invasive Lobular Ca	**4 (3breasts)**	**2**	**0**	**2**
Colloid Ca	**1**	**1**	**0**	**0**
Adeno Ca	**1**	**0**	**1**	**0**
Phylloides Tumour	**1**	**0**	**0**	**1**
Fibroadenoma	**7**	**4**	**3**	**0**
Lipoma	**1**	**0**	**0**	**1**
Fibrocystic Disease	**5 (4 breasts)**	**3**	**0**	**2**
Fat Necrosis	**4**	**0**	**2**	**2**
Fibrosis/Sclerosis	**1**	**1**	**0**	**0**
Inflammatory Lesions *	**5 (5 breasts)**	**3**	**0**	**4**
Breast Cyst	**5 (4 breasts)**	**0**	**5**	**0**
Fibroadipose Tissue	**3**	**0**	**2**	**1**
Normal Adipose Tissue	**4**	**0**	**4**	**0**

* *Only 5 lesions in 5 breasts with inflammatory changes were biopsied, whereas SMM showed 7 lesions in 5 breasts.*

Figure 4.1. Normal scintimammogram. Prone left and right lateral views show normal Tc-99m MIBI breast uptake

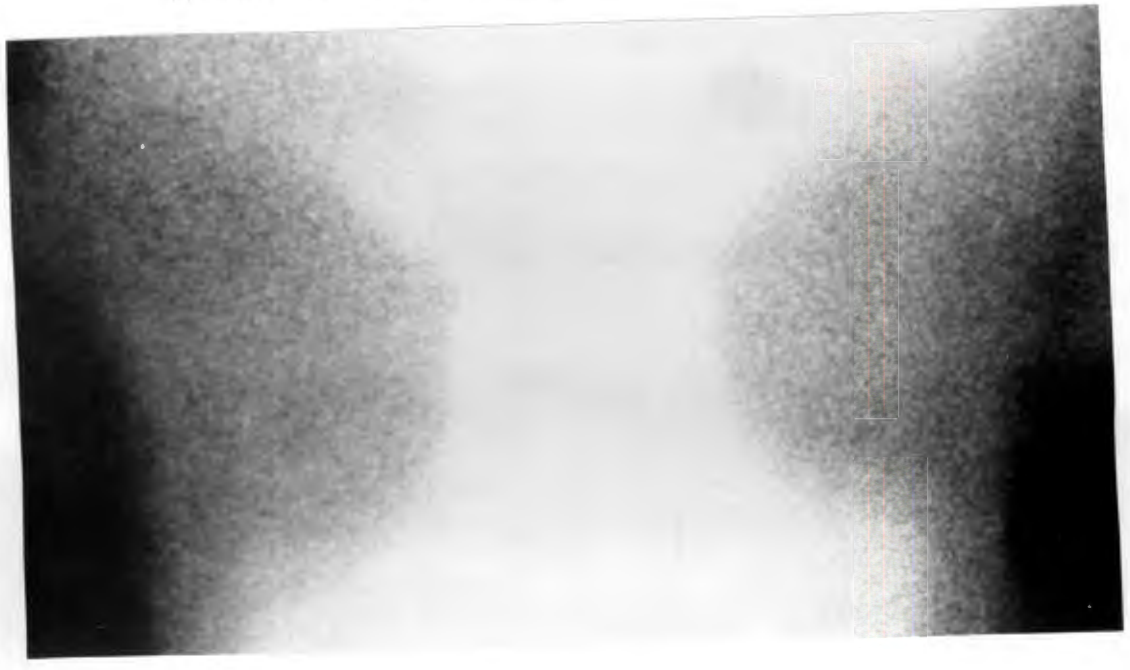


Figure 4.2. Examples of true-positive Tc-99m SMM (prone lateral views).
(i) shows a well defined rounded mass with central necrosis and metastatic lymph node involvement (arrow). Histology confirmed an infiltrative ductal ca.
(ii) shows intense focal uptake in a patient with palpable breast lump. Conirmed to be invasive ductal ca on histology.

(i) *(ii)*

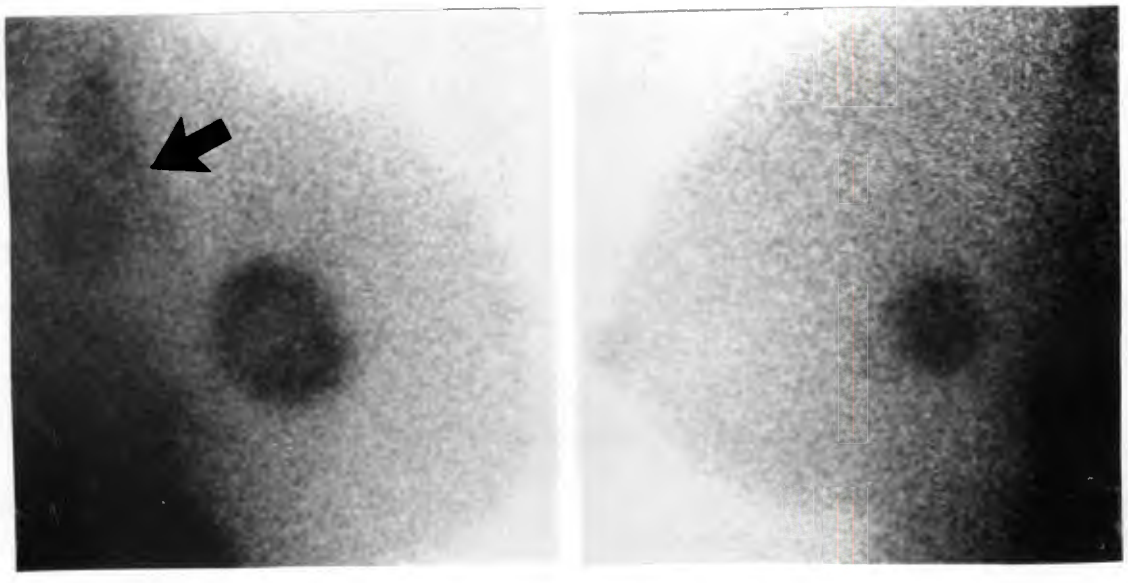
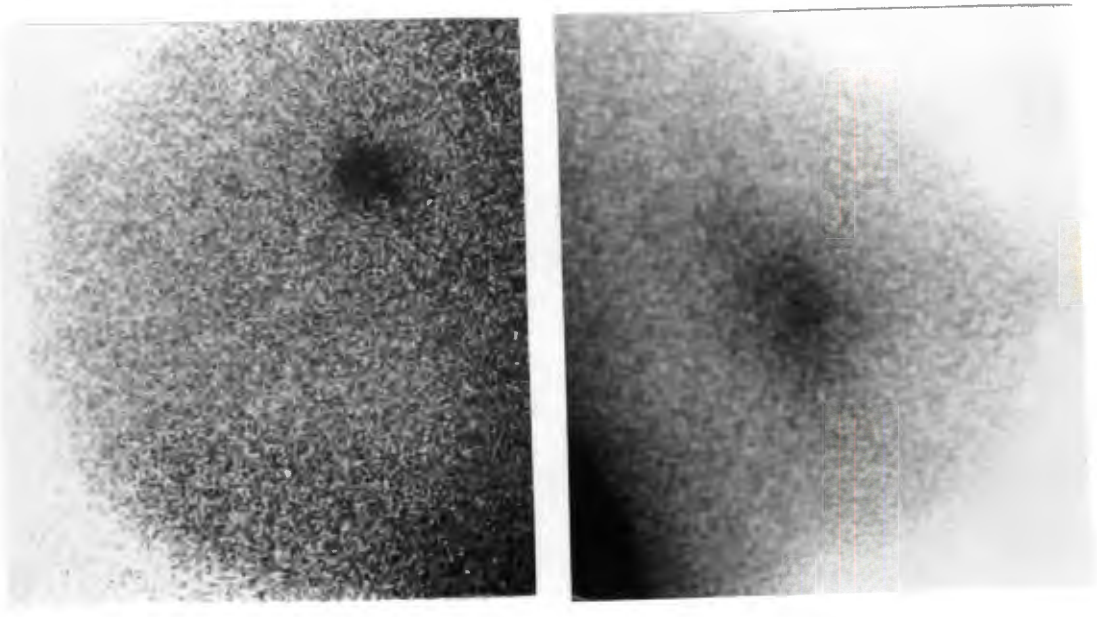


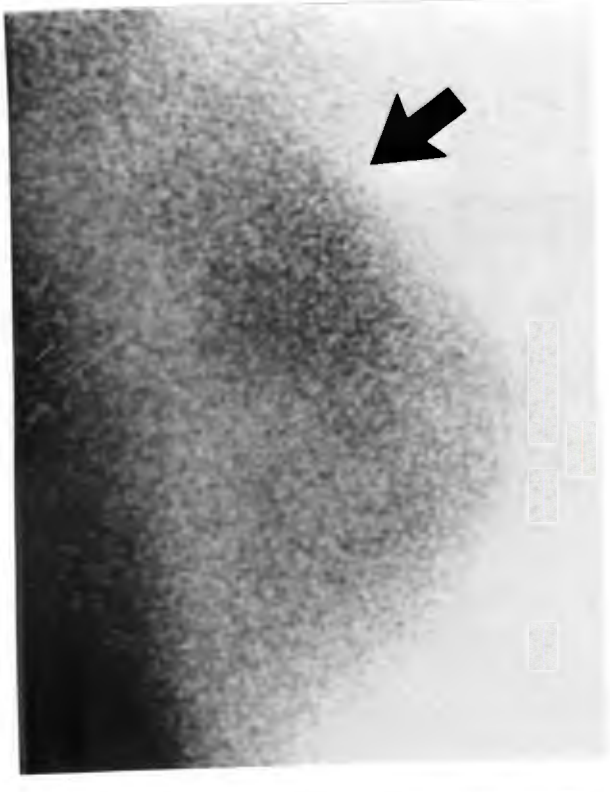
Figure 4.3.

(i) Examples of false-positive Tc-99m MIBI SMM. A, Fibroadenoma. B, Fibrosis.

A ***B***



(ii) An Indeterminate Tc-99m MIBI SMM. A Phylloides tumour (arrow)



4.5. SEMIQUANTITATIVE ANALYSIS

Malignant breast lesions usually showed higher T/B ratios as compared to benign breast lesions as shown in Figures 4.4 (a) and (b).

Our results showed low sensitivity (66.6%) and specificity (65.5%) for T/B ratio of 2.0 in differentiating between benign from malignant breast lesions. As the T/B ratio increased to 3.0, a steep drop in the sensitivity (33%) and dramatic rise in specificity (100%) was noted. (see Figure 4.5).

Figures 4.6 (a) and (b) show the proportion of benign to malignant lesions with increasing T/B ratios.

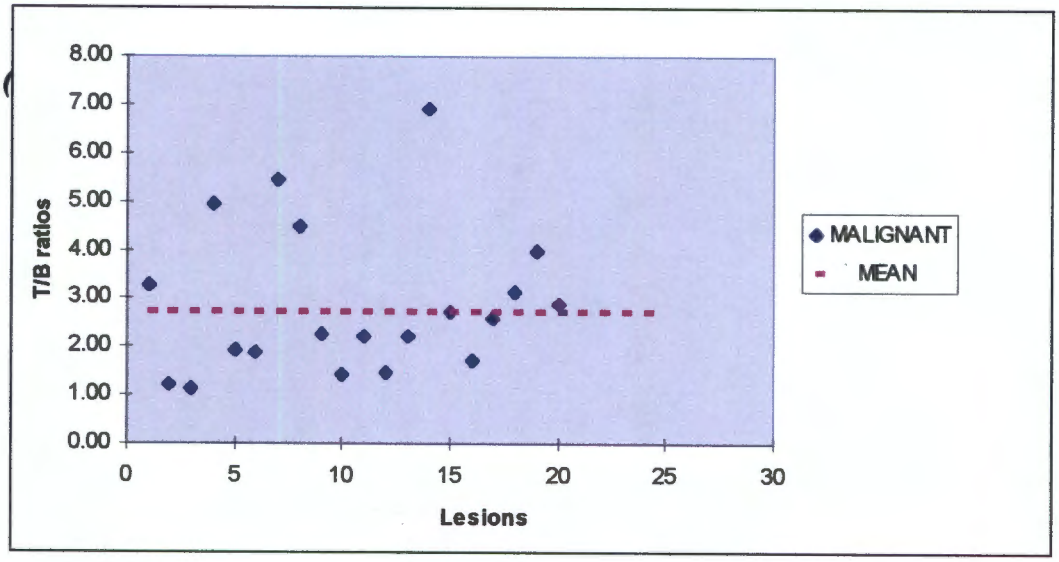
Total counts obtained in each view during 5 minutes images, total counts obtained in the irregular ROI for each breast in lateral view and area in pixels of these ROI to determine counts per pixels for each breast; and total counts in target and background regions and area in pixels, were recorded in Table 5 of Appendix B.

Figure 4.7 a and b show the relationship between counts per pixel in right and left breasts with values of T/B ratio calculated in the breast. These figures show that there is no linear relationship between counts per pixel in a breast and the T/B ratio.

Figure 4.8 shows distribution of the counts per pixel (in the lateral view) of right versus left breast. The points that lie further from the diagonal line show more counts per pixel in that breast and are due to a lesion (increased MIBI uptake) in that breast or occasionally due to diffuse increased uptake in that breast.

Figure 4.4. Illustrate the individual and mean values for (a) malignant (b) benign breast lesions

(a)



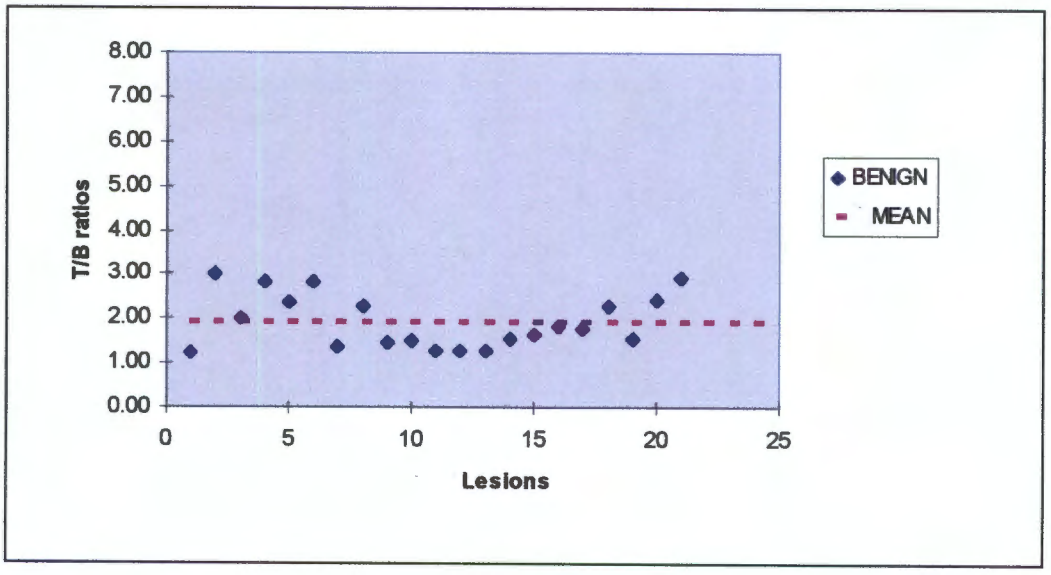


Figure 4.5

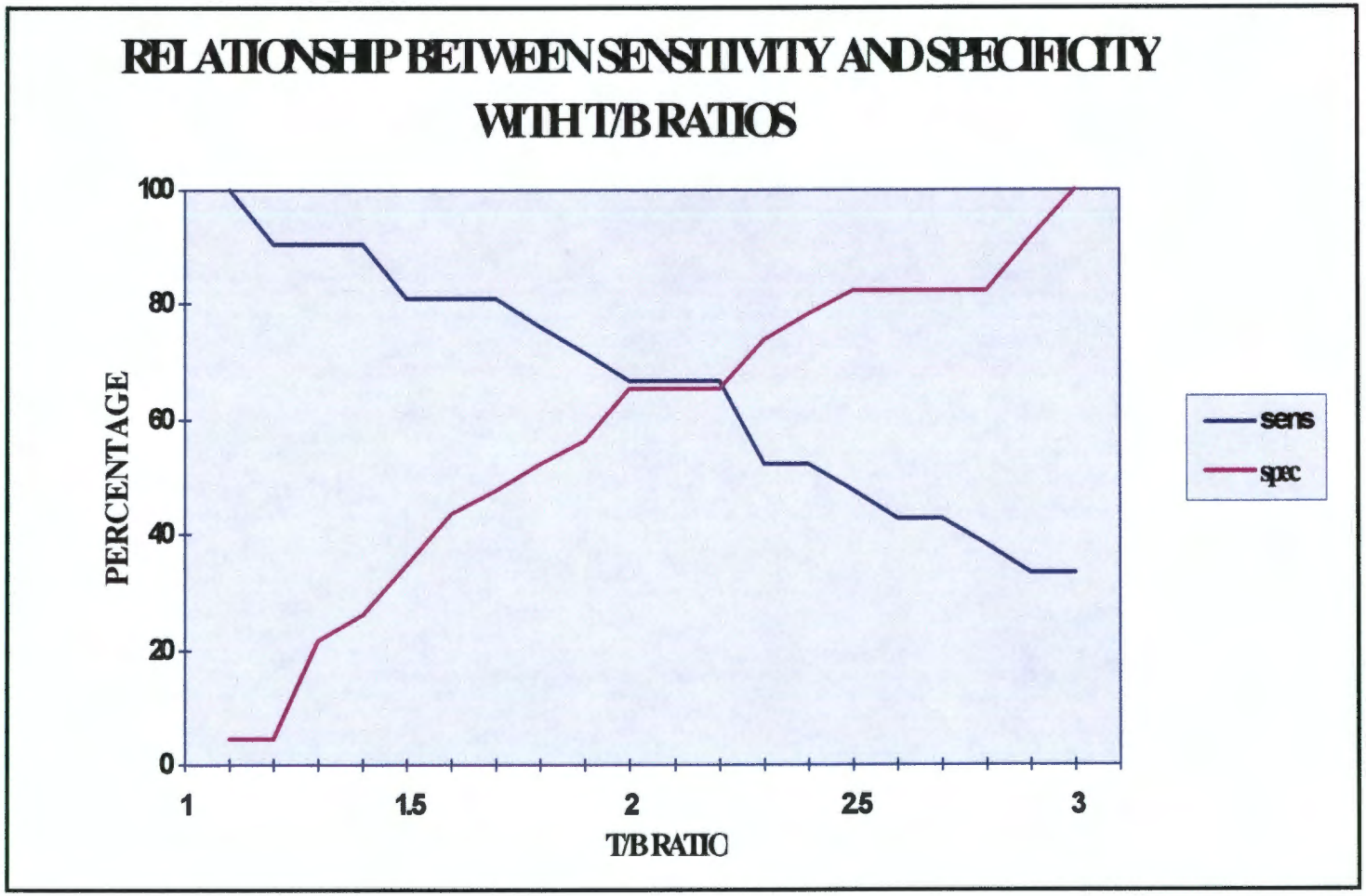

RELATIONSHIP BETWEEN SENSITIVITY AND SPECIFICITY WITH T/B RATIOS
PERCENTAGE
100
80
60
40
20
0
1
1.5
2
2.5
3
T/B RATIO
sens
spec

Figure 4.6 (a)

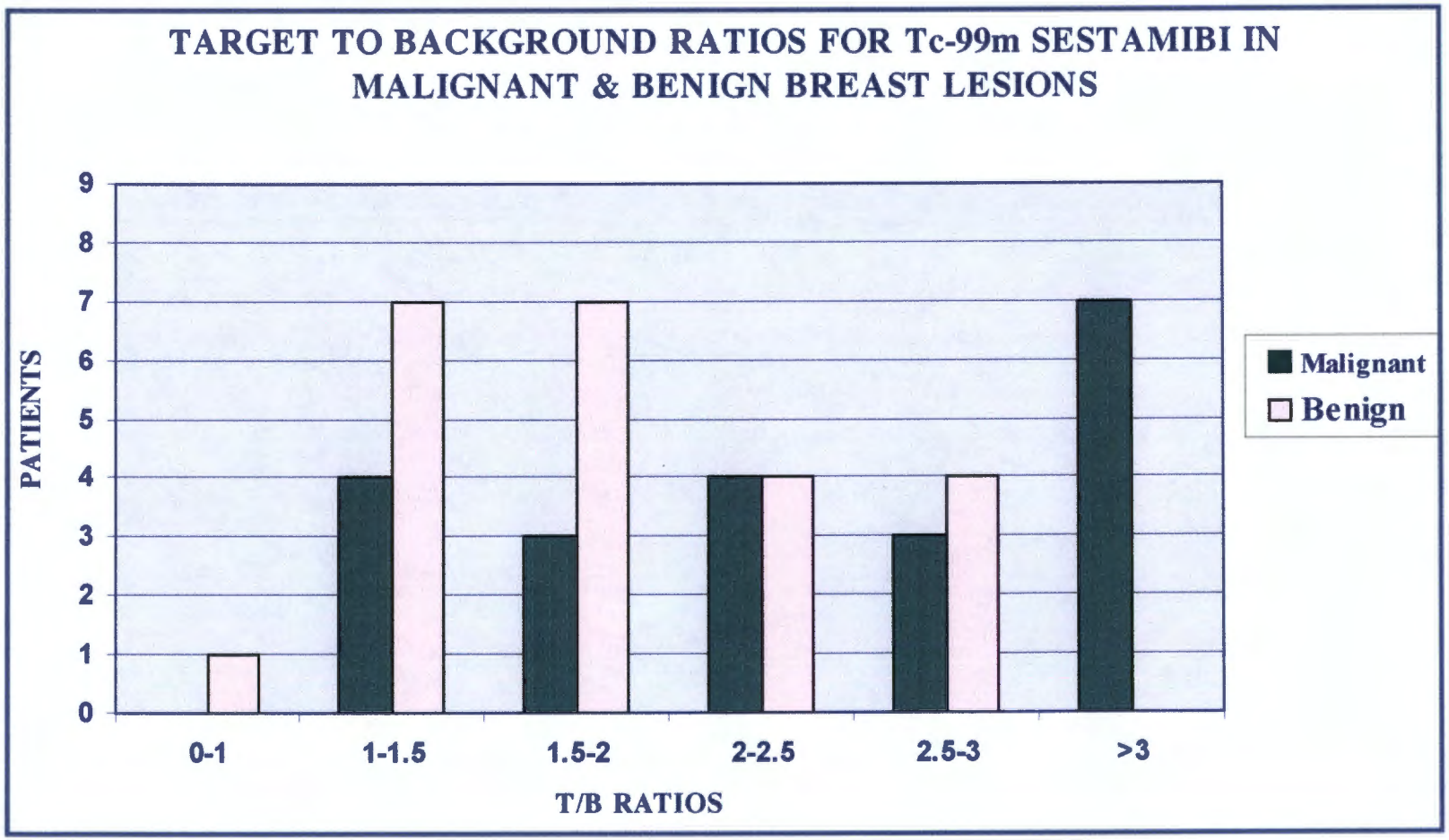

TARGET TO BACKGROUND RATIOS FOR Tc-99m SESTAMIBI IN MALIGNANT & BENIGN BREAST LESIONS
PATIENTS
9
8
7
6
5
4
3
2
1
0
0-1
1-1.5
1.5-2
2-2.5
2.5-3
>3
T/B RATIOS
Malignant
Benign

Figure 4.6 (b)

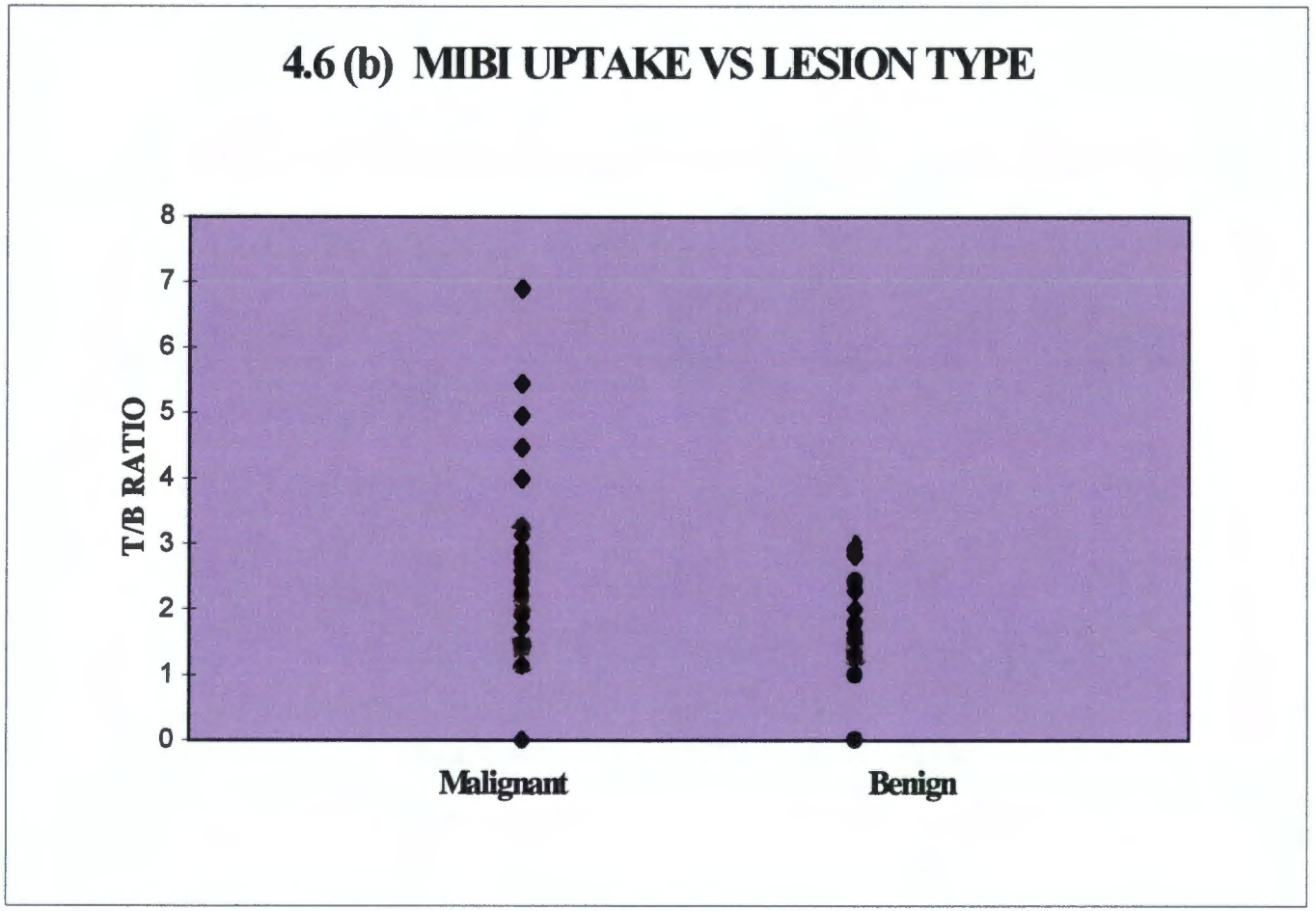
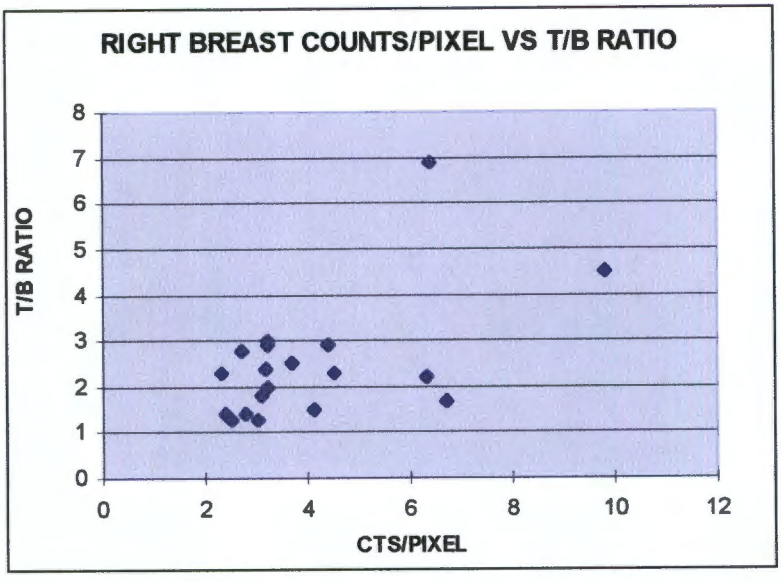

4.6 (b) MIBI UPTAKE VS LESION TYPE
T/B RATIO
8
7
6
5
4
3
2
1
0
Malignant
Benign

Figure 4.7. Relationship between counts per pixel versus T/B ratio in each breast.

(a)



(b)

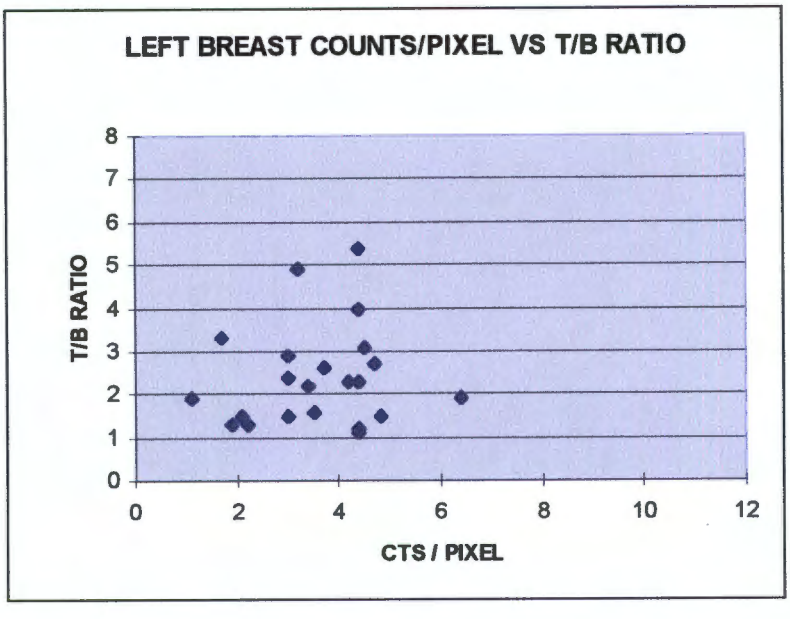
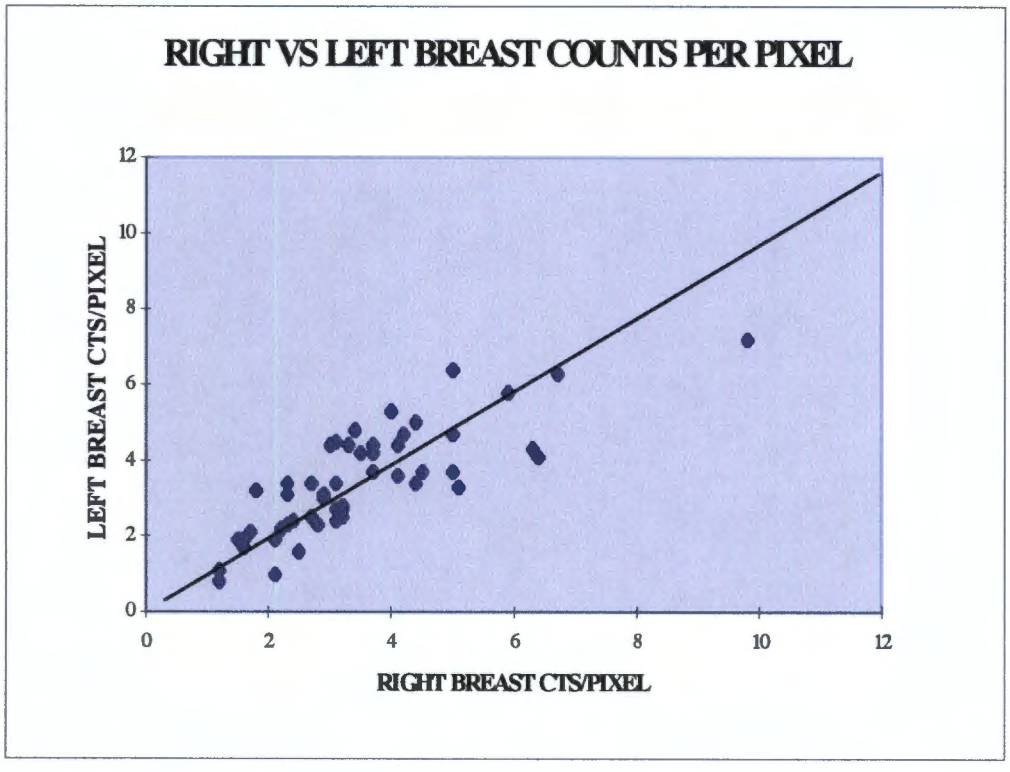


Figure 4.8. Illustrate the number of counts per pixel in lesions detected in right and left breasts on SMM.



4.6. BIOPSY VS SCINTIMAMMOGRAPHY VS MAMMOGRAPHY RESULTS

The comparative results of SMM and mammography were compared with biopsy results, considered as a standard. These results are illustrated in tabulated form in Table 4.7.

Table 4.7 includes a patient who showed 2 lesions (1 indeterminate & 1 malignant) in one breast on SMM, but the mammography and biopsy results indicated that both lesions were consistent with benign pathology (fibrocystic disease).

Table 4. 7 Comparison Between Histopathological, Tc-99m Scintimammographic and Mammography Results

Lesions (n)	*Histology*	*SMM*	*Mammo*	*Comment*
14	**Malignant**	**Positive**	**Positive**	
1	**Malignant**	**Positive**	**Negative**	
2	**Malignant**	**Positive**	**Indeterminate**	
2	**Malignant**	**Indeterminate**	**Positive**	**Lobular ca (2)**
1	**Malignant**	**Negative**	**Positive**	**Adeno ca**
1	**Malignant**	**Negative**	**Negative**	**Ductal ca**
1	**Malignant**	**Indeterminate**	**Negative**	**Phylloides T**
15	**Benign**	**Negative**	**Negative**	
9	**Benign**	**Indeterminate**	**Negative**	
***8**	**Benign**	**Positive**	**Negative**	
1	**Benign**	**Negative**	**Indeterminate**	**F/adenoma**
1	**Benign**	**Positive**	**Indeterminate**	**F/adenoma**
1	**Benign**	**Indeterminate**	**Indeterminate**	**Lipoma**

** One of these breasts showed further 2 lesions on SMM which were clinically impalpable and therefore were not biopsied.*

Fourteen histologically confirmed malignant breast tumours and 15 benign lesions showed concordant SMM and mammography results.

Eight benign breast lesions showed negative mammography but positive SMM scans (false +ve SMM). This includes a patient (patient 24) with 3 lesions in one breast (one palpable and 2 nonpalpable). All 3 lesions were positive on SMM. The 2 nonpalpable lesions were not biopsied as they were negative on mammography.

In one patient (patient 44) mammography detected a small 1x1 cm solid lesion confirmed to be an adenocarcinoma *in situ*, in a clinically normal breast. The SMM scan was negative in this case (false -ve SMM). In another patient with a clinically solitary lump, SMM showed 2 separate lesions (one clinically palpable and the other nonpalpable) in that breast and were classified as positive and indeterminate. Mammography showed features suggestive of benign pathology and were confirmed on biopsy results (both lesions were consistent with fibrocystic disease).

Thirteen lesions in 11 breasts had indeterminate results on SMM, out of which 9 lesions (in 8 breasts) showed benign pathology and negative mammography. Two lesions in a breast were malignant on biopsy and had positive mammography. Further 2 lesions were detected on SMM as indeterminate. One was malignant with negative mammography and the other a benign lesion with indeterminate mammography.

The most important group consisted of five breasts with indeterminate mammography results, of which one breast had an indeterminate SMM result. The histology.on this lesion showed features of benign disease (lipoma). Two breasts had positive SMM scans and histology results confirmed malignant lesions. Of the remaining 2 breasts, one showed a false positive SMM scan and no uptake in the other. Both of these breasts had a fibroadenomas on histology.

4.7. STATISTICAL ANALYSIS

The statistics were based on the number of histopathologically reported biopsied lesions. Comparison of summarised results statistics between SMM and mammography for formal and pilot studies is shown below in Table 4.8 (a). If all *indeterminate* SMM results were considered as *negatives,* then for the formal study, SMM results showed a sensitivity of 89.5%, specificity of 76.3% and accuracy of 80.7%. Table 4.8 (b) shows similar results for the pilot and formal studies combined together.

Sensitivity: (true positives/true positives + false negatives)

Specificity: (true negatives/true negatives + false positives)

PPV: positive predictive value (true positives/truepositives + false positives)

NPV: negative predictive value (true negative/true negatives + false negatives)

Accuracy: (true positives + true negatives/ total number)

IND: Indeterminate

Table 4.8. Summary of results statistics, (a) formal and pilot studies (b) whole study.

(a)

	FORMAL STUDY		**PILOT STUDY**	
	SMM	***MAMMO***	***SMM***	***MAMMO***
Sensitivity:	(17/19) 89.5%	(16/20) 80%	(4/4) 100%	(4/4) 100%
Specificity:	(16/25) 64%	(32/32) 100%	(6/8) 75%	(3/3) 100%
Accuracy	(33/44) 75%	(48/52) 92.3%	(10/12) 83.3%	(7/7) 100%
PPV:	(17/26) 65%	(16/16) 100%	(4/6) 66.6%	(4/4) 100%
NPV:	(16/18) 89%	(32/36) 89%	(6/6) 100%	(3/3) 100%

(b)

	WHOLE STUDY	**(PILOT AND FORMAL)**
	SMM	***MAMMO***
Sensitivity:	(21/23) 91.3%	(20/24) 83.3%
Specificity:	(22/33) 66.7%	(35/35) 100%
Accuracy	(43/56) 76.8%	(55/59) 93.2%
PPV:	(21/32) 65.6%	(20/20) 100%
NPV:	(22/24) 91.6%	(35/39) 89.7%

4.8. AXILLARY LYMPH NODE INVOLVEMENT:

Six out of 21 patients with breast cancer were found to have metastatic ipsilateral axillary lymph node involvement on histology. For these 6 patients, SMM showed 3 and mammography one concordant result. SMM and mammography could not detect ipsilateral axillary lymph node involvement in the rest of 3 and 5 patients (false -ve), respectively.

SMM showed positive lymph node involvement in a further 5 patients in which the biopsy results were negative (false +ve SMM). Two of these patients also showed features of metastatic lymph node involvement on mammography.

The diagnosis of lymph node involvement shown by SMM and mammography are compared with the histological results in Table 4.9. It must be remembered that this is not sentinel node imaging which is done specifically for the lymphatic system using colloids.

Table 4.9: Comparison between Tc-99m MIBI scan, Mammography and Biopsy Results In Axillary Lmph Node Involvement

Paient No.	*Histopathology*	*Metastatic Biopsy*	*Lymph Node SMM*	*Involvement Mammography*
1.	Ductal Ca	P (2/17)	N	N
2.	Ductal Ca	P (5/12)	P	N
3.	Ductal Ca Poorly Differeniated	P (3/10)	N	N
4.	Ductal Ca	N	P	N
5.	Ductal Ca	P (1/7)	N	N
6.	Fat Necr.& Inflamm.	N	P	N
7.	Ductal Ca	N	P	P
8.	Ductal Ca	P (1/12)	P	P
9.	Ductal Ca	N	P	N
10.	Ductal Ca	P (1/6)	P	N
11.	Ductal Ca	N	P	P

(P = Positive, N = Negative,(number.of L.N involved / number.of nodes explored).

CHAPTER FIVE

ADDITIONAL STUDY

5.1 INTRODUCTION

Despite recent improvements in mammographic techniques and equipment radiologically dense breasts continue to to be difficult to image and evaluate. Patients with nondiagnostic mammographic lesions, especially those with architectural distortion due to previous surgery or radiation therapy may benefit from a nuclear scan which is independent of breast density or distortion and can therefore make a significant contribution to clinical management in patients with clinically suspected breast abnormalities.

As the results of our formal study and those of others [21,84] suggest that SMM has high sensitivity and negative predictive value, it could be useful in patients with indeterminate mammographic results. Therefore we conducted an additional prospective study in 25 patients with palpable breast lesions and indeterminate mammography.

5.2. LITERATURE REVIEW

Khalkhali et al. [21] have shown the usefulness of SMM in patients with dense breasts on mammogram. In 48 patients with palpable breast lesions, not clearly interpreted by mammography, SMM showed a sensitivity of 93.7 % and specificity of 90.6 % as compared to a sensitivity of 82.2 % and specificity of 46.1% by standard mammography. According to Mekhmandarov et al. [85] SMM improved the diagnostic accuracy in cases of palpable breast lesions with probably normal or indeterminate mammographic results.

According to Prat et al. [86], the use of a joint mammography-SMM diagnostic protocol could significantly reduce the number of biopsies performed in patients with breast lesions of low or indeterminate mammographic suspicion of malignancy. Bombardieri et al. [8] have also proposed SMM as a complementary examination in patients with difficult to interpret mammograms, as is most often the case in patients with high breast density.

5.3. METHODOLOGY

5.3.1. PURPOSE

This subgroup of patients was studied to determine whether Tc-99m MIBI scintimammography can differentiate between benign and malignant breast lesions in patients with clinically palpable breast lumps and indeterminate mammography.

5.3.2. SAMPLE SELECTION

The study population consisted of 25 women between ages of 34 and 80 years with a mean age of 47 years.

The selection criteria differed from those in the main (formal) study in that only patients with indeterminate mammography were selected. In addition, clinical evaluation, scintimammography and data recording were integrated to ensure that there could be *"lesion by lesion"* comparison of each breast lesion detected by clinical examination or scintimammography or both with the biopsy results of that particular lesion.

The rest of the criteria for patient selection were the same as for the formal study.

All patients were selected by an experienced surgeon at the Combined Breast Clinic at Groote Schuur Hospital. The patients selected for breast scan (SMM) underwent biopsy on the same day. As in the main study, mammography and SMM were done before biopsy.

All patients gave informed consent before SMM and the research was explained to them.

5.3.3. PROCEDURE

Tc-99m MIBI SMM scan were performed using fractionated *Cardiolite* produced by Du Pont Pharmaceuticals of USA.

Each vial contains:

Tetrakis (2-methoxy isobutyl isonitrile) copper(1) *tetrafluoroborate*	*1.00 mg*
Stannous chloride dihydrate	*0.075 mg*
L-cysteine hydrochloride monohydrate	*1.0 mg*

For reconstitution with oxidant-free Sodium Pertechnetate Tc-99m injection.

We used fractionated *Cardiolite* for this study because locally produced sestamibi *(Myotek)* was no longer commercially available. Fractionation of *Cardiolite* was performed using exactly the same method as for *Myotek* in the formal study. Each sestamibi vial was reconstituted with sterile saline and divided into 10 fractions.

The reconstituted sestamibi was stored in a chest freezer at a temperature below (-)10°C. In order to compensate for oxidation of tin during the storage of sestamibi, additional tin was added to the fractionated sestamibi. The tin was obtained from invivo *Red Blood Cell Labelling Agent,* manufactured by *AEC of South Africa.* Each vial of invivo *Red Blood Cell Labelling Agent* contains 2504g of tin.

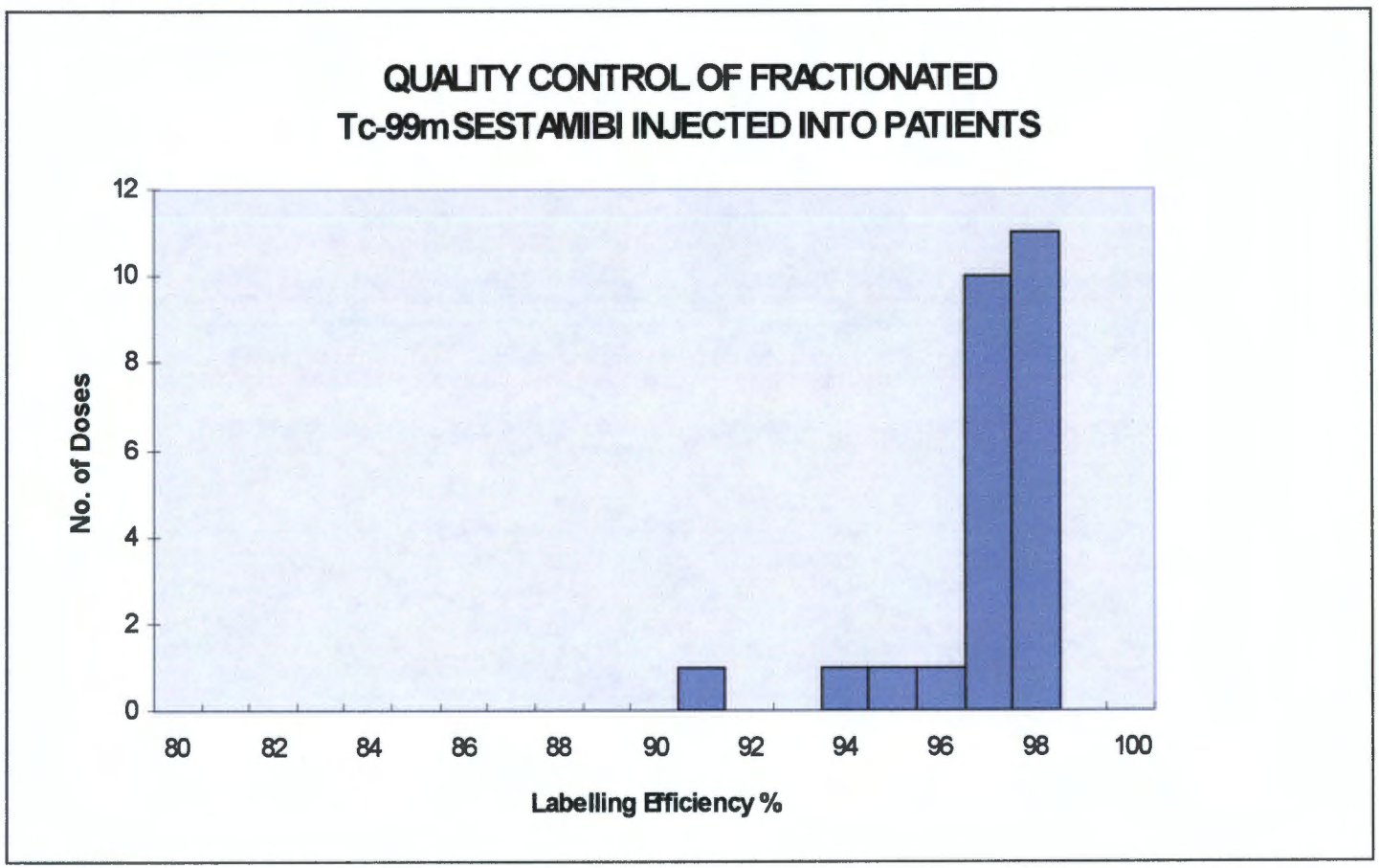
When required, the individual dose was thawed at room temperature and mixed with Tc-99m pertechnetate. Each dose was prepared using the same method as used in the formal study.

5.3.3.1. Quality Control of Fractionated Tc-99m Sestamibi

Each reconstituted dose was tested before use, to ensure high labelling efficiency. In this study we also used the *ascending paper chromatography* procedure as for the formal study.

The radiochemical purity of the Tc-99m MIBI injected into the patients was always more than 90% (see Fig 5.1.)

Figure 5.1.


QUALITY CONTROL OF FRACTIONATED
Tc-99m SESTAMIBI INJECTED INTO PATIENTS
No. of Doses
0
2
4
6
8
10
12
80
82
84
86
88
90
92
94
96
98
100
Labelling Efficiency %

5.3.3.2. Scintimammography Procedure

The SMM methods regarding patient and camera position and acquistion parameters were exactly the same as for the formal study. Similarly, total counts obtained in each view were recorded. On the lateral view, irregular regions of interest were drawn around each breast excluding chest wall. The total counts in each ROI and area in pixels were used to calculate counts per pixel for each breast. The data can be seen in Table 6 of Appendix B. Semiquantitative analysis (target to background ratios) were also performed as in the formal study.

5.3.3.3. Scan Interpretation

The scans were classified as *positive, negative and indeterminate* using the same criteria of visual assessment as for the formal study.

All scans were evaluated by the researcher and another experienced nuclear medicine physician.

5.4. RESULTS

Table 5.1. summarises the total number of breast lesions and clinical, scintimammography and biopsy findings:

Table 5.1. Summary of Number of Breasts and Lesions as seen on Clinical Examination and SMM and Comparative Histology.

Patient No.	Breasts Involved	Side Involved	Lesions in Breasts	Clinical Exam Palp / Non palp	SMM Pos/ Neg/ Ind	Biopsy Malign/ Benign/ No	Histology
1	1	Right	1	Palpable	Positive	Malignant	Squamous cell ca
2	1	Right	1	Palpable	Positive	Malignant	Infiltrative Ductal ca
3	1	Right	1	Palpable	Negative	Benign	Fibroadipose tissue
4	1	Right	3	Palpable	Positive	Malignant	Infiltrative Ductal ca
				Non palpable	Indeterminate	No Biopsy	
				Non palpable	Indeterminate	No Biopsy	
5	1	Left	1	Palpable	Negative	Benign	Cyst
6	1	Right	2	Palpable	Positive	Malignant	Infiltrative Ductal ca
				Palpable	Positive	Malignant	Infiltrative Ductal ca
7	1	Right	1	Palpable	Negative	Benign	Fibroadipose tissue
8	1	Right	2	Palpable	Positive	Benign	Fibroadenoma
				Non palpable	Indeterminate	No Biopsy	
9	1	Left	1	Palpable	Negative	Benign	Periductal Mastitis
10	1	Left	2	Palpable	Positive	Benign	Fibroadenoma
				Non palpable	Indeterminate	No Biopsy	
11	2	Left	1	Palpable	Positive	Benign	Fibrosis
		Right	1	Non palpable	Positive	No Biopsy	
12	1	Right	1	Palpable	Indeterminate	Benign	Cyst
13	1	Right	1	Palpable	Positive	Malignant	Infiltrative Ductal ca
14	1	Right	1	Palpable	Negative	Benign	Fat necrosis

continued on next page..

Patient No.	Breasts Involved	Side Involved	Lesions in Breasts	Clinical Exam Palp / Non palp	SMM Pos/ Neg/ Ind	Biopsy Malign/ Benign/ No	Histology
15	1	Right	3	Palpable	Positive	Malignant	Infiltrative Ductal ca
				Non palpable	Positive	Malignant	Infiltrative Ductal ca
				Non palpable	Indeterminate	Benign	Normal breast tissue
16	2	Left	1	Palpable	Positive	Benign	Fibroadenoma
		Right	1	Non palpable	Indeterminate	No Biopsy	
17	2	Left	1	Palpable	Positive	Benign	Fibroadenoma
		Right	2	Non palpable	Indeterminate	No Biopsy	
				Non palpable	Indeterminate	No Biopsy	
18	1	Right	2	Palpable	Negative	Benign	Normal breast tissue
				Palpable	Negative	Benign	Normal breast tissue
19	2	Left	2	Palpable	Positive	Malignant	Infiltrative Ductal ca
				Non palpable	Indeterminate	No Biopsy	
		Right	1	Non palpable	Indeterminate	No Biopsy	
20	2	Right	1	Palpable	Negative	Benign	Fibrocystic disease
		Left	2	Palpable	Negative	Benign	Fibrocystic disease
				Palpable	Negative	Benign	Fibrocystic disease
21	1	Right	1	Palpable	Negative	Benign	Fibrosis
22	1	Right	1	Palpable	Positive	Benign	Atypical Duct Hyperplasia
23	1	Left	1	Palpable	Positive	Benign	Fibroadenoma
24	1	Right	1	Palpable	Indeterminate	Benign	Fibrocystic disease
25	1	Right	1	Palpable	Negative	Benign	Cyst
Total	**30**		**41**	**Palpable 29**	**Positive 17**	**Malignant 9**	
				Non palp. 12	**Negative 12**	**Benign 22**	
					Indetermine. 12	**No Biopsy 10**	

5.4.1. CLINICAL EXAMINATION

A total of 29 lesions were palpated in 26 breasts of 25 patients on clinical examination. Solitary breast lesions were present in 22 breasts. One patient had bilateral breast lumps, one in her right and 2 in the left breast (Patient 20). A further 2 patients (patients 6 and 18) had 2 lesions in one breast.

One patient had a clinical suspicion of tumour recurrence. Six patients had a positive family history of breast cancer. Three of the patients were nulliparous, including one with a positive family history of breast cancer.

The distribution of 29 breast palpable breast lesions in 25 patients (26 breasts) are shown in Table 5.2. with the Tc-99m MIBI SMM results.

Table 5.2: Number and Distribution Of Lesions On Clinical Examination and Scintimammography.

RIGHT BREAST	Palpable Lesions on Clinical Exam.	Lesions Detected on SMM	Lesions Detected on Clinical Exam. & SMM	Total Lesions
Upper Outer Quadrant:	10	9	5	14
Upper Inner Quadrant:	3	4	1	6
Lower Outer Quadrant:	1	3	1	3
Lower Inner Quadrant:	1	1	1	1
Other / Periareolar:	4	4	3	5
TOTAL	**19**	**21**	**11**	**29**

LEFT BREAST	Palpable Lesions on Clinical Exam.	Lesions Detected on SMM	Lesions Detected on Clinical Exam. & SMM	Total Lesions
Upper Outer Quadrant:	4	2	2	4
Upper Inner Quadrant:	2	1	0	3
Lower Outer Quadrant:	2	3	2	3
Lower Inner Quadrant:	0	0	0	0
Other / Periareolar:	2	2	2	2
TOTAL	**10**	**8**	**6**	**12**

5.4.2. TECHNETIUM-99m MIBI SCINTIMAMMOGRAPHY RESULTS

All 25 patients had SMM scan.

The right breast showed 21 and left breast 8 lesions on SMM as shown in Table 5.2.

Of 29 clinically palpable lesions, 17 were detected on SMM (15 positive, 2 indeterminate). The other 12 lesions were regarded as negative on SMM.

Of 29 lesions detected on SMM (17 positive and 12 indeterminate), 17 were palpable and 12 were non palpable.

In the right breast upper outer quadrant, 9 lesions were detected on SMM. Five were classified as positive and 4 as indeterminate. Of the 5 positives, 4 were shown to be malignant and one benign on biopsy. Out of 4 indeterminate lesions on SMM, one was benign on biopsy while the other 3 lesions were nonpalpable and were not biopsied. There were 5 palpable lesions which were negative on SMM. All of these were shown to be benign on biopsy.

In the right upper inner quadrant, 4 lesions were seen on SMM. One was malignant on biopsy while 3 non palpable lesions were indeterminate and were not biopsied. Two palpable lesions were negative on SMM.

In the right lower outer quadrant 3 lesions were detected on SMM. One was shown to be malignant on biopsy (patient 13) while 2 were indeterminate on SMM. Both these lesions were clinically non palpable. One was shown to be benign lesion (patient 15) while the other was not biopsied (patient 8).

In the right lower inner quadrant, a clinically palpable lesion was positive on SMM. This lesion was shown to be a benign lesion on biopsy (patient 22).

In the right breast periareolar area, 4 lesions were seen on SMM. Of these, 3 were palpable and one non palpable. Two were positive on SMM and shown to be malignant; while one was indeterminate on SMM and was confirmed to be a benign lesion on biopsy. The clinically impalpable lesion in the deep breast tissue was detected on SMM but its

exact position could not be determined on the scan. It was regarded as positive on SMM but could not be biopsied as it was nonpalpable and situated in a clinically and mammographically normal breast. Another palpable lesion in the periareolar region was negative on SMM and confirmed to be a benign lesion on biopsy (patient 14).

In the left breast upper outer quadrant 2 lesions were seen as positive on SMM. Both were benign on biopsy, while the other 2 palpable lesions did not show any MIBI uptake (negative SMM). Both were benign on biopsy.

In the left breast upper inner quadrant SMM detected an indeterminate lesion which was clinically non palpable and was not biopsied; while 2 palpable lesions were negative on SMM. Both these lesions were shown to be benign on histology.

In the left breast lower outer quadrant 3 lesions were detected on SMM. Two were palpable and one non palpable. Both palpable lesions were positive on SMM and were shown to be benign on biopsy, while the non palpable lesion was regarded as indeterminate on SMM and was not biopsied.

There were no lesions present in the left breast lower inner quadrant on clinical examination or on SMM.

In the left periareolar area 2 lesions were seen as positive SMM. One was shown to be malignant while the other one benign on biopsy.

In total 41 lesions in 30 breasts were evaluated on SMM. Of these, 17 were regarded as positive, 12 as negative and 12 as indeterminate on SMM The results are shown in Table 5.1.

5.4.3. BIOPSY RESULTS

All 25 patients had biopsies. A total of 41 lesions in 30 breasts were detected on clinical examination and SMM. Of these, 29 palpable and 2 nonpalpable lesions in 26 breasts were biopsied, while 5 non palpable lesions, detected only on SMM, were not biopsied. Further 5 nonpalpable lesions in 4 breasts, detected only on SMM, also were not biopsied. All these nonpalpable lesions could not be biopsied because the surgeon could not locate the exact site to biopsy.

The only patient (patient 7) in this subgroup of 25 patients, with clinically suspected tumour recurrence, had fibroadipose tissue on cytology examination.

Five of the 6 patients with positive family history of breast cancer had benign breast lesions, while one had 2 malignant lesions in one breast. Out of the 3 nulliparous patients, one had a squamous cell carcinoma, one had atypical ductal hyperplasia and the third had a breast cyst.

A total of 9 malignant lesions in 7 breasts were confirmed on histology. Eight lesions in 6 breasts were infiltrative ductal carcinomas. These include a patient (patient 6) with 2 clinically palpable lesions in her right breast and a patient (patient 15) who had a clinically palpable breast lesion but showed further 2 nonpalpable lesions on SMM. Of these 2 nonpalpable lesions, one was regarded as positive on SMM and confirmed to be another ductal carcinoma on biopsy, while the other the other lesion was indeterminate on SMM and was proven to be normal breast tissue. One patient had solitary squamous cell carcinoma.

There were 22 benign lesions noted in 20 breasts in 19 patients. These lesions included 2 patients each with 2 palpable lesions in one breast (patients 18 and 20) and another patient with a benign lesion together with 2 malignant lesions in one breast (patient 15).

The histopathological results are listed in Table 5.3.

Table 5.3: Summary of Histopathological Results of 25 patients with 31 breast lesions.

HISTOPATHOLOGY	LESIONS	BREASTS
Malignant Tumours:		
Infiltrative Ductal ca.	8	5+1*
Squamous cell ca.	1	1
Benign Tumours:		
Fibroadenoma	5	5
Other Benign Lesions:		
Fibrocystic Disease	4	3
Fibroadipose Tissue	2	2
Fat Necrosis	1	1
Fibrosis	2	2
Inflammatory Lesions	1	1
Cyst	3	3
Atypical Ductal Hyperplasia	1	1
Normal Breast Tissue	3	1+1*
Total	**31**	**26**

1* (Patient 15); one breast had 3 lesions (2 infiltrative ductal carcinomas and one normal breast tissue).

5.4.4. TECHNETIUM-99m MIBI SCINTIMAMMOGRAPHY VS BIOPSY RESULTS

Table 5.4.: Summary of Histopathological and Tc-99m Scintimammography Results.

		HISTOLOGY	
		Malignant	**Benign**
SMM	**Positive**	**9**	**7**
	Negative	**0**	**12**
	Indeterminate	**0**	**3**

As shown in Table 5.4. SMM had positive results in all 9 malignant breast lesions in 7 patients. In patients with palpable malignant breast lumps, there were no negative or indeterminate SMM scan findings.

However, in 3 of these 7 patients with malignant lesions SMM detected further 6 lesions in 4 breasts which were clinically non palpable. Of these, one lesion showed ductal carcinoma on histology in a patient (patient 15) who also had a clinically *palpable* infiltrating ductal carcinoma in the same breast. Both these lesions were positive on SMM. The other 5 nonpalpable lesions seen on SMM were classified as indeterminate. Of these, one was shown to be a normal breast tissue (patient 15) while the rest of 4 lesions were not biopsied as the surgeon was not able to identify an area to biopsy.

There were a total of 22 benign lesions in 20 breasts. This included a patient (patient 15) with a nonpalpable lesion, regarded as indeterminate on SMM and confirmed to be normal breast tissue on histology. This patient had further 2 lesions in the same breast (both infiltrative ductal carcinoma). Twelve lesions in 10 breasts showed negative SMM scans i.e. no MIBI uptake. This includes a patient (patient 20) with bilateral fibrocystic lesions. There were 7 lesions in 7 breasts which showed positive MIBI uptake.

Out of these 7 lesions, 5 were fibroadenomas. Further 3 lesions in 3 breasts were classified as indeterminate on SMM.

In these patients with benign breast lesions, SMM detected 6 extra lesions in 5 breasts of 5 patients. All of these lesions were clinically non palpable and none of them were biopsied. One of the lesion was classified as positive and the rest of 5 as indeterminate on SMM.

Scintigraphic results for each pathological diagnosis are give in Table 5.5.

Table 5.5. Scintigraphic Findings Correlating with Histopathological Results.

Histology	*Number of Lesions*	*Tc-99m MIBI uptake*		
		Positive	*Negative*	*Indeterminate*
Infiltrative Ductal Ca.	8	8	0	0
Squamous Cell Ca.	1	1	0	0
Fibroadenoma	5	5	0	0
Fibrocystic Disease	4	0	3	1
Cyst	3	0	2	1
Fat Necrosis	1	0	1	0
Atypical Duct Hyperplasia	1	1	0	0
Fibrosis	2	1	1	0
Fibro Adipose Tissue	2	0	2	0
Inflammatory Lesions	1	0	1	0
Normal Adipose Tissue	3	0	2	1

5.4.5. SEMIQUANTITATIVE ANALYSIS (T/B RATIOS)

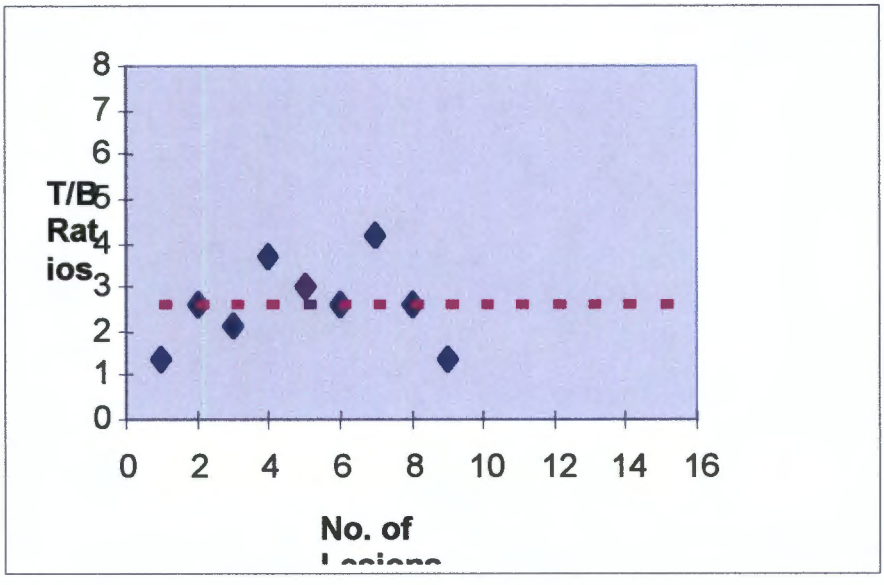
Malignant breast lesions usually showed higher T/B ratios as compared to benign lesions. Figures 5.2 a and b show T/B ratios in malignant and benign lesions. T/B ratios of lesions which were not biopsied are not included in these graphs.

Figures 5.3 a and b show the relationship between counts per pixel in right and left breast (x axis) with T/B ratio value (y axis) of the lesion detected in the breast. These figure show that there is no linear relationship between counts per pixel in a breast and T/B ratio.

Figure 5.4 shows distribution of the counts per pixel in the lateral view of each breast of each patient. The points that lie further from the diagonal line show more counts per pixel in that breast and is mostly due to a lesion (increased MIBI uptake) in that breast.

Figure 5.2. The individual and mean values for (a) malignant and (b) benign breast lesions

(a)



(b)

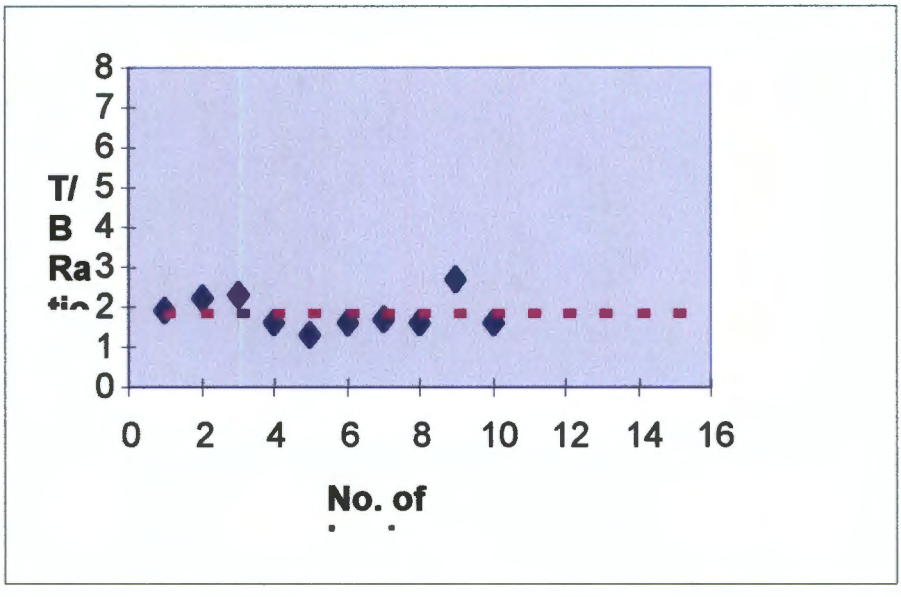
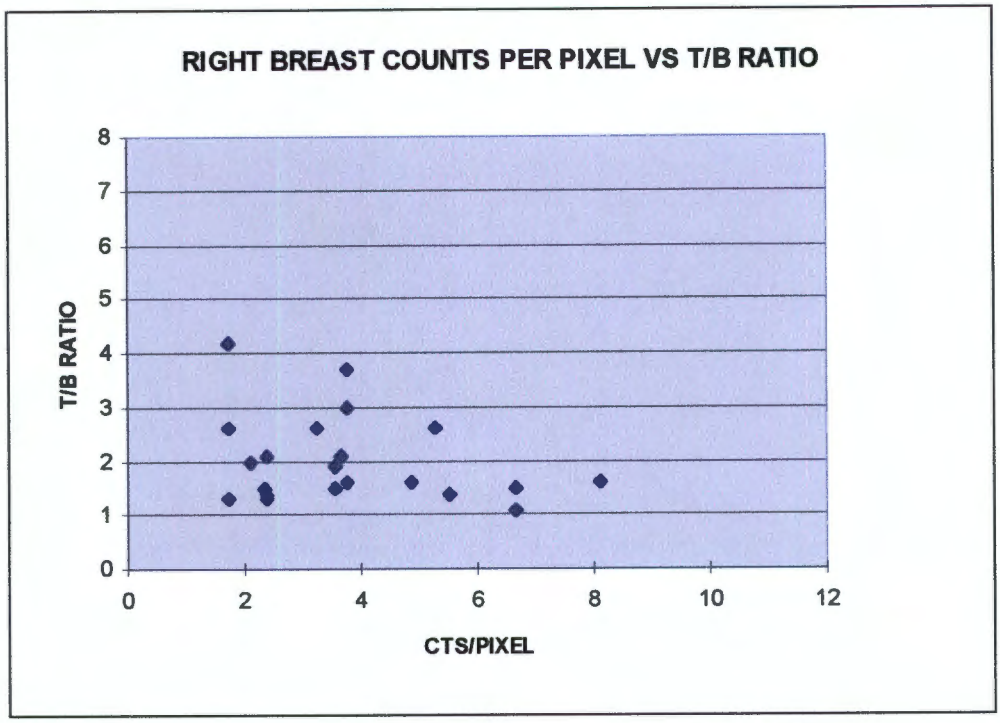


Figure 5.3. Relationship between counts per pixel versus T/B ratio



(b)

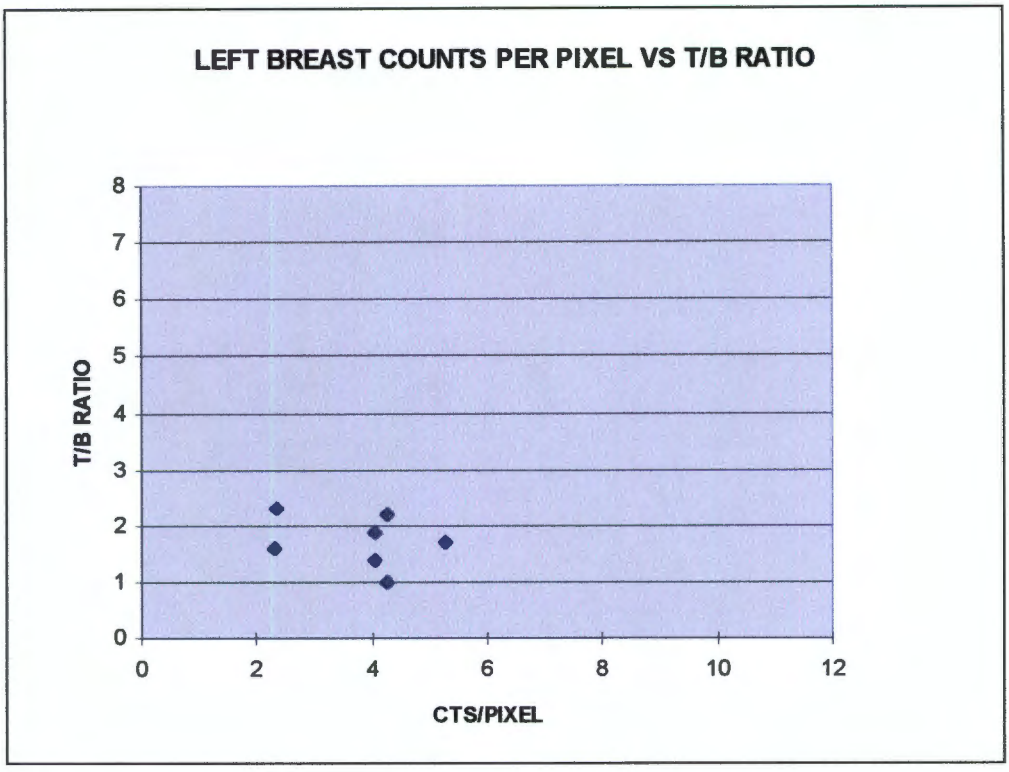
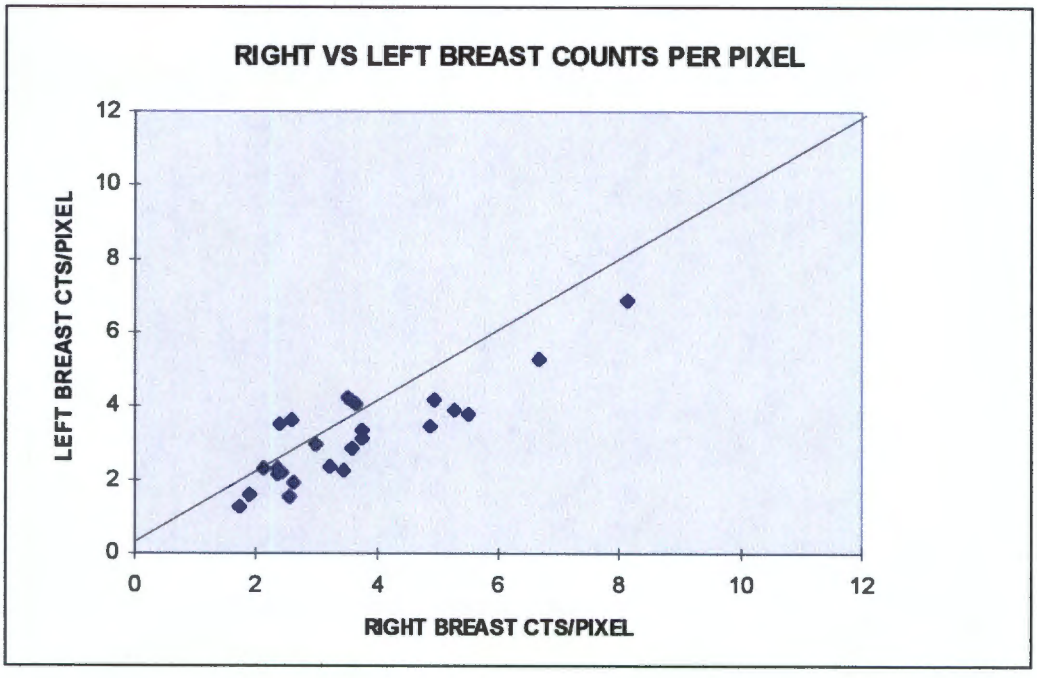


Figure 5.4. The number of counts per pixel in lesions detected in right and left breasts on SMM.



5.4.6. STATISTICAL ANALYSIS

Our study showed a sensitivity of 100% and specificity of 63% in detecting malignant breast lesions, in this subgroup of patients. The accuracy was shown to be 75%. The negative and positive predictive values were 100% and 56% respectively.

5.4.7. AXILLARY LYMPH NODE INVOLVEMENT

In this series 5 of the patients with malignant breast tumours had axillary lymph node clearance. None of the excised lymph nodes showed metastatic involvement. However, SMM showed definite focal increased MIBI uptake in ipsilateral axillary lymph nodes of 2 patients with infiltrative ductal carcinomas in their breasts. The axillary lymph nodes were also visible on mammography but were not palpable. In one of these patients no cancerous lymph nodes were noted on histology while in the other patient axillary clearance was not performed.

CHAPTER SIX

DISCUSSION

6.1. RADIOPHARMACEUTICAL USED IN THIS STUDY

Fractionation reduces the costs of using sestamibi and makes the method affordable. We used locally produced sestamibi for our pilot and formal studies. One vial of South African produced sestamibi (Myotek) used to cost R 1014.60. Our hospital cannot afford to use one vial per patient. However one vial can be divided into ten fractions, reducing the cost of an individual dose of Myotek to R 101.46. This is affordable and the decision to use it for SMM then rests on sensitivity, specificity and accuracy, not cost. Indeed, *fractionation* is so useful that aliquots can be used over a period of 6 months from the date of initial reconstitution [87]. Sampson has suggested that, provided full testing and validation of the product is performed, kit splitting is an acceptable alternative to the manufacturer's recommended method [82].

Unfortunately, the locally produced sestamibi (Myotek) was no longer available commercially at the time when we decided to do an additional study on 25 patients. Therefore we used Cardiolite® produced by Du Pont Pharmaceuticals, USA. Each vial of Cardiolite® was also divided into ten fractions using the same procedure as for Myotek, in order to reduce the cost.

The principle of achieving cost savings by fractionating various radiopharmaceuticals has been described by many other workers [88-91]. Solanki et al. [92,93] developed a method of fractionation of *hexamethylpropyleneamine oxime* (HMPAO). They found that, at the time of radiopharmaceutical preparation, additional tin was required to compensate for the tin that was oxidised during the storage period. This method of *tin enhancement* was applied successfully to leukocyte labelling and cerebral perfusion studies. In particular, it was demonstrated that cerebral perfusion SPECT scans performed with unfractionated and fractionated HMPAO did not significantly differ from each other. This implies that the biodistribution of the fractionated HMPAO does not differ from that of the unfractionated product. Baker [94] demonstrated, using chromatography, animal biodistribution studies and imaging, that fractionated and tin-enhanced HMPAO and MIBI produced the same results as the unfractionated product. Similarly, Chowdhury and Hung [88], using *high pressure liquid chromatography* (HPLC) on fractionated and tin-enhanced sestamibi (Cardiolite®), have shown identical radiochemical species in both the regular and fractionated product.

Mr. John Boniaszczuk and Dr. Michael J Byrne from our department extended the principle of fractionation and tin-enhancement to the South African produced MIBI (Myotek). They decided to fractionate to ten fractions as this had been validated by others [89,93]. As a precaution against oxidation of the tin in the original vial, we added additional tin at the time of radiopharmaceutical preparation. This approach of tin-enhancement of fractionated kits is based on the work of Solanki et al. [93] and has been successfully applied by others [88,94].

We stored fractionated Myotek at (-)4°C for our pilot and formal studies. Storage temperatures recommended for fractionated kits appear to vary considerably in the literature, ranging from (-)70°C to (-)10°C [88,89,95,96]. All these authors store the fractionated kits in frozen form. Nevertheless, storage temperature for Myotek appeared to be satisfactory, as the radiochemical purity of the MIBI was always between 89% to 98%, except for one case where it was 80%. However, for the additional study, we stored the reconstituted Cardiolite® in a chest freezer at a temperature below (-)10°C as recommended by most authors aforementioned. We always achieved radiochemical purity of sestamibi of 90% or more at this storage temperature.

6.2. CAMERA AND PATIENT POSITIONING AND IMAGING

Positioning and acquisition parameters are important in obtaining high quality images. Initially breast imaging protocols using Tl-201 relied on *supine* techniques in which the patient was positioned supine with the arms raised in order to evaluate both breasts and the axilla [9]. Theoretically the potential for not localising a deep lesion against the chest wall using the supine only technique was of concern. Khalkhali et al. [97] and Diggles et al. [40] developed a *prone* imaging technique using MIBI. A specially designed table allowed the patient to be placed in a prone position with the breast dependent. We adopted a combination of prone and supine imaging which seems to be the method of choice [7,18]. We used the conventional gamma-camera bed, rather than a specially designed table or table overlay, and made it comfortable for the patients by placing thin pillows at the lateral edges of the bed. Diggles and co-workers [40] have shown that the technique of *planar prone breast imaging* is more favourable than imaging in the supine position because of excellent separation of breast tissue from the thoracic wall. Relaxation of the pectoralis muscles allows evaluation of deep breast tissue adjacent to the chest wall. This position also excludes any activity from the contralateral breast and improves separation of the breast tissue from the liver and myocardium, allowing improved lesion

detection. They also showed that prone dependent breast imaging results in visualization of more breast tissue, as well as a natural breast contour, which aids in lesion localization.

Incorrect positioning, such as accidental compression of the breast on the imaging table, can produce false localisation. Extending the ipsilateral arm over the head allows the axilla to come into contact with the collimator surface and be included in the field of view. A potential disadvantage of a lateral view is the possibility of missing a small or low-intensity medial lesion because of attenuation.

The timing of the examination is another important matter. Much experience with MIBI in oncology seems to confirm that adequate visualization of neoplastic lesions can be obtained at 10 minutes after injection [13]. In our study, imaging was started 5 minutes after intravenous injection of the tracer, in the contralateral arm. The opposite arm was injected in order to minimise the potential of transient adherence of the tracer to the regional veins after the injection, making evaluation of the axilla and upper breast somewhat difficult. Because of initial high lung background, the anterior supine image was obtained after the lateral images.

A *radioactive anatomical marker* was used as an additional guide in localising the site of a lesion in a breast quadrant.

The image zoom of factor 2 was selected for lateral and posterior oblique views, except in patients with very large breasts, for whom appropriately less magnification was selected in order to include the entire breast in the field of view, keeping the breast in the centre of the field of view. This acquisition magnification improved the quality of images.

6.3. INTERPRETATION OF SCINTIMAMMOGRAPHY RESULTS

Various investigators have developed different criteria for interpretation of SMM results. Our criteria for interpretion was essentially *visual*, as any focal lesion with uptake above the normal breast activity was considered malignant. However, many benign breast lesions showed increased MIBI uptake. We used 3 categories for SMM scan interpretation: *positive, negative and indeterminate.* The criteria for these categories are defined in section 3.3.5. of Chapter 3 (pages 27,28). Total counts obtained in each view were recorded to ensure that enough counts

were acquired for each image. We also recorded the counts per pixel in each breast on lateral view, as it always best separates the breast from the chest wall, by drawing an *irregular region of interest* around the breast excluding chest wall. This was to demonstrate the difference of activity (count rate) between two breasts. Higher counts in a breast is usually due either to a lesion with increased tracer uptake or less frequently due to high counts in the entire breast as compared to the contralateral breast, which may be regarded as a normal variant. The graphs dipicting these results is shown in Figures 4.7(a,b) and 5.3. The data on individual patients with these results can be seen in Tables 4, 5 and 6 (for *pilot, formal and additional* studies, respectively) in Appendix B. The *objective* assessment was done using target to background ratio technique on each breast lesion detected on SMM.

Definitions for interpretation of *positive, negative* and *indeterminate* SMM in literature are not entirely consistent, for example Burak et al. [14] and Taillefer et al. [18] have used different criteria of interpretation for SMM in their papers. When we tried to apply Burak's criteria to our data, *indeterminate* scans in our study were regarded as *positive* according to Burak's criteria, as they did not have a category for *indeterminate* SMM. On the other hand Taillefer et al. [18] did have provision for an *indeterminate* SMM scan but did not define it.

We compared the results of our ***formal study***, using Burak et al. [14] and Taillefer et al. [18] criteria with those of ours in order to demonstrate that our criteria for interpretation of SMM scan were as reliable as those of others.

Burak et al. [14] in their study, had evaluated all images semiquantitaively. The lesions were graded as: 0: less than background activity; 1: equal to background activity; 2: less than heart but more than background activity; 3: equal to heart activity and 4: more than heart activity. When compared to our criteria for different categories, their grades 0 and 1 corresponded to our category for *negative,* as it suggests no increased MIBI uptake. Likewise, their grades of 2, 3 and 4 corresponded to our categories for *indeterminate* and *positive*. It must be emphasised that in Burak's criteria there was no category for an *indeterminate* SMM.

Taillefer et al. [18] defined *positive* SMM result for malignant breast tumour as a focal area of increased MIBI uptake compared to the surrounding normal breast tissue which corresponded to our category of *positive* SMM scan. There is no specific description of the criteria for an *indeterminate* SMM scan in their paper. They used a semiquantitative analysis

technique to determine the relative degree of diagnostic certainty. These included, 0: definitely normal; 1: probably normal; 2: equivocal; 3: probably abnormal and 4: definitely abnormal. When compared to our categories, their categories of 0 and 1 corresponded to our category for *negative,* their category of 2 corresponded to our category for *indeterminate* and their categories of 3 and 4 corresponded to our category for *positive* SMM scan.

If we re-analyse our data using Burak et al. [14] or Taillefer et al [18] criteria and compared those results with ours, the results we would have got are shown in Table 6.1 (a) and (b).

Table 6.1. Summary of Comparative Results using Burak's (a) and Taillefer's (b) Criteria of SMM with our Results and Histology.

(a)

HISTOLOGY	SMM Our study	SMM Burak et al. [14]	LESIONS
Malignant	Positive	Positive	17
Malignant	Negative	Negative	2
Malignant	Indeterminate	Positive	3
Benign	Negative	Negative	16
Benign	Positive	Positive	9
Benign	Indeterminate	Positive	10
Not done (non-palpable lesions)	Positive	Positive	2

(b)

HISTOLOGY	SMM Our study	SMM Taillefer et.al [18]	LESIONS
Malignant	Positive	Positive	17
Malignant	Negative	Negative	2
Malignant	Indeterminate	Indeterminate	3
Benign	Negative	Negative	16
Benign	Positive	Positive	9
Benign	Indeterminate	Indeterminate	10
Not done (non-palpable lesions)	Positive	Positive	2

There were 2 malignant breast lesions in 2 patients which showed negative SMM according to our, Burak's and Taillefer's criteria.

One of the patients had a clnically palpable lump situated at upper outer quadrant of the breast. On histology a 2x1 cm recurrent infiltrating ductal carcinoma was confirmed. Mammography was also negative in this patient. All the other 14 infiltrative ductal carcinomas were positive on SMM on all 3 criteria. The mammogram showed positive results on 12 of these lesions while 2 lesions were classified as indeterminate.

Palmedo et al. [15] in their study showed 3 false negative SMM, using Tc-99m MIBI, out of a total of 22 breast lesions. Two were invasive ductal carcinomas, including one with local tumour recurrence and was clinically palpable while the other was nonpalpable. The third lesion was clinically palpable recurrent invasive lobular carcinoma. Two of these lesions were located in the medial part of the breast and were less than 1 cm in diameter. Mammography was not performed in 2 cases with suspected recurrent breast cancers and was negative (false negative) in one case. Rest of the 12 malignant lesions (all ductal carcinomas) were positive on SMM in their study. Similarly Khalkhali et al. [16] showed 4 false negative lesions on SMM out of 153 breast lesions. All were infiltrating ductal carcinomas (4 palpable and one nonpalpable). All of these lesions were less than 1 cm in diameter and were located in medial aspect of the breast. Rest of 33 patients with ductal carcinomas were positive on SMM. Tiling et al. [84] showed 6 false negative SMM out of 82 patients with indeterminate and / or clinical examination. Four of these were infiltrative and 2 were ductal carcinoma *in situ.* Rest of the 15 lesions with ductal carcinomas were positive while 5 were indeterminate on SMM. The mean diameter of all the tumours was 2.1 cm and the smallest carcinoma was 2 mm in greatest dimension. Taillefer et al. [18] showed 4 out of 38 ductal carcinomas (including a microscopic ductal ca *in situ*) as negative (false negative) on SMM and the rest of 34 lesions as positive. Burak et al. [14] showed positive SMM all 19 patients with infiltrative ductal carcinomas. The 3 false negative SMM included 2 with invasive lobular and one with tubular carcinoma.

Another lesion with false negative SMM in our study was clinically nonpalpable small (10 mm in diameter) adenocarcinoma *in situ.* It was detected as a suspicious lesion on mammography. This was the only patient with adenocarcinoma in our study. Kao et al. [12] showed 27 adenocarcinomas (84%) in their study with 32 patients with palpable breast lesions.

Out of these, 4 adenocarcinomas could not be detected on SMM. The smallest detectable cancer measured 2x1x1 cm, while the largest undetectable carcinoma measured 7x4x3 cm on mammography. None of tumours in their study were less than 1 cm in size. Adenocarcinoma of the breast appeared to be a relatively uncommon tumour type as non of the patients had this tumour in studies conducted by Palmedo et al. [15], Khalkhali et al. [16], Tiling et al. [84], Taillefer et al. [18] and Burak et al. [14].

It is possible that false negative SMM is associated with small (less than 1 cm) size and / or with the metabolic activity of the tumour, and not the tumour type.

Burak et al. [14] did not have an indeterminate category in their study. There were 3 malignant lesions in 2 breasts which were indeterminate on SMM according to our and Taillefer's criteria and were categorised as positive according to Burak's criteria.

One of these patients (patient 17) had 2 lowgrade illdefined foci close to each other. Histology confirmed these as invasive lobular and lobular carcinoma *in situ.* The mammogram also showed features of malignancy. Rest of the 2 lobular carcinomas in our study, showed positive SMM on our, Burak's and Taillefer's criteria. The mammogram was negative in one and positive in the other case. The other patient had a low malignancy type Phylloides tumour. The tumour showed illdefined and lowgrade uptake and was not classifiable as benign or malignant according to our or Taillefer's criteria.The mammography was negative (false negative).This was the only patient with Phylloides tumour in our study.

Tiling et al. [84] in their study showed 5 indeterminate breast lesions on SMM in the malignant group. All were ductal carcinomas. However, their criteria for indeterminate SMM was different from ours. They classified diffuse uptake with high intensity (uptake comparable to or higher than the upper chest as seen in the lateral projection) as indeterminate, while diffuse uptake with low intensity was interpreted as probably benign. On the other hand, we classified any area of illdefined diffuse uptake as indeterminate, including low intensity uptake. They showed 2 false negative SMM (probably benign) which would be indeterminate according to our criteria, hence reducing the number of false negatives.

Ten patients with 10 benign lesions were categorised as indeterminate according to our and Taillefer's criteria and as positive on Burak's criteria. Out of these 10 lesions, 4 were

inflammatory lesions, 2 with fibrocystic disease, 2 with fat necrosis, 1 with lipoma and 1 with fibroadipose tissue. The mammography showed features suggestive of benign pathology.

Tiling et al. [84] in their study showed 7 out of 53 benign breast lesions as indeterminate on SMM. Out of these 7, 4 were fibroadenomas, 2 fibrocystic and one with an inflammatory lesion. All patients had indeterminate mammograms.

Nine patients had 9 benign lesions in 9 breasts which were categorised as positive on our, Burak's and Taillefer's criteria. These included rest of 3 lesions with fibrocystic disease, one fibrotic lesion one inflammatory lesion. The patient with a clinically palpable inflammatory lesion, showed further 2 lesions in the same breast but were clinically impalpable and therefore could not be biopsied. These 2 lesions were also shown as positive on our, Burak's and Taillefer's criteria. The mammography was suggestive of benign disease in all these patients. Also included were 4 fibroadenomas. The mammography was suggestive of benign pathology in 3 and indeterminate in one case.

False positive SMM is not uncommon. Fibrocystic disease and fibroadenomas are the most common, like in our study. Khalkhali et al. [16] showed 11 false positive lesions out of 102 benign breast lesions. These included 8 fibrocystic and 3 fibroadenoma lesions. Similarly Tiling et al. [84] showed 9 out of 53 false positive SMM scans. These included 4 fibroadenomas, 2 fibrocystic disease, 2 inflammatory and one with papilloma. Burak et al. [14] showed 2 out of 14 and Palmedo et al. [15] 1 out of 7 false positive SMM. All were fibroadenomas. Taillefer et al. [18] had one out of 18 false positive SMM, a fibrocystic lesion, while Kao et al. [12] showed 6 benign breast lesions with no false positives.

It has been suggested that the "hypercellularity" of a breast lesion with or without atypia can accumulate Tc-99m MIBI , which results in false positive findings [16].

The rest of our study had 3 more patients with fibroadenomas, 2 patients with fat necrosis and one patient with 2 bilateral palpable fibroadipose tissue masses. All these showed negative SMM on our, Burak's and Taillefer's criteria. The mammography was suggestive of benign pathology in all these patients except in one case of fibroadenoma which showed indeterminate mammography. In our study further 9 benign breast lesions showed negative SMM. These included 5 cysts and 4 normal adipose tissue.

These comparative results show no significant difference between the three studies. Our and Taillefer's results exactly match to each other. When compared to Burak's criteria, the number of true-positive SMM tend to improve slightly but at the expense of much higher false-positive rate because all *indeterminate* SMM scans, according to our and Taillefer's criteria, were regarded as *positive* using Burak's classification.

Our method of data analysis for SMM results also constituted objective assessment using target to background ratio technique on each breast lesion detected on SMM. A *semi-quantitative* method was therefore investigated to determine if the intensity of the lesion as compared to the rest of the breast activity (background) would help to differentiate between benign and malignant lesions.

Quantitation has been suggested previously as an aid in differentiating between benign and malignant abnormalities [18]. Piccolo et al. [47] have studied semiquantitative analysis of Tc-99m methylene diphosphonate (MDP) uptake in breast lesions, using the normal breast to define the background region and generating time-activity curves. More recently, Dunnwald et al. [98] investigated the utility and reproducibility of semiquantitaive analysis on Tc-99m MIBI breast imaging and observed good separation between malignant and benign lesions, with some overlap occuring between small, low grade malignancies and benign lesions. Table 6.2 shows the comparison between their T/B ratio results and those obtained in the present study.

Table 6.2 Comparative Sestamibi Uptake Ratio Results

	Dunnwald et al. [98]		Our Formal study	
	Malignant	*Benign*	*Malignant*	*Benign*
Mean	4.2	1.9	2.9	2.0
Std. Deviation	2.3	0.7	1.5	0.6
Range	1.9-9.4	1.0-2.7	1.0-6.9	1.3-3.0

Our study showed a broader spectrum of T/B ratio overlap between benign and malignant lesions and could not be used to discriminate between cancerous and non-cancerous breast lesions. For benign lesions, our results were almost identical with those of Dunnwald et al. [98]. However, there were some differences between their method of determining T/B ratios and that used in our study. One difference was in the image analysis. They used the contralateral breast as the background, whereas we used the apparently normal breast tissue of the affected side for the same purpose. The other difference was that they used *different* sized box shaped region of interests (ROI), which were standardised for each area, for the lesion and background. On the other hand, we used *identical* sized box shaped ROIs for the lesion and the background in each patient and calculated total counts in each region to obtain T/B ratio. The results show that enough counts were obtained within each ROI for target and background. Total number of counts acquired for each target and background ROIs and their ratios are shown in Table 5 and 6 in Appendix B.

Dunnwald and associates [98] used an additional quantitative measure by determining the ratio between the lesion and the right chest wall (L/CW). Both indices showed excellent intra-observer and inter-observer reproducibility. They observed that the L/CW ratio was less variable than the T/B ratio. They thought that diffuse uptake, which at times is visualised in apparently normal breast may result in more variability in the T/B ratio as compared to L/CW ratio method. We did not use the L/CW ratio in our study. Dunnwald et al. also suggested that these semiquantitative measures of tracer uptake reflected lesion characteristics and therefore, helped distinguish benign from malignant lesions and correlated with lesion size.

Tilling et al. [99] reported similar observations to ours. At low tumour to non-tumour ratios (1.0-1.5) it was not possible to discriminate between benign and malignant breast lesions. Our results, however, suggested that this technique is not reliable to differentiate between benign and malignant breast lesions with T/B ratios under 3.0. Waxman [7] showed that numerous benign abnormalities have T/B ratios of greater than 1.4 while small malignancies can show ratios of less than 1.4. Our results as well those of others [98,99] were unlike those of Palmedo et al. [15], who showed that every lesion with a T/B ratio of 1.5 or more was histopathologically malignant.

As discussed earlier, Burak et al. [14] and Taillefer et al. [18] have used different semiquantitive methods to evaluate breast masses with Tc-99m MIBI SMM. Burak et al. [14] in their study evaluated all images using a semiquantitative analysis technique which was graded from 0 to 4 (described earlier in this chapter). Their results revealed that no breast lesion had activity greater than grade 3. Most of the malignant pathologies and 2 benign breast lesions had focal increased MIBI uptake of grade 2. They also found that there was no significant correlation between the pathological diagnosis of the malignant mass and the grade of MIBI accumulation.

Taillefer et al. [18] used semiquantitative analysis to determine the relative diagnostic certainty: graded from 0 (definitely normal) to 4 (definitely abnormal) as described earlier in this chapter. The ROIs were placed over the primary breast tumour, surrounding apparent normal breast tissue, axillary lymph nodes (if detected on SMM) and ipsilateral lung to determine four activity ratios: breast tumour-to-normal breast tissue, breast tumour-to-axillary lymph nodes, normal breast tissue-to-lung and axillary lymph nodes-to-lung. Based on these diagnostic certainty gradations, 42 of the 43 true-positive cases were classified as definitely abnormal, whereas one was viewed as probably abnormal. Fifteen of the 17 true-negative cases were definitely normal and 2 were probably normal. Four different activity ratios were: primary breast tumour-to-normal breast tissue was 2.2 ± 0.7 (from 1.2 to 3.7); breast tumour-to-positive axillary nodes was 0.7 ± 0.2 (from 0.3 to 1.1); normal breast-to-lung was 0.3 ± 0.1 (from 0.1 to 0.6); and axillary nodes-to-lung was 0.8 ± 0.3 (from 0.6 to 1.5).

6.4. COMPARATIVE SENSITIVITY AND SPECIFICITY OF Tc-99m SESTAMIBI SCINTIMAMMOGRAPHY

Our *formal* study has shown that Tc-99m MIBI scintimammography is more sensitive than mammography in detecting primary breast carcinoma but significantly less specific than mammography in differentiating between benign and malignant breast lesions. Similar sensitivities for Tc-99m MIBI have been found by most of the other investigators. However, as compared to our results of SMM, others have reported better specificity with Tc-99m MIBI in differentiating benign from malignant breast lesions (Table 6.3).

Our *formal* study showed a sensitivity of 89.5% and specificity of 64% for SMM, as compared to mammography, which showed sensitivity and specificity of 80% and 100%. Palmedo et al. [100] showed similar findings for SMM. In their study, SMM showed a sensitivity of 91% and specificity of 62% for detecting palpable breast carcinomas whereas mammography showed a sensitivity of 95% but specificity of only 10%. Their entire study consisted of 43 palpable and 13 non-palpable breast lesions and overall results for palpable and non-palpable lesions showed a sensitivity and specificity of 85% and 66%, respectively for SMM. The results of Kao et al. [12] who used Tc-99m MIBI in studying 38 women with palpable breast lumps, showed sensitivity of 84% and specificity of 100% in differentiating benign from malignant breast masses. Similarly Khalkhali et al. in a study with 147 patients, showed sensitivity of 92.2% and specificity of 89.2% [16] and, in another study with 59 patients [17], reported sensitivity of 95.8% and specificity of 86.8%, in detecting breast carcinoma, both studies using Tc-99m MIBI. Taillefer et al. [18] have reported similar sensitivity and specificity, of 91.5% and 94.4%, in detecting primary breast cancer using Tc-99m MIBI in 65 consecutive patients with suspicious breast lesions on clinical examination and/or with abnormal mammographies suggestive of malignancies.

In summary, we have shown lower specificity for SMM than has been reported in the literature. The factors affecting specificity and sensitivity of SMM are discussed below.

Table 6.3. Summary of Published Results of Tc-99m MIBI Scintimammography

Main Author	*Patients (N)*	*Breast Lesions (N)*	*Palpable:Nonpalpable*	*Sensitivity*	*Specificity*	*Malignant: Benign*
Kao [12]	38	38	All : Nil	84%	100%	32 : 06
Burak [14]	41	41	All : Nil	93%	86%	27 : 44
Taillefer [18]	65	65	44 : 21	91.5%	94.4%	47 : 18
Khalkhali [16]	153	153	113 : 40	92.2%	89.2%	51:102
Palmedo [100]	56	56	43 : 13	85%	66%	27 : 29
Mekhmandarov [85]	140	140	85 : 55	83.5%	85.4%	85 : 55

6.4.1. Patient Selection

In our *pilot* and *formal* studies, *patient selection* might account for the difference in specificity, when compared to other studies. We selected any patient with palpable breast lump/s rather than selecting only those patients who had breast lumps with suspicion for malignancy. Our selection criteria were therefore different from those in the other studies, where more patients with clinically and/or mammographically suspicious breast lumps were selected.[15,16,18,19]. Study populations high in patients with proliferative breast disorders like fibrocystic disease are more likely to have a relatively high false-positive rate [7]. The low specificity in our study was due to high number of *false-positive* scans.

Our *additional study* differed from *pilot and formal studies* in two aspects. First, we included only patients with indeterminate mammography findings. Second, a lesion by lesion comparison of each breast lesion detected clinically and/or scintimammographically with biopsy results of a particular lesion was performed, which was not performed in the formal study.

Sensitivity and specificity are critically dependent upon the selection of the patient population. Patient referral bias will influence the results. If clinicians refer only "difficult" cases for study, both sensitivity and specificity may differ from those obtained with an unselected pool of patients. In our *formal* study with 51 patients, 41% of the women had malignant and 55% had benign breast lesions. In contrast, Kao et al. [12] had 84% of patients with malignant and 16% of cases with benign breast lesions in their series of 38 patients, and Taillefer et al. [18], in their study with 65 patients, had 72% of patients with malignant and 28% with benign breast lesions. The relatively poor specificity in our *formal* study may therefore be accounted for by the similar proportions of patients with benign and malignant breast lesions; the other studies [15,16,19] selected more patients with clinically and/or mammographically suspicious breast lesions, so favouring the likelihood of correctly detecting malignant lesions and decreasing the chances of *false-positive* scans.

6.4.2. Size of Lesion

Another factor which might affect the sensitivity of SMM study is the size of the lesion. Small lesions are likely to be missed resulting in *false-negative* SMM. In our *formal* study the false-negative rate was 3.51%. There were 2 patients with breast carcinomas who showed negative Tc-99m MIBI uptake. One of the patients had a small recurrent infiltrating ductal carcinoma, measuring 2 x 1 cm, with central haemorrhage. The possible cause of the absence of MIBI uptake could be the relatively small size of the actual tumour. The other patient had a small *nonpalpable* lesion in the clinically normal breast, which was detected by mammography. The entire lesion (adenocarcinoma in situ) was only 10 mm in diameter with an even smaller focus of invasion (approximately 2 mm in diameter). The other *(symptomatic)* breast of the patient had 2 benign cystic lesions.

Khalkhali et al. have reported two studies with different results for patients with *nonpalpable* breast lesions. In one study [17] they reported a low sensitivity of 50% but a specificity of 89.5% for detecting small *nonpalpable* breast lesions on Tc-99m MIBI scintimammography. In this study, only 2 out of 21 breast masses were malignant, of which one was true positive and the other false negative on SMM, giving it a low sensitivity. In the other study [16], with a subgroup of 40 *nonpalpable* breast lesions, they showed SMM results with relatively high sensitivity of 88.8% and specificity of 93.5%. In this study there was only one case of false negative and 2 cases of false-positive SMM, resulting in high senisitivity and specificity, respectively. Waxman et al. have also reported low sensitivities of 50% [101] and 27% [102] in two studies with *nonpalpable* breast lesions. The results of these studies by Khalkhali and Waxman suggest that in general the sensitivity of SMM detecting *nonpalpable* breast lesions (mostly small lesions < 1 cm) is significantly less than that for *palpable* breast lumps.

Aktolun et al. [13] showed that the smallest breast carcinoma detectable by SMM was 1.5 x 1 cm. Similarly, Palmedo et al. [15] and Peller [73] showed that *false-negative* breast imaging with Tc-99m MIBI most frequently occurs in breast lesions which are less than 8 mm in diameter. These results suggest that with current gamma camera technology, with its limited resolution, very small lesions, less than 1 cm in diameter are less likely to be detected on SMM.

6.4.3. Location of Lesion

Medially placed lesions may also create some difficulty in prone breast imaging as they are further away from the detector surface with more interposed breast tissue. Although, in our formal study, we were able to detect all palpable lesions (4 malignant and 7 benign) located in the medial aspect of both breasts, they were more than 1 cm in size. Khalkhali et al. [16] have shown 3 patients (4 lesions), in their study on 147 patients (153 lesions), who had medially placed breast lesions which escaped detection on prone lateral breast imaging. Three of these were palpable and one was a nonpalpable lesion but they were all less than 1 cm in the greatest diameter. All were malignant.

6.4.4. Nature of Lesion

Falsely positive Tc-99m MIBI uptake occurs in benign hypercellular breast lesions and inflammation [73]. In our *formal study*, 9 out of 35 benign breast masses (in 33 breasts) showed positive MIBI accumulation. The histological diagnoses were *fibroadenomas* in 4 cases, *fibrocystic disease* in 3 cases, *inflammatory lesion* in one and *fibrosis* in one case. The study reported by Khalkhali et al. [17], with 59 cases, showed false positive SMM in 5 patients (3 patients had *fibrocystic disease* and 2 had *fibroadenomas*). In all these patients hypercellularity with extensive florid hyperplasia and adenosis was a common pathologic feature. They suggested that the mechanism of MIBI uptake in fibroadenomas and fibrocystic disease could be related to "increased metabolic activity" of these lesions due to the augmentation of a cellular component in comparison to fibrous tissue. Similar results were reported in a study by Lu et al. [38], where 4 out of 7 patients with fibroadenoma had increased uptake of MIBI, all of which revealed active cellular hyperplasia. Kao et al. [12], in their study with 38 patients, showed no false positive MIBI uptake (all benign lesions were due to fibrocystic disease). This differs from most of the other studies done so far.

Van Eijck and Krenning [103] have suggested that it is not possible to differentiate on scintimammography between epithelial hyperplasia, severe atypia, and sclerosing adenosis or microscopic intraductal and / or infiltrating ductal carcinoma. Chiu et al. [104] have demonstrated that Tc-99m MIBI is sequestered within the cytoplasm and

mitochondria of cultured mouse fibroblasts. Their results suggested that normal and abnormal tissues with a large number of mitochondria per cell show higher Tc-99m MIBI uptake than tissues with fewer mitochondria. Gupta et al. [105] have demonstrated MIBI uptake in benign disease to be highly associated with the presence of proliferative changes, and speculated that the false positive MIBI breast uptake may reflect premalignant potential. However, more research in this area is needed to confirm these findings. Palmedo et al. [106] found most false positive studies to be associated with highly mitotic juvenile adenomas or local inflammation. Increased Tc-99m MIBI uptake has been reported in "metabolic active cells" of an *in vitro* cell culture line of normal tissues [11].

6.4.5. Other Factors

It has been reported that mild, diffuse increased breast activity can be seen just prior to the onset of menses, especially in women under the age of 30 years [73]. Unfortunately, we did not record data on menstrual cycle in our study. However, on retrospective analysis, we found that there were no women under the age of 30 years among those selected. Among the patients with *indeterminate* SMM results, there were 3 women between the ages of 30 and 35 years and 4 women between the ages of 36 and 46 years, but none of the patients had pathology and therefore the results could not be attributed to the phase of the menstrual cycle.

The large number of *indeterminate* SMM results also accounted for low specificity and accuracy in our *formal* study. They were mostly benign lesions with T/B ratios of less than 2.0. We used different interpretative criteria as compared to other studies [16,84]. The visual interpretation of our *indeterminate* SMM studies corresponded to the scoring criteria for *probably normal / negative* (mild to moderate diffuse uptake with no region of focal increased uptake) in the studies conducted by Khalkhali et al. [16] and Tiling et al. [84]. We thought that our criteria for *indeterminate* could be more objective than the *probably negative* criteria used by others. We have observed that the relatively high numbers of *indeterminate* scans in our study were due to the difference in our interpretation of *indeterminate* SMM scans. If all *indeterminate* SMM scans in our series were considered as negative, the specificity would have increased to 76.3%.

6.5. MAMMOGRAPHY

Mammography is the only imaging procedure validated as useful in screening for breast cancer. In our *formal study*, mammographic evaluation correctly detected 73% (16 out of 22 of malignant breast carcinomas) in 21 breasts, with a sensitivity of 80% and very high specificity of 100%. Burak et al. [14] have shown, in their comparative study between Tc-99m MIBI and mammography, that the sensitivity and specificity of mammographic interpretation in the differentiation of malignant breast masses from benign lesions was 100% and 78%, respectively. Reported specificity of mammography varies from 15 to 75% [107-109].

6.5.1. False Positive Results and Positive Predictive Value

As there were no false positive and only three false-negative mammograms in our *formal* study, it showed 100% values for the specificity and positive predictive value for mammography. Other studies have shown a general lack of mammographic specificity. As many benign lesions have significant density differences when compared with normal breasts, they result in false-positive mammography [7]. Calcifications revealed on mammography may be the only evidence for malignancies within the breast and, as many benign conditions also result in calcifications, the false-positive rate has been extremely high for this technique [6]. It is important to note that, at our institution, the rate of false positive mammograms among *palpable* breast masses is generally very low. If the radiologist cannot decide whether the mass is benign or malignant, it is called *indeterminate*. Therefore, a benign mass with unclear features would be interpreted as *indeterminate*, rather than as *malignant*, unless it fulfils the criteria for a malignant lesion. The criteria for malignancy is a mass with irregularity and/or spiculation and/or microcalcification, which in difficult cases may be visible with special views (focal compression or magnification). Strict and specific interpretation criteria are used. In patients with mammographically suspicious breast lumps, an attempt is made to analyse the nature of the mass by the use of extra views, for example a *repeat view, lateral view, focal compression and magnification views,* in addition to standard *cranio-caudal* and *medio-lateral views.*

Mammography is capable of detecting lesions of very small size, especially when calcifications are present [110]. Kopans [25] suggested that, despite the fact that mammography does not detect all cancers, a cancer that is detected by mammography alone is usually at a smaller size and earlier stage than a clinically apparent cancer, and this translates into a survival and mortality benefit. In one of our cases, mammography demonstrated a small, spiculated mass with microcalcification suggestive of a malignant lesion in a clinically and scintimammographically normal breast. Histopathological examination showed an adenocarcinoma *in situ*, the entire lesion measuring about 10 mm in diameter with a focus of invasion measuring approximately 2 mm in diameter.

The basis of mammography is to find an abnormality which requires biopsy and to be able to exclude those that do not need further investigations. Although mammography frequently cannot be relied on to differentiate benign from malignant lesions, when certain morphological criteria are present it is extremely accurate [111]. Bird et al. [112] have reported sensitivity between 85-90% for screening mammography. The positive predictive value (the number of carcinomas diagnosed per number of biopsy results) of screening mammography ranges from approximately 15 to 75% [5].

6.5.2. False Negative Results

It has been shown that a false-negative mammogram could cause a considerable delay in the decision to perform a biopsy in a patient subsequently shown to have carcinoma of the breast [26]. Mammography is often difficult to interpret in patients who have a *scar* within the breast from previous biopsy.

In our *formal study,* 4 malignant breast lesions (in 3 breasts) were falsely interpreted as benign on mammography. The first patient (patient 14) was found to have a recurrent infiltrating ductal carcinoma (2 x 1 cm) with central haemorrhage on excisional biopsy, but on mammography no definite mass was seen, besides the scarring. Tc-99m MIBI SMM was also negative in this case. The second patient (patient 17) had a clinically solitary lesion in her right breast. SMM showed 2 ill-defined lesions close to each other and were regarded as *indeterminate.* Histology confirmed an invasive lobular carcinoma with another lobular ca. *in situ,* which was clinically not palpable, and was not detected on mammography. In the third patient, (patient 39) a 35 year old nulliparous woman with

positive family history of breast cancer, had mammographic features were suggestive of a benign lesion and SMM was indeterminate. However, histology confirmed a low-malignancy type phylloides tumour, measuring 4 x 4 x 3 cm. In the last patient (patient40), mammography showed a vague density in the lower half of the breast with no specific signs of malignancy. This small breast lesion (1 x 1 cm on clinical examination) showed positive MIBI uptake consistent with malignancy.

The false-negative rate of 7% for mammography found in *formal* study is representative of general results. At our institution, 10 to 15% of palpable breast lumps are missed or misdiagnosed. It is well established that mammography misses 5% to 15%.of cancers that are present and palpable at the time of screening, and as many as 20% of cancers become clinically evident within one year of a negative mammogram [113]. Bird et al. [112] showed a much higher false negative rate of 24% in detection of breast carcinoma by mammography. Similarly when Mann et al. [26] examined 165 patients with palpable breast masses that were histopathologically determined to be malignant. Only 105 selected patients had mammography during their initial examination. Thirty-six patients were found to have false normal mammograms (34.2%). This group also concluded that mammography had certain limitations, particularly in young women with dense breasts. In another report from New Mexico [114] the false-negative rate for mammography was 45%. Many false-negative mammograms also occur in women whose tissues are not dense.

There are several reasons why cancers are not shown by mammography. As in SMM, the importance of positioning cannot be overemphasized. According to Kopans [115], cancers will be missed if the breast is not properly positioned. There is also a significant danger of missing lesions near the chest wall. Similarly, if a neoplastic lesion is surrounded by tissue of similar x-ray attenuation and there is no architectural distortion or deposition of calcium, a large cancer may be invisible mammographically. Interpretative errors will always occur, but they can be minimised by proper training [115].

6.5.3. Indeterminate Mammography Results

Mammography has limitations in the differential diagnosis of fibroadenoma as it may be indistinguishable from malignancy [116]. In our *formal* study 2 out of 7 fibroadenomas showed indeterminate mammography masses. Burak et al. [14] demonstrated similar findings: in 4 out of 6 patients with fibroadenomas, mammographic evaluation could not differentiate benign from malignant mass. In our *additional* study of 25 patients with indeterminate mammographic results, out of 22 benign lesions, there were 5 fibroadenomas.

It has been reported that in patients with mammographically dense breasts and with indeterminate opacities or microcalcifications, mammography is less reliable for differentiating between benign and malignant lesions [3,112]. In our *formal* study, there were 2 malignant lesions, one infiltrative lobular and one infiltrating ductal carcinoma (in 2 breasts), and 3 benign neoplastic lesions, 2 fibroadenomas and one lipoma (in 3 breasts), which showed *indeterminate masses* on mammography. In the *additional* study with 25 patients with indeterminate mammograms, there were 8 infiltrative ductal carcinomas (in 6 breasts) and one squamous cell carcinoma. Of the 22 benign lesions, there were 5 fibroadenomas, 4 fibrocystic disease, 3 cystic lesions, 2 fibrosis, 2 fibroadipose tissue, one lesion each of inflammatory tissue, fat necrosis and atypical ductal hyperplasia. In addition there were 3 lesions confirmed to be normal breast tissue. Holland et al. [117] studied patients with mammographically occult (nonpalpable) breast cancers. They felt that invasive ductal carcinomas are mostly associated with a strong desmoplastic reaction, but if the tumour is embedded in dense fibroglandular tissue the difference in density may not be enough to be appreciated mammographically as a focal mass. Similarly an invasive lobular carcinoma in dense breast can reach a size of several centimeters and still lack mammographic signs. Studies in the United States show that mammograms done on dense breasts have only a 20% rate of specificity and a positive predictive value of only 30% [5]. This means that only 1 in every 4 to 6 biopsies done to confirm malignant lesions in dense breasts would reveal malignancy. A more recent study, with 48 women with palpable abnormalities and grades III and IV dense breasts according to American College of Radiology classification, showed the sensitivity and specificity of mammography to be 82.2% and 46.1% respectively, whereas sensitivity and specificity of SMM in this group were 93.7% and 90.6% respectively [118].

Our study group consisted of 25 patients with 29 palpable and 2 nonpalpable breast lesions which were biopsied. There were further 10 nonpalpable lesions, detected on SMM and/or mammography which were not biopsied as the surgeon could not locate the exact site to biopsy in clinically normal breast. Of the breast lesions which were biopsied, we found that Tc-99m MIBI has a high sensitivity of 100% and a specificity of 63% for detecting breast cancer. Our results were comparable to those of Palmedo et al. [100] who studied a group of 56 patients with 43 palpable and 13 nonpalpable breast lesions. All abnormalities were dubious at mammography. For palpable breast lesions they showed a sensitivity of 91% and specificity of 62%. The reason for relatively low specificity in our *additional* study and that of Palmedo et al. [100] might be the higher incidence of false-positive scans, especially fibroadenoma.

Our *additional* study showed 7 out of 22 (32%) false-positive SMM; 5 of these were fibroadenoma. Palmedo et al. [100] showed similar observations. In another study, Prats et al. [86] showed a false-positive rate of 22% in their study of 31 mammographically indeterminate breast lesions. In their study too, there was a high incidence of fibroadenomas (4 out of 6 false-positive scans were fibroadenomas). As discussed in earlier in this chapter, possible causes of false-positive SMM are hyperproliferative breast disorders, especially hyperplasia associated with atypia [7]. Conversely, Mekhmandarov et al. [85] showed no false-positive scans in a subgroup of 8 patients with indeterminate mammographic results, including 2 nonpalpable fibroadenomas, which might be the reason for no MIBI uptake.

Our *additional study* showed *negative predictive value* of 100% which supported the idea that SMM helps exclude breast cancer. In this study SMM detected all cases of breast cancer and none of the patients with negative SMM results had breast cancer. Therefore, it might be suggested that in lesions with low or indeterminate mammographic probability of malignancy, especially in palpable lesions (> 1cm in diameter), inclusion of Tc-99m MIBI SMM may have important consequences in reducing the number of biopsies.

In the *additional* study, of the 2 nonpalpable lesions which were biopsied, one was scintimammographically positive and confirmed to be a ductal carcinoma, while the other

lesion consisted of a normal breast tissue and was indeterminate on SMM. Palmedo et al. [100] showed sensitivity of 60% and specificity of 75% for nonpalpable lesions. Bombardieri et al. [8] showed a much highr prevalance of non palpable breast lesions in their study with 24 patients which showed only microcalcifications on mammography. They showed a specificity of 90% but a rather poor sensitivity of 50%. The reason for poor sensitivity could be explained by the fact that they only chose patients with clinically non demonstrable lesions with indeterminate mammographic lesions while in our study most of the non palpable lesions, detected on SMM and/or mammography were not biopsied. These results suggested that in the event of a positive SMM the likelihood of a breast cancer is definitely elevated. There were no false-negatives scans in the *additional* study. In our *formal* study, both mammography and SMM showed similar negative predictive values of 89%.

It has also been shown that as breast tissue density increases, the sensitivity for detection of malignancy decreases [26,117,119]. Approximately 25% of women of all ages (especially young patients) exhibit dense breasts on mammography [3]. In the *additional* study with 25 patients, only 2 patients had mammographically dense breasts. Both lesions were benign on histology. One showed a negative SMM (inflammatory lesion) while the other was indeterminate on SMM (cyst). While in our *formal* series, 20 patients had mammographically dense breasts. Of these, 9 breasts had histologically malignant and 11 breasts had benign breast masses. Of the 9 malignant lesions, mammography showed 3 false-negative and one indeterminate result as compared to SMM which showed 2 false-negative and one indeterminate result. Of the 11 benign lesions, mammography showed 2 indeterminate results as compared to one indeterminate SMM. But SMM showed 5 false-positive results whereas there were no false-positives in mammography

6.6. COMPARISON BETWEEN SCINTIMAMMOGRAPHY AND MAMMOGRAPHY RESULTS

On comparison of the results of Tc-99m MIBI scintimammography and mammography in this study, both methods demonstrated a high sensitivity for the detection of palpable breast carcinoma but mammography showed a clearly higher

specificity in comparison with scintimammography. Our results corresponded with the study by Palmedo et al. [100] in respect of scintimammography. They showed a sensitivity of 91% and specificity 62% on SMM but their mammography results (sensitivity 95% and specificity 10%).were remarkably different as compared to our results.

In patients with indeterminate mammographic opacities, the differentiation between benign and malignant lesions become less reliable [3,4]. These patients may benefit from a test that is independent of breast density or distortion. Khalkhali et al. [21,120] have suggested that SMM may be useful in patients in whom mammography is difficult to perform (eg, in patients with fibroglandular dense breasts or breasts with scarring due to biopsy or lumpectomy. Their results showed a higher sensitivity and better specificity with SMM as compared to conventional mammography in correct identification of malignant and benign lesions in patients with indeterminate mammographic results.

The results of our *additional* study also support the idea that in patients with indeterminate mammographic findings, the use of SMM scan may reduce the number of unnecessary biopsies, by about 50%. There were no false-negative SMM in this study and as a negative scan is more indicative of a benign aetiology, this might prove to be very useful in diagnosis of patients with suspect mammograms.

The use of Tc-99m MIBI SMM can potentially define a population of patients in whom the presence of a negative SMM study is highly suggestive of benign etiology for palpable breast masses since the sensitivity for detecting breast carcinoma is high. But the possibility of false-negative scintigraphic diagnosis must be kept in mind as small tumours, particularly below 1 cm diameter and carcinomas in situ are poorly detectable by SMM. The presence of a positive SMM test would justify/encourage a biopsy due to high sensitivity for detecting carcinoma.

6.7. AXILLARY LYMPH NODE DETECTION

Axillary lymph node resection is an important part of staging breast cancer. The status of axillary lymph nodes also plays a key role in therapeutic decisions and prognosis of the disease [121]. Presently, axillary lymph node status is determined either clinically or pathologically. The clinical evaluation of lymph node status is not reliable as, among patients with clinically negative axillary lymph nodes, up to 39% may have histologically positive nodes. Conversely, among patients with clinically palpable lymph nodes thought to be positive, 38% would have normal histological results [122].

A complete axillary node resection requires general anesthesia and added expense and risks. According to Khalkhali et al. [22], the expense and extent of surgical staging exceeds that of surgical treatment of the primary cancer. None of the anatomic imaging modalities (i.e., CT, MRI and ultra-sound) can determine the presence or absence of axillary lymph node disease with reasonable sensitivity and specificity. Commonly, lymph node involvement as determined microscopically consists of only a few malignant cells, without structural distortion within the lymph node.

The strategic importance of determining the degree of lymph node involvement in the breast region prior to surgery has greatly stimulated the use of sentinal node imaging (lymphoscintigraphy) with colloids in the last decade [123,124]. This technique is entirely different from Tc-99m MIBI and other tracers used for detecting breast cancer and has shown variable sensitivity ranging from 60% to 70% and the specificity from 65% to 90% [125-127]. It remains to be seen whether nuclear medicine imaging (PET or SPECT) can help to differentiate between benign and cancerous lymph nodes. False-positive results with nuclear medicine imaging may occur in lymph nodes with inflammatory changes.

Taillefer et al. [18] showed metastatic lymph node involvement in 19 of 41 patients. The sensitivity of SMM in detecting metastatic axillary lymph nodes was 84.2% and the specificity was 90.9%. Another study [42] using Tc-99m MIBI showed sensitivity of 66% and specificity of 100%. Khalkhali and Diggles [128] have reported sensitivity and specificity of 60% and 90%, respectively , using SMM in diagnosing axillary lymph node metastases. Burak et al. [14] have shown that the sensitivity of Tc-99m MIBI to detect

axillary metastases is low (57%), unless enlarged lymph node groups are present. SPECT imaging may improve the axillary node statistics [7].

Our *formal* study showed a sensitivity of 50% (3 true positive and 3 false negative) and specificity of 75% (15 true negative and 5 false positive) in the detection of lymph node involvement by SMM. There were 2 patients with highly positive SMM and mammographic features of lymph node involvement, but histopathological results were normal. We feel that these 2 cases lowered/dropped the specificity of our results. The low sensitivity could be due to early lymph node involvement with few malignant cells in some patients, as a low number of lymph nodes (6 out of 33 lymph nodes in 3 patients) were shown to be involved on histopathology. The SMM showed substantially better sensitivity to detect metastatic lymph node involvement as compared to mammography, as mammography could detect lymph node involvement in only one out of 6 patients with axillary metastases.

Krag et al. [121] have described the use of a gamma probe to detect axillary lymph node metastases. Using a gamma detector to locate the site of the sentinal lymph node, they evaluated 22 women with proven breast cancer. Their results suggested that it is technically feasible to localise a sentinal lymph node using a gamma probe and Tc-99m sulphur colloid, in a majority of breast cancer patients. It could help the surgeon to avoid complete axillary lymph node dissection in patients with small primary tumours, in whom the likelihood of a micrometastases is very small.

CHAPTER SEVEN

CONCLUSION AND RECOMMENDATIONS

The following conclusions and recommendations arise from this study.

With regard to methodology, we suggest that fractionation of MIBI can be easily performed in a nuclear medicine laboratory. Fractionated MIBI can be safely used, without compromising the quality of the scan, for nuclear medicine studies, including breast imaging, and this significantly reduces the cost of the sestamibi.

The technique of prone breast imaging provides excellent separation of the left breast deep structures from the myocardium and separation of the right breast from the liver. Relaxation of the pectoralis muscle improves the resolution of small deep-seated lesions. Semiquantitative analysis of sestamibi breast imaging may be helpful in objectively interpreting imaging results in patients with T/B uptake ratios of 3.0 or more.

Our results and those of others [38] suggest that delayed imaging does not provide any additional information as compared to the early images. Therefore imaging could be performed from 5 to 10 minutes after injection.

Based on this research, we believe that mammography is the basic screening modality for palpable breast masses and cannot be replaced by MIBI breast imaging. Our results suggest that the addition of Tc-99m MIBI scintimammography to mammography is of limited value when the mammogram shows a high probability of malignancy. However, Tc-99m MIBI scintigraphy is probably of value in the evaluation of lesions shown by mammography to have moderate and low probability of malignancy and may allow the reduction of unnecessary biopsies indicated by mammography. Therefore Tc-99m MIBI SMM might provide additional information on the differentiation of malignant pathologies from benign lesions in patients with palpable breast anomalies.

Tc-99m MIBI breast imaging may have advantages over mammography in patients with dense breasts and make a significant contribution to clinical management in patients with suspected breast abnormalities [129]. Tc-99m MIBI study may improve the specificity of detection especially in women with a high risk for the development of breast cancer and who have suspect mammograms.

SMM has a clinical role in the evaluation of mammographically negative or indeterminate lesions, especially palpable lesions not clearly categorised by mammography and in dense breast tissue. As a negative MIBI study is highly indicative of a benign aetiology, the additional information given by a negative Tc-99m MIBI SMM in an indeterminate mammograhic lesion is very useful in diagnosis. While, the possibility of false-negative SMM diagnosis must be kept in mind, clinical follow up and routine mammography would be suggested in cases with negative SMM results.

APPENDIX A

PILOT STUDY

1. METHODOLOGY

1.1. PURPOSE

The **main objective** of this study was to determine whether the selected imaging technique was practical.

1.2. SAMPLE SELECTION

The study population consisted of 11 women between the ages of 16 and 69 years with a mean age of 43 years.

The patient selection and exclusion criteria were the same in this study to those applied for the formal study.

1.3. PROCEDURE

Locally produced sestamibi *(Myotek)* by the AEC of South Africa was used for scintimammography (SMM). Each vial of MIBI was fractionated into 10 fractions and quality control was performed on each fractionated dose, using exactly the same methods that were used in the formal study. The *radiochemical purity* of Tc-99m MIBI was always more than 90% (range 90-98%).

1.3.1. Scintimammography Procedure

A gamma camera *(GE 400 AC Starcam)* equipped with low energy, high resolution, parallel hole collimator was used for imaging. The imaging procedure was explained to each patient before scanning.

An intravenous injection of a standard dose of 740 MBq of Tc-99m MIBI was given in the arm contralateral to the affected side.

1.3.2. Patient and Camera positions

Two sets of planar images were acquired of lateral and posterior oblique (25°) views on each breast. On delayed imaging, additional anterior chest/axillary views were acquired on both sides in supine position. These views were always acquired after lateral and posterior oblique views.

Patients were requested to undress down to the waist. Both breast and axillae were examined for palpable lesions before starting the imaging procedure.

Lateral and Posterior oblique views were acquired in the prone position. The patient lay in the prone position on the imaging bed. The breast to be imaged was positioned by moving that side of the chest across the edge of the bed so that the breast on that side hung freely dependent from the bed and avoided any compression of the breast

by the edge of the bed. The patient lay on the wider lower part of the bed from the hips down as it helped in stabilising the patient's posture. The sternum of the patient was positioned along the edge of the bed which was padded to be comfortable. A pillow was placed under the head of the patient for support. The patient's arm on the side to be imaged was straightened above the head, without tilting the back, and keeping the shoulder girdle relaxed.

For *lateral* and *posterior oblique* views, patient position on the bed remained unchanged. For the *lateral view*, the surface of the detector was positioned vertically, parallel and very close to the pendulous breast. For the *posterior oblique* view the detector was tilted to 25 degrees keeping the entire breast in the field of view. Ipsilateral axilla and adjacent anterior chest wall were also included in the field of view to detect any lymph node involvement and deep seated lesion in the breast or chest wall, respectively.

For the *anterior chest/axillary view*, imaging was done with the patient in a supine position. The patient lay in the middle of the bed with her head on a pillow and the arm on the side to be imaged, abducted, bent at the elbow and hand placed under her head. The bed was moved across to the side in order to include the entire breast and the axilla in the field of view. The detector was positioned facing the anterior chest from above and close to the breast.

The nipple was marked with a ***radioactive marker***. The marker was made from the needle of the syinge used for injection of the tracer. The needle was removed from the syringe and its base, containing some residual activity, was sealed with cellophane tape. A marker image was taken at the start of each view. Marker position was recorded with a "cross +" using the image marking facility of the camera. The radioactive marker, based on the ECG electrode was developed later in the pilot study and was used in a few patients during this study and in all patients in the formal study.

Other acquisition parameters of the study included:

1. An image zoom of factor 2 for *lateral* and *posterior oblique views* to magnify the breast image and to exclude unnecessary activity from the heart and liver from the field of view.

2. The images were acquired in a 256 x 256 matrix. The photopeak was centered over 140 keV with a 10% window on its either side.

Two sets of images were acquired on each breast. The *first set* started at 5 minutes after the injection of the tracer and the *second set* commenced immediately after the first set of images had been recorded. The images in the *first set* were acquired at 5 minutes per image and in the *second set* at 10 minutes per image. The anterior chest / axillary views were only performed with the second set of images at 10 minutes per image.

The injection site was always kept out of the field of view. Patients were allowed to rest for few minutes after each set of images was completed.

After acquisition had been completed, the study was transferred to another computer terminal to make *hard copies* of all the images. All images were interpreted *visually* both on the computer screen and on the hard copies, to detect any abnormal increased activity of the tracer in the breast or axilla. The *objective assessment* was performed by semiquantitative analysis using *target to background (T/B) ratio*, as described below.

1.3.3. Statistical Methods

The intensity of MIBI uptake within the visually detected breast lesion was evaluated by determining the *T/B ratio*. Either the *lateral* or *posterior oblique* view of the breast was selected to draw the region of interest, depending upon which view better illustrated the lesion.

The total counts obtained in each view, in both sets of images, were recorded. In addition, on lateral view, *irregular region of interest* were drawn around each breast, excluding the chest wall. The total counts in each irregular ROI and area in pixels were used to calculate counts per pixel for each breast. The *T/B ratios* were used as a *quantitative* measure to determine whether it could help to distinguish between true malignant and scintimammographically false malignant / indeterminate breast lesions

(*False Positives*). This recorded data can be seen in Table 4 of Appendix B.

A square region of interest was drawn within the outline of the breast lesion. Another region of the same dimensions was drawn over the normal breast tissue of the same breast. The background region was drawn at a variable distance, ranging from 0.5 to 1.5 cm from the target region, in different patients. In breasts with more than one target lesion, a common background region was drawn in the same breast, at approximately the same distance from the target regions. *T/B ratios* were the ratios of the total counts for each region of interest.

1.4. SCAN INTERPRETATION

Visual assessment of the SMM scans was done on each set of images. The breast lesions were classified as *positive, negative* or *indeterminate.* The following criteria were used:

POSITIVE:	A well defined area of increased uptake with an intensity greater than the normal surrounding breast tissue.
NEGATIVE:	No focal increased uptake in the breast.
INDETERMINATE:	An ill defined area of low-grade increased uptake which is unclassifiable as benign or malignant; as there is increased uptake, it cannot not be termed normal, but the uptake is not intense or well enough defined to be classified as malignant.

All studies were evaluated by the researcher and another experienced nuclear medicine physician. A third observer, another nuclear medicine physcian, was referred to in cases of disagreement.

2. RESULTS

Eleven patients were evaluated in this trial.

2.1. CLINICAL EXAMINATION

Clinically there were 12 palpable lumps in 12 breasts in 11 patients. Five patients presented with solitary masses in their right and 5 patients in their left breasts. One patient had bilateral breast masses. The number and distribution of palpable breast lesions are shown in Table 2.1.

Of the total number of patients one had a possible tumour recurrence after the surgery, radio and chemotherapy and one had a positive family history of breast cancer. The youngest patient was a 16 year old nulliparous girl.

Individual patient details are shown in tabulated form in Table 1 of Appendix B.

Table 2.1. Number and Distribution of Lesions in Each Breast on Clinical Examination.

RIGHT BREAST	LESIONS
Upper Outer Quadrant	4
Upper Inner Quadrant	1
Lower Outer Quadrant	0
Lower Inner Quadrant	1
Other	0
TOTAL	**6**

LEFT BREAST:	LESIONS
Upper Outer Quadrant	3
Upper Inner Quadrant:	1
Lower Outer Quadrant:	1
Lower Inner Quadrant:	1
Other:	0
TOTAL	**6**

2.2. BIOPSY RESULTS

All 12 palpable breast lesions had biopsies.

There were 4 malignant lesions in 4 breasts and 8 benign lesions in 8 breasts. A patient (patient 8) had one palpable lesion in each breast. Both were confirmed to be fibroadenomas. On SMM, another lesion was detected in the left breast which was clinically not palpable and therefore was not biopsied.

Both patients with possible tumour recurrence and positive family history of breast cancer had benign lesions (fat necrosis and fibrosis, respectively). The histopathological results are listed in Table 2.2.

Table 2.2: Histopathological Results of 12 Palpable Breast Lesions.

HISTOPATHOLOGICAL FINDINGS	LESIONS	BREASTS
Malignant Tumours :		
Infiltrative Duct Ca.	3	3
Mucinous Ca.	1	1
Benign Tumours :		
Fibroadenoma	4	4
Other Benign Lesions :		
Fat Necrosis	1	1
Fibrosis/Sclerosis	2	2
Mastitis	1	1
Total	**12**	**12**

2.3. MAMMOGRAPHY RESULTS

Nine out of eleven patients underwent mammography.

Four patients showed positive mammography suggestive of malignancy, while one patient had negative mammography suggestive of a benign lesion. In 2 cases the results were indeterminate. The patient with a positive family history of breast cancer showed a negative mammography result.

Two patients did not have mammography. One of the patients (patient 8) presented clinically with bilateral breast lesions and refused to have mammography, but later returned for the operation (excision biopsy was performed). The other patient had a solitary breast lesion clinically and has had prior biopsy with the diagnosis of fibroadenosis, so the radiologist deemed mammography would not be of further benefit.

2.4. TECHNETIUM-99m MIBI SMM RESULTS

All 11 patients had SMM. Both early and late images were evaluated visually and by semi-quantitative method.

All 4 lesions in 4 breasts with histopathologically confirmed breast cancers, showed positive SMM. There were no negative SMM scans in patients with malignant breast lesions.

Of the 8 palpable benign lesions in 8 breasts, 6 lesions had negative SMM scans suggestive of benign pathology, while 2 palpable lesions noted in a patient with bilateral breast lumps showed positive SMM. Both these lesions were shown to be fibroadenomas on biopsy. Another lesion was detected in the left breast of the same patient as positive SMM. This lesion was clinically nonpalpable and was not biopsied.

There no indeterminate SMM scans.

The Tc-99m MIBI scintimammography results are illustrated in Table 2.3.

Table 4 of Appendix B shows the total counts obtained in each view in both sets of images. Counts per pixel in right and left breast and area in pixel, were calculated for each patient. Comparison of distribution of counts per pixel of right versus left breast showed more counts per pixel in a breast due to a lesion (increased MIBI uptake) or occasionally due to diffuse increase uptake in that breast as compared to the contralateral side, as a normal variant.

Target to background ratios were calculated on all breast lesions in both sets of images. The early set of images always showed higher *T/B ratios* as compared to the late set. There was almost no difference in delineation of lesions seen on either sets of images.

Figure 2.1 illustrates the difference in T/B ratios in early and late sets of images on SMM.

The evaluation of SMM by delayed breast imaging did not alter our results when compared with early images.

Figure 2.1

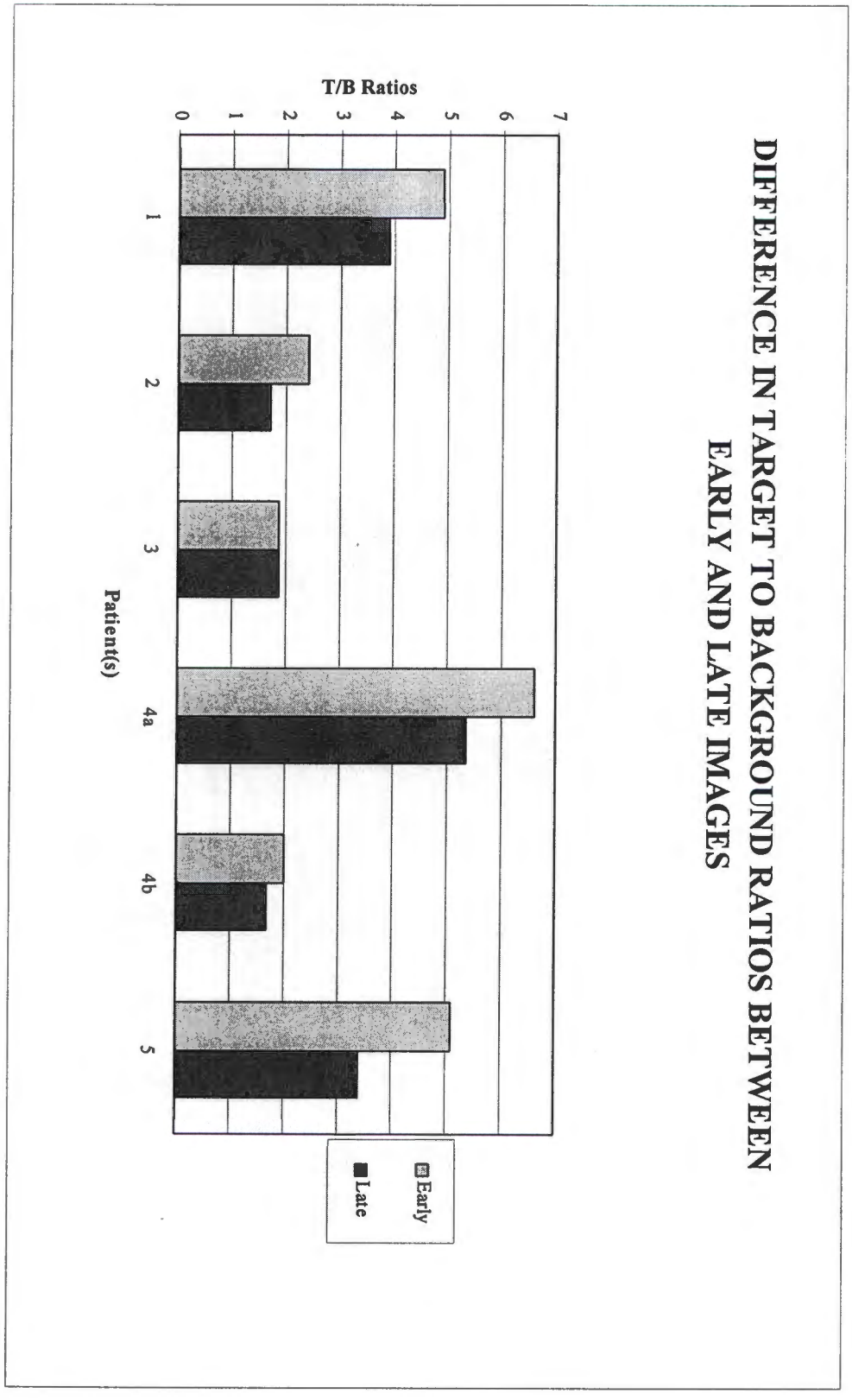

DIFFERENCE IN TARGET TO BACKGROUND RATIOS BETWEEN EARLY AND LATE IMAGES
T/B Ratios
0
1
2
3
4
5
6
7
Patient(s)
1
2
3
4a
4b
5
Early
Late

Table 2.3. Scintigraphic Findings Correlating With Histopathological Results.

Histological Diagnosis	*Number of Lesions*	*Tc-99m MIBI uptake*		
		Positive	*Negative*	*Intermediate*
Infiltrative Ductal Ca	**3**	**3**	**0**	**0**
Mucinous Ca	**1**	**1**	**0**	**0**
Fibroadenoma	**4**	**2**	**2**	**0**
Fat Necrosis	**1**	**0**	**1**	**0**
Fibrosis/Sclerosis	**2**	**0**	**2**	**0**
Mastitis	**1**	**0**	**1**	**0**

Note: A clinically non palpable lesion detected only on SMM (patient 8) was not biopsied and therefore is not included in this table.

2.5. BIOPSY VS MAMMOGRAPHY RESULTS

Table 2.4. Summary of Histopathological and Mammography Results

		HISTOLOGY	
		Malignant	**Benign**
MAMMO	**Positive**	**4**	**0**
	Negative	**0**	**3**
	Indeterminate	**0**	**2**

All 4 patients with histological diagnosis of malignant breast lesions showed positive mammography results. Two patients with 3 benign lesions (including the patient with bilateral breast lumps) did not undergo mammography, as described earlier; while 3 patients showed negative mammography suggestive of benign lesions. Rest of 2 lesions showed indeterminate mammographic features.

2.6. BIOPSY VS SCINTIMAMMOGRAPHY RESULTS

Table 2.5. Summary of Histopathological and Tc-99m MIBI SMM Results.

		HISTOLOGY	
		Malignant	**Benign**
SMM	**Positive**	**4**	**2**
	Negative	**0**	**6**
	Indeterminate	**0**	**0**

In total, 10 out of 11 patients showed concordant results between SMM and histology.

All 4 patients with histological diagnosis of malignant breast lesions showed positive SMM results. Six patients with benign breast lesions (2 neoplastic and 4 non-neoplastic) showed negative SMM results. Increased MIBI uptake was noted in 2 breast lesions in a patient with bilateral fibroadenomas. Another lesion was noted on SMM in the left breast of the same patient. This lesion was clinically nonpalpable and was not biopsied.

2.7. BIOPSY VS SCINTIMAMMOGRAPHY VS MAMMOGRAPHY RESULTS

The comparative results of SMM and mammography were compared with biopsy results which is considered as a gold standard.These results are shown in Table 2.6.

Table 2.6 Comparison Between Histopathological, Tc-99m SMM and mammography Results

Lesions	Histology	SMM	Mammo	Comment
4	Malignant	Positive	Positive	
3	Benign	Negative	Negative	
2	Benign	Negative	Indeterminate	
1	Benign	Negative	Not Done	Fibroadenoma
2	Benign	Positive	Not Done	Fibroadenoma

2.8. AXILLARY LYMPH NODE INVOLVEMENT

Metastatic ipsilateral axillary lymph node involvement was confirmed in 2 patients on biopsy. In each patient, out of 8 lymph nodes explored, 2 showed metastatic involvement. SMM did not demonstrate lymph node involvement in any of the patients whereas mammography demonstrated positive metastatic involvement of lymph nodes in one case.

3. REMARKS

This study demonstrated that the activity of the breast lesion was always higher than the apparent normal breast tissue and that the addition of late images were not helpful in terms of lesion detectability. Thus, we suggest that early imaging for the detection of breast carcinoma was preferable as there was no difference in delineation of lesions seen on the scan between the two sets of images. In fact, the late images showed lower T/B ratios in all the lesions as compared to the early images (see Fig 2.1).

Therefore a revised acquisition technique was implemented for the formal study with modified protocol in which the late images were excluded. The rest of the protocol remained unchanged.

APPENDIX B

TABLE 1. PILOT STUDY: Summary Data on Each Patient

PT. NO	NAME	AGE YRS	PARITY	F/HIST	SITE (CLIN)	HISTOLOGY	MAMMO	SMM
1.	S. S	28	$G_1 P_1$	NO	LT UO	SCLEROSIS	IND	NEG
2.	J. C	44	$G_3 P_3$	NO	LT UO	FAT NECROSIS	IND	NEG
3.	J. D	59	$G_7 P_7$	NO	RT UO	DUCTAL CA	POS	POS
4.	B. J	43	$G_1 P_1$	YES	LT LO	FIBROSIS	NEG	NEG
5.	C. M	35	$G_3 P_3$	NO	RT PA	MASTITIS	NEG	NEG
6.	B. J	64	$G_3 P_3$	NO	RT UO	DUCTAL CA	POS	POS
7.	T. H	60	$G_3 P_3$	NO	LT UI	MUCINOUS CA	POS	POS
8	R. C	23	$G_1 P_1$	NO	RT UO LT UO (1)	F/ADENOMA F/ADENOMA(1)	NOT DONE	POS POS (2)
9.	R. N	33	$G_3 P_2$	NO	RT UI	F/ADENOMA	NEG	NEG
10.	B. S	16	$G_0 P_0$	NO	LT LI	F/ADENOSIS	NOT DONE	NEG
11.	M. S	69	G P	NO	RT UO	DUCTAL CA	POS	POS

F/HIST: Family History, (CLIN): on clinical examination, RT: right, LT: left.
Breast quadrants (UO: upper outer , UI: upper inner, LO: lower outer, LI: lower inner, PA: periaerolar).
F/ADENOMA: fibroadenoma, F/CYSTIC DIS: fibrocystic disease, F/ADIPOSE: fibroadipose tissue,
POS: positive, NEG: negative, IND: indeterminate.

TABLE 2. FORMAL STUDY: Summary Data on Each Patient

PT. NO	NAME	AGE YRS	PARITY	F/HIST	SITE (CLIN)	HISTOLOGY	MAMMO	SMM
12.	H. M	65	G_3 P_3	NO	LT LI	DUCTAL CA	POS	POS
13.	I. S	52	G_1 P_1	NO	RT UO	NORMAL	NEG	NEG
14.	F. S	38		NO	LT UO	DUCTAL CA	NEG	NEG
15.	T. A	71		NO	RT UO	NORMAL	NEG	NEG
16.	P. C	33		NO	RT LO	FAT NECROSIS	NEG	IND
17.	D. T	58	G_3 P_3	NO	RT UI	LOBULAR CA LOBULAR CA IN SITU	POS (1)	IND (2)
18.	B. J	59	G_9 P_9	YES	LT LO	DUCTAL CA	POS	POS
19.	M. B	35	G_0 P_0	NO	RT LO	F/ADENOMA	IND	NEG
20.	A. G	36	G_2 P_2	NO	LT UO	F/ADENOMA	NEG	NEG
21.	K. A	41	G_1 P_1	NO	LT UO	CYST	NEG	NEG
22.	V. D	36	G_2 P_2	YES	LT PA	DUCTAL CA	POS	POS
23.	M. N	48	G_1 P_1	NO	LT UO	DUCTAL CA	POS	POS
24.	S. D	72	G_7 P_7	NO	RT PA	INFLAMM. CELLS	NEG	POS (3)
25.	D. S	58	G_6 P_6	NO	RT PA LT UO	F/CYSTIC DIS DUCTAL CA	NEG POS	POS POS
26.	A. B	53	G_0 P_0	NO	RT LO	LOBULAR CA	POS	POS

TABLE 2 CONTINUED.

PT. NO	NAME	AGE YRS	PARITY	F/HIST	SITE (CLIN)	HISTOLOGY	MAMMO	SMM
27.	S. M	60	$G_4 P_4$	NO	RT UO	DUCTAL CA	POS	POS
28.	R. F	43	$G_2 P_2$	NO	RT LI	F/ADENOMA	NEG	POS
29.	B. F	37	$G_1 P_1$	NO	RT LO	EPITHILIOSIS	NEG	IND
30.	H. J	65	$G_5 P_5$	NO	RT UI	DUCTAL CA	POS	POS
31.	B. E	46	$G_0 P_0$	NO	RT PA	F/CYSTIC DIS	NEG	POS
32.	M. S	62	$G_3 P_3$	NO	LT LO	DUCTAL CA	POS	POS
33.	L. R	56	$G_3 P_3$	NO	RT LO LT LO	F/ADIPOSE TISSUE B/L	NEG NEG	NEG NEG
34.	D. J	46	$G_0 P_0$	YES	LT UO	INFLAMMATORY CELLS	NEG	IND
35.	K. M	75	$G_3 P_3$	NO	LT LO	CYST	NEG	NEG
36.	N. A	43	$G_5 P_5$	NO	LT LO	F/CYSTIC DIS	NEG	IND
37.	L. M	43	$G_4 P_4$	NO	RT UI	F/ADENOMA	IND	POS
38.	H. M	44	$G_3 P_3$	NO	LT LO	REACTIVE DUCT CELLS	NEG	IND
39.	N. D	35	$G_0 P_0$	YES	RT UO	PHYLLOIDES T	NEG	IND
40.	S. S	51	$G_1 P_1$	NO	RT LO	LOBULAR CA	NEG	POS
41.	S. V	81	$G_3 P_3$	YES	LT UI	FAT NECROSIS	NEG	IND
42.	P. B	52	$G_3 P_3$	NO	LT UO	LIPOMA	IND	IND
43.	P. D	68	$G_8 P_8$	NO	LT LO	REACTIVE DUCT CELLS	NEG	IND
44.	H. S	44	$G_5 P_4$	NO	LT UO& LO	LT CYSTS (2) RT ADENO CA	NEG (2) POS	NEG (2) NEG

TABLE 2 CONTINUED

PT. NO	NAME	AGE YRS	PARITY	F/HIST	SITE (CLIN)	HISTOLOGY	MAMO	SMM
45.	C. M	35	$G_3 P_3$	YES	RT UO	NORMAL	NEG	NEG
46.	N. E	63	$G_3 P_3$	NO	LT UO	FAT NECROSIS	NEG	NEG
47.	J. S	45	$G_4 P_4$	NO	RT UO	FAT NECROSIS	NEG	NEG
48.	M. N	62	$G_6 P_4$	NO	RT UO	DUCTAL CA	POS	POS
49.	V. C	41	$G_2 P_2$	NO	LT UO	F/ADENOMA	NEG	NEG
50.	A. M	62	$G_4 P_4$	NO	LT UO	DUCTAL CA	POS	POS
51.	R. G	36	$G_2 P_2$	NO	RT UI	DUCTAL CA	POS	POS
52.	A. A	36	$G_2 P_2$	NO	LT UO	COLLOID CA	POS	POS
53.	M. G	38	$G_3 P_2$	NO	RT UI	NORMAL	NEG	NEG
54.	L. L	43	$G_2 P_2$	NO	RT UO	FIBROSIS	NEG	POS
55.	F. J	57	$G_3 P_3$	YES	LT UO	DUCTAL CA	POS	POS
56.	A. S	34	$G_5 P_5$	YES	RT UI	F/ADIPOSE TIS	NEG	IND
57.	A. E	34	$G_1 P_1$	NO	LT UI	F/ADENOMA	NEG	POS
58.	B. A	56	$G_3 P_3$	NO	LT UO	F/CYSTIC DIS	NEG NEG	IND POS
59.	N. S	41	$G_2 P_2$	YES	RT LO	CYST	NEG	NEG
60.	M. R	44	$G_0 P_0$	NO	LT UO	F/ADENOMA	NEG	POS
61.	B. A	52	$G_1 P_1$	NO	LT UO	DUCTAL CA	IND	POS
62.	A. J	59	$G_6 P_6$	NO	RT UI	DUCTAL CA	IND	POS

F/HIST: Family History, (CLIN): on clinical examination, RT: right, LT: left.
Breast quadrants (UO: upper outer , UI: upper inner, LO: lower outer, LI: lower inner, PA: periaerolar).
F/ADENOMA: fibroadenoma, F/CYSTIC DIS: fibrocystic disease, F/ADIPOSE: fibroadipose tissue,
POS: positive, NEG: negative, IND: indeterminate.

TABLE 3. ADDITIONAL STUDY: Summary Data on Each Patient

PT. NO	NAME	AGE YRS	PARITY	F/HIST	SITE (CLIN)	HISTOLOGY	MAMMO	SMM
1.	A.B	54	$G_0 P_0$	NO	RT UO	SQUAMOUS CELL CA	IND	POS
2.	A.S	54	$G_3 P_3$	NO	RT PA	DUCTAL CA	IND	POS
3.	M.L	54	$G_4 P_4$	NO	RT UO	F/ADIPOSE	IND	NEG
4.	M.A	80	$G_6 P_6$	NO	RT UI	DUCTAL CA NOT DONE (2)	IND IND	POS IND (2)
5.	C.O	40	$G_2 P_2$	YES	LT UO	CYST	IND	NEG
6.	G.O	46	$G_2 P_2$	YES	RT UO RT PA	DUCTAL CA DUCTAL CA	IND IND	POS POS
7.	E.O	39	$G_3 P_3$	YES	RT UO	F/ADIPOSE	IND	NEG
8.	K.B	38	$G_1 P_1$	YES	RT UO	F/ADENOMA NOT DONE	IND IND	POS IND
9.	G.O	43	$G_4 P_3$	NO	LT UI	MASTITIS	IND	NEG
10.	W B	34	$G_2 P_2$	NO	LT LO	F/ADENOMA NOT DONE	IND IND	POS IND
11.	A.C	43	$G_1 P_1$	NO	LT PA	FIBROSIS NOT DONE	IND IND	POS POS
12.	P.M	37	$G_0 P_0$	YES	RT UO	CYST	IND	IND
13.	Y.D	66	$G_3 P_3$	NO	RT LO	DUCTAL CA	IND	POS
14.	F.S	34	$G_4 P_3$	NO	RT PA	FAT NECROSIS	IND	NEG

F/HIST: Family History, (CLIN): on clinical examination, RT: right, LT: left.
Breast quadrants (UO: upper outer , UI: upper inner, LO: lower outer, LI: lower inner, P A: periaerolar).
F/ADENOMA: fibroadenoma, F/CYSTIC DIS: fibrocystic disease, F/ADIPOSE: fibroadipose tissue,
POS: positive, NEG: negative IND: indeterminate.

TABLE 3 CONTINUED

PT. NO	NAME	AGE	PARITY	F/HIST	SITE (CLIN)	HISTOLOGY	MAMMO	SMM
15.	M.B	43	$G_1 P_1$	NO	RT UO	DUCTAL CA (2) NORMAL	IND (2) IND	POS (2) IND
16.	E.S	36	$G_3 P_3$	NO	LT UO	F/ADENOMA NOT DONE	IND IND	POS IND
17.	V.S	36	$G_4 P_4$	NO	LT LO	F/ADENOMA NOT DONE (2)	IND IND (2)	POS IND (2)
18.	B.S	44	$G_2 P_2$	NO	RT UI (2)	NORMAL TIS	IND	NEG
19.	E.R	49	$G_3 P_3$	NO	L PA	DUCTAL CA NOT DONE (2)	IND IND	POS IND (2)
20.	K.L	47	$G_3 P_3$	NO	RT UO LT UO LT UI	F/CYSTIC DIS (3)	IND (3)	NEG (3)
21.	J.S	67	$G_5 P_5$	YES	RT UO	FIBROSIS	IND	NEG
22.	R.S	59	$G_0.P_0$	NO	RT LI	DUCT HYPER-PLASIA	IND	POS
23.	J.M	55	$G_7 P_7$	NO	LT UO	F/ADENOMA	IND	POS
24.	N.S	39	$G_3.P_3$	NO	RT PA	F/CYSTIC DIS	IND	IND
25.	M.S	47	$G_3 P_2$	NO	RT UO	CYST	IND	NEG

F/HIST: Family History, (CLIN): on clinical examination, RT: right, LT: left.
Breast quadrants (UO: upper outer , UI: upper inner, LO: lower outer, LI: lower inner, PA: periaerolar).
F/ADENOMA: fibroadenoma, F/CYSTIC DIS: fibrocystic disease, F/ADIPOSE: fibroadipose tissue,
POS: positive, NEG: negative, IND: indeterminate.

TABLE 4: PILOT STUDY: Data on Individual Patient

		RIGHT BREAST						LEFT BREAST									
Pt. No	Imaging	Lat view	PO view	Ant view	Breast *	Area	Breast	Lat view	PO view	Ant view	Breast *	Area	Breast	Lesion	Area of	Target	BKG	T/B
		Kcts	Kcts	Kcts	Kcts	(Pixels)	cts/px	Kcts	Kcts	Kcts	Kcts	(Pixels)	cts/px	side	ROI	cts	cts	ratio
1	Early	145	198		24.0	14921	1.61	257	167		18.6	12756	1.46					
	Late	not done		1000				267	232	331	19.7	12780	1.54					
2	Early	173	149		24.2	14912	1.62	326	172		21.4	11383	1.88					
	Late	217	131	982	35.3	13325	2.65	170	117	1238	17.5	12927	1.35					
3	Early	301	270		63.7	23963	2.66	157	224		30.0	15244	1.97	Right	122	1239	253	4.9
	Late	209	191	2010	85.9	23956	3.59	223	128	1525	30.5	13365	2.28		121	1546	397	3.9
4	Early	134	65		41.6	21913	1.90	130	254		51.5	29099	1.77					
	Late	180	104	1334	47.9	21302	2.25	178	114	1214	64.0	25986	2.46					
5	Early	62	70		30.7	28706	1.07	41	55		26.1	28059	0.93					
	Late	70	70	837	45.5	28300	1.61	76	57	697	45.7	34724	1.32					
6	Early	140	248		73.8	34878	2.12	102	73		35.1	31013	1.13	Right	289	1749	719	2.4
	Late	290	208	1230	102.7	36781	2.79	227	78	1259	47.2	26477	1.78		289	1716	1002	1.7
7	Early	243	279		54.1	31280	1.73	262	215		54.3	30105	1.80	Left	272	919	489	1.9
	Late	201	166	1964	60.4	28233	2.14	214	161	2528	80.7	33085	2.44		272	1281	690	1.9
8	Early	605	926		11.1	5692	1.95	821	1108		20.9	6017	3.47	Left (1)	108	1768	268	6.6
														Left (2)	108	539	268	2
														Right	110	9173	5943	1.5
	Late	734	1438	3339	32.1	8453	3.80	1084	1626	3067	27.3	4899	5.57	Left (1)	108	2260	423	5.3
														Left (2)	108	715	423	1.7
														Right	110	9393	7163	1.3
9	Early	371	187		18.4	7359	2.50	351	175		19.5	10055	1.94					
	Late	344	not done	1578	33.5	9775	3.43	not done	not done	1101								
10	Early	2080	1380		90.1	8406	10.72	1760	1310		106.6	6854	15.55					
	Late	2040	1180	9990	185.5	8406	22.07	1850	2080	9820	156.2	6854	22.79					
11	Early	1130	1060		153.9	17816	8.64	604	535		82.5	13470	6.12	Right	81	2583	513	5
	Late	1520	955	7950	206.5	17816	11.59	1180	817	7780	159.0	13470	11.80		81	3146	921	3.4

*Counts: Region of interest drawn on lateral view around breast excluding chest wall.

Early Images were acquired for a preset time of 5 minutes per image.

Late Images were acquired for a preset time of 10 minutes per image.

Pt 10 & 11 show high counts in breasts because GP (general purpose) collimator was used for these patients.

TABLE 5: FORMAL STUDY: Data on Individual Patient

	RIGHT BREAST						LEFT BREAST										
Pt. No.	Lat view	PO view	Ant view	Breast*	Area	Breast	Lat view	PO view	Ant view	Breast*	Area	Breast	Lesion	Area of	Target	BKG	T/B
	Kcts	Kcts	Kcts	Kcts	(Pixels)	cts/px	Kcts	Kcts	Kcts	Kcts	(Pixels)	cts/px	side	ROI	cts	cts	ratio
12	150	195	673	image lost			300	194	653	29.7	17830	1.67	Left	110	540	165	3.3
13	414	269	411	29.8	14249	2.09	254	284	342	12.8	12343	1.04					
14	430	409	970	23.4	15072	1.55	541	474	767	23.1	12346	1.87					
15	865	857	2177	17.9	5626	3.18	433	360	1675	26.9	9549	2.82					
16	476	1574	1863	73.5	26470	2.78	326	1039	1297	64.8	27762	2.33	Right	224	1503	1083	1.4
17	462	297	1670	43.4	12939	3.35	694	340	1755	72.9	16716	4.36	Left (1)	122	885	790	1.1
													Left (2)	120	809	790	1
18	578	431	2082	11.5	6328	1.82	820	517	1619	41.2	12811	3.22	Left	121	1139	230	4.9
19	642	752	2686	5.8	1571	3.69	664	744	2043	6.2	1460	4.25					
20	244	184	1022	21.8	17993	1.21	107	93	502	20.6	26781	0.77					
21	746	455	2007	29	7221	4.02	440	774	1782	31.3	5927	5.28					
22	818	610	2400	35.1	7062	4.97	653	394	2152	66.9	10453	6.40	Left	81	817	420	1.9
23	80	51	595	45.5	37306	1.22	117	63	498	30.73	28637	1.07	Left	120	215	113	1.9
24	340	271	2730	101.6	31496	3.23	298	329	1422	53.9	21244	2.54	Right (1)	15	90	30	3
													Right (2)	15	85	30	2.8
													Right (3)	15	60	30	2
25	473	415	1468	43.6	11690	3.73	562	509	1687	76.5	17200	4.45	Left	49	763	140	5.4
													Right	600	3352	1330	2.5
26	804	643	2185	204.7	20895	9.80	625	568	2379	139.5	19322	7.22	Right	90	1886	422	4.5
27	533	467	3479	49	10943	4.48	558	446	2623	29.6	7981	3.71	Right	49	402	177	2.3
28	1101	822	2494	34.6	12919	2.68	451	522	2119	34.5	13922	2.48	Right	42	131	46	2.8
29	803	385	2082	32.3	12745	2.53	337	352	1832	34.9	21268	1.64	Right	121	458	360	1.3
30	384	303	2085	32.7	13423	2.44	240	241	1669	26.7	10917	2.45	Right	64	254	180	1.4
31	323	574	1634	34.1	14659	2.33	518	377	1236	21.7	9498	2.28	Right	49	312	137	2.3
32	424	266	1276	27	9771	2.76	500	402	1359	33.6	9814	3.42	Left	36	244	109	2.2
33	367	359	2539	53.5	18601	2.88	517	517	2446	36.1	11684	3.09					
34	692	624	2524	43.8	12428	3.52	898	808	2238	63.3	15147	4.18	Left	81	934	410	2.3

* Counts: Region of interest drawn on lateral view around breast excluding chest wall.

TABLE 5: contiued

	RIGHT BREAST						LEFT BREAST										
Pt. No.	Lat view	PO view	Ant view	Breast*	Area	Breast	Lat view	PO view	Ant view	Breast*	Area	Breast	Lesion	Area of	Target	BKG	T/B
	Kcts	Kcts	Kcts	Kcts	(Pixels)	cts/px	Kcts	Kcts	Kcts	Kcts	(Pixels)	cts/px	side	ROI	cts	cts	ratio
35	619	423	1746	51.6	11797	4.37	663	627	1564	36.7	10970	3.35					
36	249	330	1275	22.8	13000	1.75	218	263	1052	34	15916	2.14	Left	81	322	215	1.5
37	514	739	2012	59.1	19408	3.05	401	272	1920	46.5	16984	2.74	Right	81	502	386	1.3
38	161	96	986	25	15225	1.64	168	62	1032	21.9	11263	1.94	Left		255	203	1.3
39	272	173	1096	56.7	13952	4.06	343	N/Done	1052	42.3	11757	3.60	Right	81	427	282	1.5
40	439	290	1959	114.4	18107	6.32	416	302	1374	68.4	15775	4.34	Right	110	1310	587	2.2
41	276	293	2091	55.9	25694	2.18	459	365	1455	46.8	21408	2.19	Left	156	935	718	1.3
42	300	455	2446	34.1	9887	3.45	557	609	2230	58.1	12127	4.79	Left	100	452	294	1.5
43	422	384	2196	20	8748	2.29	462	206	1944	44.3	13188	3.36	Left	121	428	261	1.6
44	499	715	2562	18.3	3089	5.92	695	501	2011	15.9	2717	5.85					
45	622	348	2617	21	4197	5.00	348	359	2085	16.9	4484	3.77					
46	196	LOST	1890	62.7	30291	2.07	223	146	1527	57.3	29607	1.94					
47	429	772	1689	26.4	8438	3.13	272	LOST	1689	19.8	8336	2.38					
48	520	585	1696	153.5	23809	6.45	477	408	1234	108.7	26294	4.13	Right	210	3203	464	6.9
49	239	240	1057	26.8	16287	1.65	161	192	927	33.3	19530	1.71					
50	436	193	2564	49.9	11991	4.16	672	301	1628	73	15488	4.71	Left	81	755	277	2.7
51	1003	1136	2268	87.4	13042	6.70	723	936	1440	84.1	13438	6.26	Right	49	796	464	1.7
52	510	368	2575	62.8	17163	3.66	537	274	2632	65.6	17700	3.71	Left	81	644	249	2.6
53	956	792	2366	79.3	15994	4.96	437	435	1673	81.8	17379	4.71					
54	829	737	2190	60.72	19170	3.17	344	344	1338	54	19478	2.77	Right	81	630	265	2.4
55	572	488	2502	63.7	20752	3.07	19170	1389	2093	91.7	20433	4.49	Left	36	946	302	3.1
56	599	435	1826	50.4	16014	3.15	528	392	2075	64.6	18924	3.41	Right	90	407	227	1.8
57	723	LOST	1454	110	27020	4.07	502	246	1333	128	28819	4.44	Left	90	789	344	2.3
58	388	279	1872	39.7	17005	2.33	429	315	1719	60.1	19725	3.05	Left (1)	81	747	310	2.4
													Left (2)	81	480	310	1.5
59	701	487	2374	75.6	14730	5.13	454	360	2145	40	12220	3.27					
60	191	198	2219	77.8	27141	2.87	224	194	1704	79.2	26557	2.98	Left	64	637	219	2.9
61	548	491	2017	49.6	16747	2.96	620	470	1613	106	24194	4.38	Left	144	2512	629	4
62	748	651	1990	36	8150	4.42	653	498	1649	58.5	11632	5.03	Right	64	991	344	2.9

* Counts: Region of interest drawn on lateral view around breast excluding chest wall.

TABLE 6: ADDITIONAL STUDY: Data on Individual Patient

	RIGHT BREAST						LEFT BREAST										
Pt. No.	Lat view	PO view	Ant view	Breast*	Area	Breast	Lat view	PO view	Ant view	Breast*	Area	Breast	Lesion	Area of	Target	BKG	T/B
	Kcts	Kcts	Kcts	Kcts	(Pixels)	cts/px	Kcts	Kcts	Kcts	Kcts	(Pixels)	cts/px	side	ROI	cts	cts	ratio
1	699	832	2863	93.5	17000	5.5	794	694	2253	55.6	14656	3.80	Right	90	784	555	1.4
2	512	485	2201	86.7	16500	5.26	609	320	1479	66.5	17058	3.90	Right	110	1511	582	2.6
3	229	243	961	59.2	24509	2.42	313	283	813	48.1	21689	2.22					
4	603	324	2660	42.2	17781	2.37	287	317	1796	41.1	19253	2.13	Right (1)	56	409	193	2.1
													Right (2)	49	179	127	1.4
													Right (3)	49	164	127	1.3
5	495	849	2749	44.6	15016	2.97	421	459	2151	43.8	14824	2.95					
6	1053	959	2950	73.7	19589	3.76	642	600	1911	66	19727	3.35	Right (1)	64	834	224	3.7
													Right (2)	64	671	224	3
7	635	598	2438	31.1	12183	2.56	476	407	1918	24	15729	1.53					
8	618	504	2226	71.6	20141	3.56	474	362	1341	44.7	15622	2.86	Right (1)	110	739	392	1.9
													Right (1)	110	615	392	1.5
9	309	249	1580	48.2	20038	2.40	430	212	1061	60.2	16996	3.54					
10	552	538	3160	41.6	11897	3.50	929	603	3478	54.6	12835	4.25	Left (1)	81	735	329	2.2
													Left (2)	81	354	329	1
11	276	284	2152	40.2	18950	2.12	423	385	1517	43.6	18790	2.32	Left	81	348	152	2.3
													Right	81	455	224	2
12	1260	1585	4653	84.3	10393	8.11	1613	1247	3617	62.3	9037	6.90	Right	81	1268	773	1.6
13	726	1164	4191	38.9	12045	3.23	817	638	3382	32.6	13768	2.37	Right	81	1108	417	2.6
14	470	404	2825	84.1	24291	3.46	509	437	2123	44.1	19668	2.24					
15	313	242	1979	55.5	32002	1.73	99	102	1323	45.4	36313	1.25	Right (1)	64	242	92	2.6
													Right (2)	64	386	92	4.2
													Right (3)	64	117	92	1.3
16	443	522	2454	46.6	19927	2.34	370	613	1932	48.8	21283	2.29	Right	64	287	187	1.5
													Left	64	334	208	1.6
17	931	702	3251	88.4	13289	6.65	754	740	3378	72.9	13840	5.27	Left	64	581	340	1.7
													Right (1)	64	480	313	1.5
													Right (2)	64	350	313	1.1

* Counts: Region of Interest drawn on lateral view around breast excluding chest wall.

TABLE 6: continued

	RIGHT BREAST						LEFT BREAST										
Pt. No.	Lat view	PO view	Ant view	Breast *	Area	Breast	Lat view	PO view	Ant view	Breast *	Area	Breast	Lesion	Area of	Target	BKG	T/B
	Kcts	Kcts	Kcts	Kcts	(Pixels)	cts/px	Kcts	Kcts	Kcts	Kcts	(Pixels)	cts/px	side	ROI	cts	cts	ratio
18	643	642	1994	28.4	15141	1.88	379	377	1563	22.9	14595	1.57					
19	388	271	1868	101.1	27695	3.65	497	345	1870	112.4	27755	4.05	Right	81	694	330	2.1
													Left (1)	81	490	350	1.4
													Left (2)	81	670	350	1.9
20	1018	1040	2647	26.8	10361	2.58	1068	812	2679	31.4	8609	3.64					
21	576	380	1909	72.8	14738	4.94	376	379	1494	59.8	14313	4.18					
22	892	674	2978	51.3	10568	4.86	598	512	2577	52.4	15170	3.45	Right	81	804	502	1.6
23	280	not done	1510	data lost	data lost	data lost	338	269	1117	data lost	data lost	data lost	Left	81	658	242	2.7
24	1195	960	1783	66.8	17844	3.75	819	538	1565	46.4	14821	3.13	Right	81	590	359	1.6
25	532	362	1553	47.2	18080	2.61	266	281	1011	36.5	19154	1.90					

* Counts: Region of Interest drawn on lateral view around breast excluding chest wall.

REFERENCES

1. Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. *CA Cancer J Clin* 1995;45:8-30.
2. Vorobiof DA, Chasen MR. Common cancers (part I). *CME* 1998;16:393-403.
3. Jackson VP, Hendrick RE, Kerg SA, et al. Imaging the radiographically dense breast. *Radiology* 1993;198:297-301.
4. Bird RE, Wallace TW, Yankaskas BC. Analysis of cancer missed at screening mammography. *Radiology* 1992;184:613-617.
5. Kopans DB. The positive predictive value of mammography. *Am J Roentgenol* 1992;158:521-526.
6. Sickles EA. Breast calcifications: Mammographic evaluation. *Radiology*1986; 160:289-293.
7. Waxman AD. The role of ^{99m}Tc methoxyisobutylisonitrile in imaging breast cancer. *Semn in Nucl Med* 1997;27:40-54.
8. Bombardieri E, Crippa F, Maffioli L, Greco M. Nuclear medicine techniques for the study of breast cancer. *Eur J Nucl Med* 1997;24:809-824.
9. Waxman AD, Ramanna L, Brachman MB, et al. Thallium scintigraphy in the evaluation of mass abnormalities of breast. *J Nucl Med* 1993;34:18-23.
10. Kao CH, Yong MD, Wang SJ, et al. The ^{99m}Tc MIBI scintigraphy in the evaluation of mass abnormalities of the breast [abstract]. *Eur J Nucl Med* 1993;20:979.
11. Maublant J, Zheng C, Rapp M, et al. In vitro uptake of ^{99m}Tc teboroxime in carcinoma cell lines and normal cells: comparison with ^{99m}Tc sestamibi and thallium-201. *J Nucl Med* 1993;34:1949-1952.
12. Kao CH, Wang SJ, Liu TJ. The use of technetium 99m methoxyisobutyl -isonitrile breast scintigraphy to evaluate palpable breast masses. *Eur J Nucl Med* 1994;21:432-436.
13. Aktolun C, Bayhan H, Kir M, et al. Clinical experience with ^{99m}Tc MIBI imaging in patients with malignant tumours: preliminary results and comparison with ^{201}Tl. *Clin Nucl Med* 1992;17:171-176.
14. Burak Z, Argon M, Memis A, et al. Evaluation of palpable breast masses with ^{99m}Tc-MIBI: a comparative study with mammography and ultrasonography. *Nucl Med Commun* 1994;15:604-612.
15. Palmedo H, Bender H, Grunwald F, et al. Comparison of fluorine-18 fluorodeoxyglucose positron emission tomography and technetium-99m methoxyisobutylisonitrile scintimammography in the detection of breast tumours. *Eur*

J Nucl Med 1997;24:1138-1145.

16. Khalkhali I, Cutrone JA, et al. Scintimammography: The complementary role of ^{9m}Tc sestamibi prone breast imaging for the diagnosis of breast carcinoma. *Radiology* 1995;196:421-426.
17. Khalkhali I, Mena I, et al. Prone scintimammography in patients with suspicion of carcinoma of the breast. *J Am Coll Surg* 1994;178:491-497.
18. Taillefer R, Robidoux A, Lambert R, Turpin S, Laperriere J. Technetium-99m sestamibi prone scintimammography to detect primary breast cancer and axillary lymph node involvement. *J Nucl Med* 1995;36:1758-1765.
19. Palmedo H, Schomburg A, Grunwald F, et al. Mammoscintigraphy with ^{99m}Tc-MIBI: Planar and SPECT imaging techniques in patients with suspicious breast nodules [abstract]. *Eur J Nucl Med* 1995;36:51P.
20. Lastoria S, Piccolo P, Varrella W, Acampa C. Comparative results of ^{99m} Tc-MIBI and ^{99m} Tc-MDP scintimammography in patients with breast abnormalities [abstract]. *Eur J Nucl Med* 1995;36:51P.
21. Khalkhali I, Cutrone J, Mena I, et al. The usefulness of scintimammography (SMM) in patients (PTS) with dense breasts on mammogram (MAMM) [abstract]. *J Nucl Med* 1995;36:52P.
22. Khalkhali I, Cutrone JA, Diggles L, Mishkin FM. The role of nuclear medicine imaging for the evaluation of patients with breast abnormalities. *Nucl Med Annual* 1996;113-142.
23. Kunni CC. Mammography in the 1990's: a plea for objective doctors and informed patients. *Am Journal of Prevent Med* 1993;9:185-190.
24. Deborah Kotz. Scintimammography:magic bullet or false promise ? [newsline]. *J Nucl Med* 1995;36:15N-20N.
25. Kopans DB. Palpable abnormalities and breast imaging. In: Kopans DB, ed. *Breast Imaging.* Philadelphia: Lipponcott-Raven Publishers;1998:747-759.
26. Mann BD, Guiliano AE, Bassett LW, et al. Delayed diagnosis of breast cancer as a result of normal mammograms. *Arch Surg* 1983;118:23-25.
27. Anderson I. Mammographic screening and mortality from breast: Malmö mammographic screening trial. *Br J Med* 1988;297:943-948.
28. Frisell J, Eklund G, Hellström L, et al. Randomized study of mammography screening-preliminary report on mortality in the Stockholm trial. *Breast cancer Res*

Treat 1991;18:49-56.

29. Miller AB, Baines CJ, To T, et al. Canada national breast screening study.*Can Med Assoc J* 1992;147:1459-1488.
30. Shapiro S, Venet W, Strax P, et al. Current results of the breast cancer screening randomised trial: the health insurance plan of greater New York study. In: Day NE, Miller AB, eds. *Screening of breast cancer.* Toronto: Hans Huber;1988:3-15.
31. Fletcher SW, Black W, Harris R, et al. Report of the International Workshop on Screening for Breast Cancer. *J Natl Cancer Instit* 1993;85:1644-1656.
32. Shapiro S. Screening: assessment of current studies. *Cancer* 1994;74(2 suppl):231-238.
33. Lannin DR, Harris RP, Swanson FH, Edwards MS, Swanson MS, Pories WJ. Difficulties in diagnosis of carcinoma of the breast in patients less than fifty years of age. *Surg Gynaecol Obstet* 1993;177:123-126.
34. Hermann G, Winsberg F. Breast imaging modalities. In: Hermann G, Schwartz WA, Tartter PI, eds. *Non-palpable breast ca: diagnosis and management.* Igaku-Shoin Medical Publishers Inc; 1992:8-18.
35. Sehweil A, McKillop J, Milroy R, et al. Thallium-201 scintigraphy in the staging of lung cancer,breast cancer and lymphomas. *Nucl Med Commun* 1990;11:263-269.
36. Waxman A, Ramamma L, Brachman M, et al. Thallium scintigraphy in primary carcinoma of the breast: evaluation of primary and axillary metastases [abstract]. *J Nucl Med* 1989;30:844.
37. Waxman A, Ramamma L, Memsic A, et al. Thallium scintigraphy in the differentiation of malignant from benign mass abnormalities of the breast [abstract]. *J Nucl Ned* 1990;31:747.
38. Lu G, Shih J, Huang H, et al. ^{99m}Tc MIBI mammoscintigraphy of breast masses: early and delayed imaging. *Nucl Med Commun* 1995;16:150-156.
39. Nathan M, Seabold J, Barloon T, et al. Panar vs SPECT ^{99m}Tc MIBI evaluation of suspicious breast lesions on mammography: Histologic correlation. *J Nucl Med* 1994;35:229.
40. Diggles L, Mena I, Khalkhali I. Technical aspects of prone dependent breast scintigraphy. *J Nucl Med Technol* 1994;22:165-170.
41. Chen S, Yin Y, Chen J, et al. The usefulness of technetium-99m MIBI scintimammography in diagnosis of breast cancer: using surgical histopathological diagnosis as the gold standard. *Anticancer Res* 1997;17(3B): 1695-1698.

42. Akcay M, Akin Y, Karabag B, Özcan O, Ören D. ^{99m}Tc tetrofosmin in breast carcinoma and axillary lymph node metastases: a comparative study with ^{99m}Tc-MIBI. *Clin Nucl Med* 1997;22:832-834.

43. Mansi L, Rambaldi P, Procaccino E, et al. Scintimammography with ^{99m}Tc tetrofosmin in the diagnosis of breast cancer and lymph node metastases. *Eur J Nucl Med* 1996;23:932-939.

44. De Jong M, Bernard B, Breeman W, et al. Comparison of uptake of ^{99m}Tc-MIBI, ^{99m}Tc-tetrofosmin and ^{99m}Tc-Q12 into human breast cancer cell lines. *Eur J Med* 1996;23:1361-1366.

45. Mansi L, Rambaldi P, La Provitera A, Di Gregorio F, Procaccini E. ^{99m}Tc tetrofosmin uptake in breast tumours. *J Nucl Med* 1995;36:83P.

46. Ballinger J, Banneman J, Boxen I, et al. Accumulation of ^{99m}Tc tetrofosmin in breast tumour cells in vitro: role of the multidrug resistance P-glycoprotein. *J Nucl Med* 1995;36:202P.

47. Piccolo S, Lastoria S, Mainolfic, Muto P, Bazzicalupo L, Salvatore M. Technetium-99m methylene diphosphonate scintimammography to image primary breast cancer. *J Nucl Med* 1995;36:718-724.

48. Van Eijck C, Krenning E, Bootsama A, Oet H, Van Pel R. Somato-statin receptor scintigraphy in primary breast cancer. *Lancet* 1994;343:640-643.

49. Vural G, Atasever T, Ozdemir A, et al. Evaluation of indium-111 octreotide in patients with suspicious breast lesions: comparison with thallium 201 [abstract]. *J Nucl Med* 1995;36:200P.

50. Krenning E, Kwekkeboom D, Pauwels S, et al. Somatostatin receptores scintigraphy. In Freeman L, ed. *Nuclear Medicine Annual 1995*. New York: Raven Press, 1995;1-50.

51. Cox P, Belfor A, van der Pompe W, et al. Thallium-201 chloride uptake in tumours, a possible complication in heart scintigraphy. *Br J Radiol* 1976;49:767-768.

52. Sutter CW, Stadalnik RC. Non-cardiac uptake of technetium-99m sestamibi: An updated Gamut. *Semn in Nucl Med* 1996;26:135-140.

53. Piwnica-Worms D, Holman L. Non cardiac applications of Hexakis (alkylisonitrile) ^{99m}Tc complexes [editorial]. *J Nucl Med* 1990;31:1166-1167.

54. Muller S, Guth-Tougelides B, Greuzig H. Imaging of malignant tumours with Tc-99m sestamibi SPECT [abstract]. *Eur J Nucl Med* 1987;28:562.

55. Owunwanne A, Patel M, Sadek S. Technetium-99m radiopharmeceuticals. In: Owunwanne A, Patel M, Sadek S, eds. *The Handbook of Radiopharmaceuticals.* Chapman & Hall Medical;1995:59-105.

56. Hassan I, Sahweil A, Constantinides C, et al. Uptake and kinetics of ^{99m}Tc hexakis 2-methoxyisobutylisonitrile in benign and malignant lesions in the lungs. *Clin Nucl Med* 1989;14:333-340.

57. O'Tuama LA, Packard AG, Treves SD, et al. SPECT imaging of pediatric brain tumour with hexakis methoxyisobutylisonitrile ^{99m}Tc. *J Nucl Med* 1990;31:2040-2041.

58. Cancer B, Kitapci M, Unlu M, et al: Technetium-99m MIBI uptake in benign and malignant bone lesions: a comparative study with technetium-99m MDP. *J Nucl Med* 1992;33:319-324.

59. Sundram FX, MackP. Evaluation of thyroid nodules for malignancy using ^{99m}Tc-sestamibi.*Nucl Med Commun* 1995;16:687-693.

60. Taillifer R, Boucher Y, Potrin C, et al. Detection and localization of parathyroid adenomas in patients with hyperparathyroidism using a single radionuclide imaging procedure with technetium-99m-sestamibi (double phase study). *J Nucl Med* 1992;33:1801-1807.

61. Khalkhali I, Cutrone J, Mena I, et al. Technetium-99m-sestamibi scintimammography of breast lesions: clinical and pathological follow-up. *J Nucl Med* 1995;36:1784-1789.

62. Scopinaro F, Schillaci O, Scarpini M, et al. Technetium-99m sestamibi: an indicator of breast cancer invasiveness. *Eur J Nucl* 1994;21:984-987.

63. Delmon-Moingeon L, Piwnica-Worms D, Vander-Abbeele A, Holman B, Davison A, Jones A. Uptake of the cation hexakis (2 methylisobutyl isonitrile) technetium-99m by human carcinoma cell lines in vitro. *Cancer Res* 1990;50:2198-2202.

64. Muller S, Reiner C, Pass M, et al. Technetium-99m MIBI and thallium-201 uptake in bronchial carcinoma [abstract]. *J Nucl Med* 1989;33:845P.

65. Crane P,, La Liberte R, Heminway S, et al. Effect of mitochondrial viability and metabolism on technetium-99m sestamibi myocardial retention. *Eur J Nucl Med* 1993;20:20-23.

66. Slomesman Do, Pugin J. Lack of correlation between tritiated deoxyglucose, thallium-201 and technetium-99m MIBI cell incorporation under various cell stresses. *J Nucl Med* 1994;35:120-126.

67. Package Insert. Cardiolite™ the DuPont Merk Pharmaceutical Company Drug insert.

68. Maddahi J, Roy L, Jan Train, et al. The first United States experience in normal human myocardial imaging with ^{99m}Tc methoxy isobutyl isonitrile RP-30 [abstract]. *Clin Nucl Med* 1986;11:17.

69. Crane P, Onthank D, Retos C, et al. Technetium-99m-sestamibi retention in the c-neu oncomouse: an in vivo model for breast tumour imaging [abstract]. *J Nucl Med* 1994;35:21P.

70. Carvalho P, Chiu M, Kronaug J, et al. Cellular distribution and analysis of ^{99m}Tc-MIBI in isolated perfused rat hearts. *J Nucl Med* 1992;33:1516-1521.

71. Piwnica-Worms D, Kronauge J, Chiu M. Uptake and resolution of hexakis (2-methoxy isobutyl isonitrole) technetium (I) in cultured chick myocardial cells: mitochondrial and plasma membrane potential dependence. *Circulation* 1990;82:1826-1838.

72. Package insert. Myotek Labelling Kit, Atomic Energy Corporation of South Africa (Ltd).

73. Peller PJ, Khedkar NY, Martinez CJ. Breast tumour scintigraphy. *J Nucl Med Technol* 1996;24:198-203.

74. Smith IE, Walsh G, Jones A, et al. High complete remission rates with primary neo-adjuvant infusional chemotherapy for large early breast cancer. *J Clin Oncol* 1995;13:424-429.

75. Mankoff DA, Gralow JR, Dunnwald LK, et al. Tc-99m sestamibi scintimammography to measure the breast cancer response to neo-adjuvant chemotherapy [abstract]. *J Nucl Med* 1996;37:252P.

76. Kabasakal L, Özker K, Hayward M, et al. Technetium-99m sestamibi uptake in human breast carcinoma cell lines displaying glutathione-associated drug-resistance. *Eur J Nucl Med* 1996;23:568-570.

77. Kostakoglu L, Elahi N, Kıratlı P, et al. Clinical validation of the influence of p-glycoprotein on technetium-99m-sestamibi uptake in malignant tumours. *J Nucl Med* 1997;38:1003-1008.

78. Piwnica-Worms D, Chiu ML, Budding J, et al. Functional imaging of multidrug-resistant P-glycoprotein with an organotechnetium complex. *Cancer Res* 1993;53:977-984.

79. Varrella P, Lastoria S, Vergara E, Acampa W, Maurea S, Salvatore M. Technetium-99m MIBI scintigraphy for monitoring tumour response in patients with advanced breast cancer [abstract]. *J Nucl Med* 1995;36 (suppl 5):193P.

80. Cwikla JB, Buscombe JR, Barlow RV, et al. The effect of chemotherapy on the uptake of technetium-99m sestamibi in breast cancer. *Eur J Nucl Med* 1997;24:1175-1178.

81. Blamey RW. The role of the radiologist in breast diagnosis: a surgeon's personal view [editorial]. *Clin Radiol* 1998;53:393-395.

82. Sampson CB. To split or not to split (radiopharmaceutical kits): That is the question [editorial]. *Nucl Med Commun* 1997;18:1-2.

83. Owunwanne A, Patel M, Jahan S. Miniturized and rapid paper chromatographic technique for radiochemical quality control of Tc-99m hexakis-2-methoxyisobutyl isonitrile (Tc-99m Sestamibi) [abstract]. *J Nicl Med* 1993;34:234P.

84. Tiling R, Khalkhali I, Sommer H, et al. Role of technetium-99m sestamibi scintimammography and contrast-enhanced magnetic resonance imaging for the evaluation of indeterminate mammograms. *Eur J Nucl Med* 1997;24:1221-1229.

85. Mekhmandarov S, Sandbank J, Cohen M, Lelcuk S, Lubin E. Technetium-99m MIBI scintimammography in palpable and non-palpable breast lesions. *J Nucl Med* 1998;39:86-91.

86. Prats E, Aisa F, Abós D, et al. Mammography and ^{99m}Tc-MIBI scintimammography in suspected breast cancer. *J Nucl Med* 1999;40:296-301.

87. Hawkin T, Keavely S, Thakker A, et al. The long term stability of reconstituted Tc-99m HMPAO: A clinical and laboratory evaluation.*Nucl Med Commun* 1991;12:295.

88. Chowdhury S, Hung JC. Reconstitution and fractionation of Cardiolite® kit into multidose cold kits for cost saving [abstract]. *J Nucl Med* 1995;36(suppl):80P.

89. Thorson LM, Hung JC, Hollar BS. Feasibility of fractionating MAG_3™ cold kit for cost reduction. *Nucl Med Commun* 1992;13:832-837.

90. Fleming WK, Jay M, Ryo UY. Reconstitution and fractionation of radiopharmaceutical kits [letter]. *J Nucl Med* 1992;33:1915.

91. Ballinger JR, Golan H, Ichise M. Cost effective preparation of ^{99m}Tc-ECD by freezing excess liquid [abstract]. *J Nucl Med* 1995;36:(suppl)80P.

92. Solanki C, Li DJ, Wong A, Miles KA, Sampson CB. Multidose use of exametazime for leukocyte labelling: a new approach using tin enhancement. *Nucl Med Commun* 1993;14:1035-1040.

93. Solanki C, Li DJ, Wong A, Barber RW, Wraight EP, Sampson CB. Stabilization and multidose use of exametazime for cerebral perfusion studies. *Nucl Med Commun* 1994;15:718-722.

94. Baker RJ. Properties of ^{99m}Tc radiopharmaceuticals prepared from fractionated cold kits utilising a stannous ion augmentation technique. *J Nucl Med* 1996;37(suppl):84P.

95. Decristoforo C, Riccabona G. Problems with fractionated cold kits [letter]. *J Nucl Med* 1996;37:1912-1913.

96. Vijay Kumar. Fractionated cold kits: address the critical issues to obviate problems [letter]. *J Nucl Med* 1997;38:1664.

97. Khalkhali I, Mena I, Diggles L. Review of imaging techniques for the diagnosis of breast cancer: a new role of prone scntimammography using technetium-99m sestamibi. *Eur Nucl Med* 1994;21:357-362.

98. Dunnwald LK, Harnett SD, Mankoff DA. Utility and reproducibility of semiquantitative analysis of sestamibi breast images. *J Nucl Med Technol* 1997;25:106-110.

99. Tilling R, Kress K, Pechmann M, et al. Integrated diagnosis of breast tumours: semiquantitative ^{99m}Tc sestamibi imaging versus dynamic MRI [abstract]. *J Nucl Med* 1995;35:51.

100. Palmedo H, Grünwald F, Bender H, et al. Scintimammography with technetium-99m methoxyisobutylisonitrile: comparison with mammography and magnetic resonance imaging. *Eur J Nucl Med* 1996;23:940-946.

101. Waxman A, Nagara J, Ashok J, et al. Sensitivity and specificity of ^{99m}Tc methoxy-isobutylisonitrile (MIBI) in the evaluation of primary carcinoma of the breast: comparison of palpable and non-palpable lesions with mammography [abstract]. *J Nucl Med* 1994;35(suppl 5):22P.

102. Waxman A, Nagaraj N, Kovalevsky M, et al. Detection of primary breast malignancy with technetium-99m methoxyisobutyl isonitrile (MIBI) in patients with non-palpable primary malignancies: the importance of lesion size [abstract]. *J Nucl Med* 1995;36(suppl 5):194P.

103. Van Eijck CH, Krenning EP. Nuclear medicine imaging of breast cancer [editorial]. *Nucl Med Commun* 1996;17:925-927.

104. Chiu ML, Kronange JF, Piwnica-Worms D. Effect of mitochondrial and plasma membrane potentials on accumulation of hexakis (2 methoxy-isobutylisonitrile) technetium in cultured mouse fibroblasts. *J Nucl Med* 1990;31:1646-1653.

105. Gupta P, Waxman A, Nguyen K, et al. Correlation of ^{99m}Tc sestamibi uptake with

histopathologic characteristics in patients with benign breast disease [abstract]. *J Nucl Med* 1996;37:250.

106. Palmedo H, Schomburg A, Grünwald F, et al. Technetium-99m MIBI scintigraphy for suspicious breast lesions. *J Nucl Med* 1996;37:626-630.

107. Meyer JE, Kopans DB, Stomper PC. Occult breast abnormalities: percutaneous needle localisation. *Radiology* 1984;150:335-337.

108. Meyer JE, Eberlein TJ, Stomper PC. Biopsy of occult breast lesions: analysis of 1261 anbormalities. *J Am Med Assoc* 1990;263:2341-2343.

109. Tabar L, Gad A. Screening for breast cancer: the Swedish trial. *Radiology* 1981;138:219-222.

110. Mills RR, Davis R, Stacey AJ. The detection and significance of calcifications in the breast: radiologic and pathologic study. *Br J Radiol* 1976;49:12-26.

111. Kopans DB. The mammographic appearance of breast cancer. In: Kopans DB, ed. *Breast Imaging.* Philadelphia: Lipponcott-Raven Publishers;1998:375-408.

112. Bird RE, Wallace TW, Yankaskas BC, et al. Analysis of cancers missed at the screening mammography. *Radiology* 1992;184:613-617.

113. Tabar L, Fagerberg G, Day NE, Holmberg L. What is the optimum interval between screening examinations ? An analysis based on the latest results of the Swedish two-county breast cancer screening trial. *Br J Cancer* 1987;55:547-551.

114. Polli RS, Mettler FA, Barstow SA, Moradian G, Moskowitz M. Occult breast cancer: prevalence and radiographic detectability. *Radiology* 1987;163:459-462.

115. Kopans DB. Breast imaging report:data management, false negative mammography and the breast imaging audit. In: Kopans DB, ed. *Breast Imaging.* Philadelphia: Lipponcott-Raven Publishers;1998:761-796.

116. Cole Beuglet C, Soriano RZ, Kurtz AB, et al. Fibroadenoma of the breast: sonomammography correlated with pathology in 122 patients. *Am J Radiol* 1983;140:369-375.

117. Holland R, Jan HC, Hendricks L, Mravunac M. Mammographically occult breast cancer: a pathologic and radiologic study. *Cancer* 1983;52:1810-1819.

118. American College of Radiology. Mammographic data base system (Bird™). Reston, VA: American College of Radiology, 1993. (As cited by Khalkhali I, Cutrone JA, Diggles L, Mishkin FM. The role of nuclear medicine imaging for the evaluation of patients with breast abnormalities. *Nucl Med Annual* 1996;113-142).

119. Feig SA, Shaber GA, Patchefskly A. Analysis of clinically occult breast cancer and mammographically occult breast tumours. *AJR* 1977;128:403-408.

120. Khalkhali I, Mena I, Diggles L. Limitations of mammography: the role of technetium-99m sestamibi scintimammography in the diagnosis of breast cancer [abstract]. *Clin Nucl Med* 1993;18:927.

121. Krag D, Weaver D, Alex J, Fairbank J. Surgical resection and radio-localization of the sentinel lymph node in breast cancer using gamma probe. *Surg Oncol* 1993;2:335-340.

122. Danforth DD, Lippman ME. Surgical treatment of breast cancer. In: *Diagnosis and management of breast cancer. Philadelphia:* Saunders;1988:95-155.

123. Ege GN. Lymphoscintigraphy: techniques and applications in the management of breast cancer. *Semn Nucl Med* 1983;13:26-34.

124. Unlu M, Ercan MT, Alanyali H, Akhan O, Bedkik CF, Allan SM. The prospects for imaging lymph nodes in breast cancer. *Eur J Nucl Med* 1992; 19:836-837.

125. Terui S, Yamamoto H. New simplified lymphoscintigraphy technique in patients with breast cancer. *J Nucl Med* 1989;30:1198-1204.

126. McLean R, Ege G. Prognostic value of axillary lymphoscintigraphy in breast carcinoma patients. *J Nucl Med* 1986;27:1116-1124.

127. Hill N, Ege G, Greyson N, Mahoney L, Jirsch D. Predicting nodal metastases in breast cancer by lymphoscintigraphy. *Can J Surgery* 1983;26:507-509.

128. Khalkhali I, Diggles L. The use of ^{99m}Tc sestamibi scintimammography for the staging of breast carcinoma [abstract]. *Eur J Nucl Med* 1994;21:1925.

129. Khalkhali I, Villanueva-Meyer J, Edell SL, et al. Diagnostic accuracy of ^{99m}Tc sestamibi breast imaging in breast cancer detection [abstract]. *J Nucl Med* 1996;37:74P