Value of dynamic phase and SPECT/CT during Parathyroid imaging of primary hyperparathyroidism: impact on reporting and radiation exposure

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Candidates Declaration

I, Ntanganedzeni Muambadzi declare that the work contained in this thesis is original and is my own work. It is being submitted for the degree of Master of Medicine at Witwatersrand University, Johannesburg in the branch of Nuclear Medicine.

Signed this 27th day of January 2017. The work reported in this dissertation was done in the Department of Nuclear Medicine and Molecular Imaging at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital.

27 January 2017

Master of Medicine in the branch of Nuclear Medicine

January 2017

To whom it may concern:

Re: Dr Ntanganedzeni Muambadzi

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MMED Nuclear Medicine

This letter is to certify that Dr Ntanganedzeni Muambadzi has done her research in Nuclear Medicne. Her topic is "**Value of dynamic phase and SPECT/CT during Parathyroid imaging of primary hyperparathyroidism: impact on reporting and radiation exposure".**

She compiled and analysed the data herself and followed the protocol for her study accordingly. The entire research article was written by herself with assistance from her supervisor.

Kind regards

Prof MDTHW Vangu

Head of division Nuclear Medicine

Dedication

This thesis is dedicated to the almighty God who always strengthens me.

Abstract

Introduction: The preferred nuclear medicine method for parathyroid imaging is a nuclear medicine scan using 99mTc-sestamibi (Tc-99m MIBI). Nuclear medicine imaging using Tc-99m MIBI is the most sensitive modality. Scintigraphy using Tc-99m MIBI is also cost-effective and scintigraphy using Tc-99m MIBI for localization of hyper functioning parathyroid tissue prior to operation is the current method of choice.

There are few similarities between the different methods for Tc-99m MIBI parathyroid scintigraphy and there has not been much evidence to support one over the other.

However up to date there is no study in literature suggesting the use of dynamic images in parathyroid imaging.

Some studies have pointed out that SPECT is more superior as compared to doing planar imaging alone without a SPECT. To improve parathyroid lesion localization, at times an addition of CT to SPECT (known as hybrid SPECT/CT) is done. However in our institution every patient has a CT component added to their SPECT.

In our institution: Injection of the radiotracer is performed intravenously, dynamic/flow and static planar images of the neck are obtained at 20 minutes and 3 hours post injection.

Further imaging with use of hybrid SPECT/CT is done in all our patients, to improve preoperative parathyroid glands localization. There have been very few investigations assessing the value of combining SPECT with CT, and in most studies adding a CT is only recommended for a selected population and not all patients.

The number of subjects studied with hybrid SPECT/CT has been few and results have been inconclusive at most studies.

Aims and objectives: This investigation compares the imaging technique we use in our institution and determines:

- Whether flow/dynamic imaging adds any value to the overall results and if no value is added by dynamic can we omit the dynamic phase of the study?, this will avoid adding extra time to our studies.
- The impact of fusing SPECT with CT (hybrid SPECT/CT) in all patients was also assessed and its value. If CT adds no value can we add CT component to only a selective population? example those with suspicion of ectopic parathyroid adenomas. This will minimize/reduce unnecessary technical issues, reducing length of procedure, and impact on increased costs and also radiation burden to patient.

Materials and Methods: There was 273 parathyroid images reported for this study and the mean age of the patients was 57 ± 15.7 years old, 85.7% were females. All patients were suspected to have primary hyperparathyroidism with a parathyroid adenoma, patients were scanned with Tc-99m MIBI to rule out a parathyroid adenoma, at initial presentation all patients had raised serum markers (calcium and parathyroid hormone).

The standard departmental imaging and reporting protocol was followed at presentation for each of the patients with flow imaging at 2sec/frame, then followed by early static at 20min and delayed static at 3 hours.

In our study the reader was blinded to the patients' final report and only the history and images of the patient were available for reporting.

All sets of images that were acquired at first presentation: Flow, planar (early and delayed), SPECT and SPECT/CT were reported without seeing the final issued report.

Second time around all sets of images were reported without the flow component to evaluate if we still get the same result as we did with initial reporting when we reported with the flow.

Thirdly combinations of delayed planar with SPECT and delayed planar with SPECT and addition of CT (SPECT/CT) were reported without knowledge of the original report. We then identified whether adding CT component to SPECT changed the results of the overall final report that had been issued.

Agreement between imaging techniques was calculated. Imaging accuracy was also measured.

Results: The dynamic phase showed positive lesions in 12.5% (34) of the patients while the SPECT and CT were positive in 50.5% (138).

The k-coefficient (certainty of adenoma focus) between the final report and the reader was 0.68 (95% confidence interval, 0.66–0.70). Dual phase studies that included SPECT/CT had the highest values. Statistically significantly superior to single-phase early or delayed imaging in sensitivity, area under the curve, and positive predictive value was dual-phase planar imaging, SPECT, and SPECT/CT. SPECT was statistically superior to planar static imaging. Single photon emission tomography fused with CT (SPECT/CT) in combination with any delayed imaging method was superior to dual phase planar imaging or SPECT alone for sensitivity, area under the curve, and positive predictive value.

The results of the analysis imaging techniques showed a poor agreement between the dynamic phase and planar imaging (k=0.09).

The measurement of agreement between the imaging techniques showed that the SPECT/CT and the SPECT alone showed a significantly very good agreement (k=0.93, p<0.001) as well as with planar.

Conclusion: There was a poor agreement seen between dynamic phase and planar static imaging. The measurement of agreement between imaging techniques showed that the SPECT/CT and the SPECT alone showed a significant very good agreement.

We therefore advise to eliminate the dynamic phase and only add the SPECT/CT in patients with high clinical index of suspicion for example patients with ectopic lesions or when the planar imaging is negative.

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Nomenclature

CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CHBAH	Chris Hani Baragwanath Academic Hospital
Cca	Corrected Calcium
kVp	Peak kilovoltage
KeV	Kiloelectric voltage
mAs	Milliamp Seconds
MIBI	Methyl isobutyl isonitrile
SPECT	Single photon emission computed tomography
CT	Computed Tomography
P Val.	P-value
AUC	Area under curve
PPV	Positive predictive value
NPV	Negative predictive value
PHPT	Primary hyperparathyroidism
ROC	Receiver Operating Curves
US	Ultrasound
Sec	Seconds
Sv	Sieverts
FDG	Fluorodeoxyglucose
Se	Selenomethionine
Sestamibi	2-methoxy isobutyl isonotrile
I-123	Iodine-123
MRI	Magnetic Resonance Imaging
^{99m}TcO4	Pertechnatate
^{201}Tl	Thallium-201

^{11}C	Carbon-11
Pgp	P-glycoprotein
Vs	Versus

1. CHAPTER 1: Introduction and Literature Review

1.1. Introduction

There are three different forms of hyperparathyroidism: primary, secondary and tertiary hyperparathyroidism. Overall the most frequent pathology involving the parathyroid glands and the most common endocrinology disorder is primary hyperparathyroidism (PHPT). Production and secretion of parathyroid hormone in excessive amounts is a hallmark of PHPT [1]. Absence of calcium regulation leads to changes biochemically: decrease in blood phosphate level, urine and blood calcium levels increase and increase phosphate levels in urine [2]. This condition will clinically cause kidney stones, urinary calcium stones, bone pathology, psychiatric manifestations, disorders involving the gastrointestinal system such as pain and neuronal manifestation evidenced by abdominal cramps, muscle weakness and muscle spasms and pains [2].

Imaging for parathyroid adenoma has involved different tracers with different mechanisms of action. The scanning methods for parathyroid localization included Thallium-201, Tc-99m sesatmibi (Tc-99m MIBI) or Tc-99m Tetrofosmin.

The technique using subtraction method with Iodine-123 and Tc-99m MIBI imaging was the first described for parathyroid localization [3], Iodine-123 is used to outline the thyroid and Tc-99m MIBI the parathyroid.

Above method is used instead of a dual phase Tc-99m MIBI is recommended in areas that have endemic goitres. This is done with both Iodine-123 (I-123) for thyroid gland and Tc-99m MIBI for parathyroid glands.

Tc-99m MIBI biodistribution in thyroid and parathyroid tissue has been studied by Taillefer et al [3,4]. In this paper Tc-99m MIBI was shown to be distributed into both the thyroid and parathyroid like thallium-201. Thallium was taken up much more in parathyroid glands than Tc-99m MIBI. The kinetics of Tc-99m MIBI are different in thyroid and parathyroid glands, Tc-99m MIBI uptake in the thyroid gland remains constant but washes from the thyroid gland This washout technique is the main cornerstone of the dual-phase imaging technique that will be discussed later in this report.

Other imaging modalities of parathyroid adenomas in Nuclear medicine and molecular imaging include Positron emission tomography. Variable success has been met with Positron emission tomography (PET) tracers. Positron emission tomography (PET) using F18-FDG for the identification of parathyroid adenomas has been found useful by some but not all authors. Other promising tracers include 11C-methionine although with still limited experience [5].

The current standard nuclear medicine imaging method of choice for parathyroid glands however is scintigraphy using Tc-99m MIBI, it is cost-effective and is a sensitive modality of hyper functioning parathyroid adenomas prior to operation [6,7].

In our setting intravenous injection of the radiopharmaceutical (Tc-99m MIBI) is done: a flow, planar static (early) image of the neck and chest with SPECT/CT are obtained at 20 minutes and only static planar(delayed) images of the neck with no SPECT/CT are acquired 3 hours post injection.

Other modes of parathyroid imaging include Tc-99m Tetrofosmin which is a similar class of radiopharmaceutical as Tc-99m MIBI and has also been investigated for imaging parathyroid. Tetrofosmin has been used for parathyroid imaging but has different kinetics in that the uptake in the parathyroid and thyroid do not demonstrate differential washout with Tc-99m Tetrofosmin[8].

Single Photon Emission Tomography (SPECT) technique or an addition of structural imaging with Computed Tomography (CT) or SPECT with CT (SPECT/CT) improves preoperative localization [8]. There has not been any literature/ studies focusing on evaluating the impact of adding a flow or SPECT/CT in parathyroid scintigraphy and numbers of patients studied for impact of SPECT/CT in parathyroid imaging have been limited.

In an attempt to reduce unnecessary technical issues, length of procedure, increased costs and radiation burden to patients the impact of a dynamic phase and SPECT/CT in parathyroid scintigraphy of patients with primary hyperparathyroidism was assessed. Patients with primary hyperparathyroidism are imaged in dual phase process, which also includes flow and SPECT/CT. However it is only our institution that adds a flow phase to parathyroid scintigraphy and it is only our institution that adds a SPECT/CT for every patient.

In our protocol the following are the processes implemented for imaging parathyroid glands:

1st a flow/dynamic phase is acquired at 2seconds/frame for 60 seconds, 2nd planar static images of the neck and chest are acquired immediately, at 20 minutes and delayed at 3hours and 3rd patient is subjected to an early (20minute) SPECT/CT.

The flow is 2s/frame for 60 seconds and SPECT/CT adds another 20minutes to the imaging procedure. The addition of flow and SPECT/CT is time consuming with long camera occupancy time that affects service delivery in a busy unit with limited number of cameras.

Current imaging protocols for parathyroid glands in nuclear medicine

Flow (dynamic phase) protocol

Flow phase for parathyroid scintigraphy is not mentioned in literature, but our institutions (CMJAH and CHBAH) does flow on all patients referred for parathyroid adenoma localization.

Our explanation of doing a flow is that Tc-99m MIBI initial high uptake in parathyroid and thyroid tissue is due to the blood flow to the parathyroid glands and thyroid gland which is high. The clearance of the MIBI tracer from thyroid tissue occurs more rapidly than from parathyroid glands [9,10].

Tc-99m sestamibi parathyroid imaging protocol

A dual-phase parathyroid imaging involves injecting patient with Tc-99m MIBI and imaging patients as described above. The differential washout from the parathyroid gland is then used to determine whether there is a parathyroid lesion.

SPECT and SPECT/CT protocols

Above two modalities have proven useful and provide more accurate localization anatomically, the two modalities are also important in ectopic site localization. Accurate localization in the ectopic parathyroid glands located in mediastinum assists in surgical approach guidance [11].

Planar static images of the neck and chest are acquired first. These images can supplement SPECT and SPECT/CT data [11]. Anterior static planar images of the neck and chest are obtained approximately 20 min after injection (early) and static planar images in the same view are repeated 3 hours post Tc-99m MIBI injection. It is not known whether addition of CT component to the SPECT actually increases sensitivity [11,12].

The combination of radiological (anatomic) and scintigraphic (functional) imaging, that is, SPECT fused with CT provides the localization of parathyroid lesion/adenoma for surgery [12]. Regarding the specific procedure for SPECT/CT Tc-99m MIBI scintigraphy, images are acquired using a hybrid system which automatically fuses the morphological and functional scan findings, there are times when an integrated/fused system is not available and one can manually fuse the 2 data sets [13].

1.2. Literature review

There are different modalities used in imaging of Parathyroid glands these include Tc-99m MIBI, high-resolution ultrasonography, CT and Magnetic Resonance Imaging [14]. The most common imaging modalities used in PHPT include ultrasonography and Tc-99m MIBI.

However other additional imaging modalities adenomas include Computed tomography and MRI [10-12]. It is of clinical importance to evaluate patients with combined modalities. Both scintigraphy methods such as SPECT/CT and PET/CT can be used as metabolic imaging with accurate localization of parathyroid lesions [13].

Combined Tc-99m MIBI with CT or US improves accuracy of parathyroid imaging and improves decisions made regarding management [13,14]. Because of lack of radiation emission, and also being a widely available technique US is an advantageous modality, its limitations are mainly due to its high subjectivity in interpretation and its highly operator dependent nature and [14].

A lower sensitivity and accuracy of US has been demonstrated on several studies compared with Tc-99m MIBI scintigraphy for showing parathyroid adenomas. The diagnostic yield is improved when US is used together with Tc-99m MIBI scintigraphy and important information for the diagnosis of parathyroid diseases is acquired [15-17]. US has pitfalls such as lower success rates in parathyroid adenomas that are within the thyroid, neoplasms that are located deeply, and lesions that are outside the usual anatomical location [15]. Ultrasound cannot be used alone instead it is often used in combination with other scans before unilateral neck exploration.

Separate interpretation by a physician is less accurate as compared to combined interpretation of a combination of scintigraphy and US. Structural US imaging combined with Tc-99m MIBI scintigraphy for functional imaging is much more useful in confirming the presence of parathyroid adenoma[15], however this is not done in our institution.

1.2.1. SPECT/CT with Tc-99m MIBI

Computerized Tomography is a more commonly used imaging scintigraphy than US for parathyroid adenomas not located within the parathyroid gland, however its detection sensitivity is low for lesions within thyroid gland. SPECT/CT systems increase sensitivity and accuracy by combining a gamma camera machine fused with an X-ray machine both within the same machine (scanner), SPECT/CT systems combining powerful CT and high quality gamma cameras are being used for this[16,17]. Studies exploring the role of SPECT fused with CT (hybrid SPECT/CT) in parathyroid imaging are limited [17,18].

It is not known whether SPECT/CT is more reliable than SPECT alone or CT alone as it has not been studied. Using SPECT fused with CT (hybrid SPECT/CT), with CT added to the SPECT and used to localize lesions in parathyroid gland, improves detection rate of adenomas in ectopic sites. The studies that have been performed did not demonstrate SPECT/CT to be superior to SPECT alone in normally located adenomas and SPECT alone has the same clinical impact as compared to SPECT fused with CT.

For major ectopic lesions on the other hand and previously operated neck SPECT/CT is more accurate and it gives exact anatomical localization of the adenoma [19].

However all patients referred and imaged at our institutions had no previous neck surgery and the SPECT/CT portion was done at initial consultation.

The modality of choice used in nuclear medicine for parathyroid imaging is scintigraphy using Tc-99m sestamibi (Tc-99m MIBI) [18]. Tc-99m MIBI radiopharmaceutical is a positively charged anion it is also a lipophilic isonitril that is taken up by abnormal cells of the parathyroid gland. Mechanism of uptake for Tc-99m MIBI is only partially understood, some studies have implicated mitochondria uptake by parathyroid cells [19,20]. A membrane transport protein known as P-glycoprotein which is encoded for by a gene known as MDR (multidrug resistance) gene, could be accountable for parathyroid taking up MIBI, the membrane transport protein carries substances which are similar to Tc-99m sestamibi structurally [21].

Another important factor of importance in visualization of the parathyroid glands is the size of the lesions however this alone cannot explain the uptake and retention of Tc-99m MIBI [22].

Takebayashi et al. in a recent study found the Tc-99m MIBI uptake correlates with the dimensions and the cellular components of the abnormal gland. There was also significantly higher count ratio in high cellular glands than in low cellular higher activities [23].

Parathyroid scintigraphy primary objective is to recognize and locate the parathyroid glands in patients who have hyperparathyroidism as evidenced biochemically and patients that are asymptomatic [23].

Imaging of thyroid gland and parathyroid glands is described in literature as statics and SPECT/CT being done at 20 minutes post injection of tracer when using Tc-99m MIBI; static images are redone again at 3 hours. Studies have shown that combination of SPECT and CT results in an increase radiation dose to the patient. Availability of CT in the nuclear diagnostic imaging has resulted in a significant dose delivered to the patient. The occurrence of cancer increases by 4% for every Sv of total effective dose received by a patient and this is the main risk to patients [24]. Tc-99m MIBI is retained by abnormal parathyroid glands however it clears from the thyroid with a half-life of about 30 minutes but the target-to-background activity is improved due to the "differential washout" phenomenon so that abnormal parathyroid tissue becomes more visible on the later static images.

Primary hyperparathyroidism in most presents with a single adenoma (~80% of cases), but multigland involvement however occurs in 10%–15% of population and the location of solitary adenomas is usually posterior to the thyroid glands lower portion, ectopic locations occur in 20%. Other causes of primary hyperparathyroidism include hyperplasia of the parathyroid glands (10%), multiple adenomas of the parathyroid glands (5%), and carcinoma (1%) [25].

Approximately 25% of patients with PHPT have parathyroid tissue that is at an ectopic site. For ectopic lesions the heart should be in the field of view when doing early and delayed planar static images [26] or alternatively one can do delayed statics of the chest. The ectopic location is then confirmed with SPECT/CT fusion technique.

There is no literature/data on interpretation of a flow study in parathyroid scintigraphy.

On early and delayed planar static images done at 20 minutes and 3hours post tracer injection, a progressive increase of a focus of activity in the neck or mediastinum over the duration of the study or persistence of activity on delayed imaging is interpreted as differential washout and is consistent with parathyroid adenoma.

Semi-quantitative analysis with regions can be drawn around normal thyroid tissue but visual analysis that is implemented in both our institutions is sufficient for clinical purposes [24]. This is due to the simplicity accompanied by less cost of the dual-phase. Tc-99m MIBI scintigraphy scan is used for routine clinical purposes in most centres. Preoperative identification and parathyroid gland localization is increasingly expected by the surgeons before the first surgery or after an exploration of parathyroid glands that failed.

Glands greater than 500 mg are easily demonstrated on Tc-99m MIBI and localization of much smaller ones can be achieved [25]. Parathyroid hormone (PTH) levels can be intra-operatively assayed to ensure resection was complete, radioactive parathyroid particularly when small or deep can also be located using intraoperative gamma probes [26-27].

To our knowledge, nothing is mentioned in the literature with regards to a dynamic phase in parathyroid imaging as we could not find a single publication. The only time a dynamic phase is mentioned or done is with regards to the use of dual tracer for studies, which is not done in our centres and which are not part of this proposed research.

Parathyroid adenomas/lesions and hyperplastic parathyroid tissue retain the Tc-99m MIBI for a longer period of time than the normal thyroid tissue, parathyroid adenomas/lesions and hyperplastic parathyroid tissue appear as areas of increased tracer uptake on the delayed static images. SPECT images of the neck are greatly helpful [27], but it is not known whether SPECT/CT is of any greater advantage than SPECT alone [28].

Some parathyroid adenomas have more rapid wash-out of Tc-99m MIBI, and the single Tc-99m MIBI isotope imaging technique has less sensitivity than the dual isotope/tracer techniques [28]. The most commonly used imaging technique is Tc-99m MIBI single tracer imaging.

Static images of the neck and chest with the heart in the field of view should be obtained with a gamma-camera with a high-resolution collimator. Images including the chest region should always be done. Residual or recurrent disease and ectopic lesions are easily spotted on the chest images [28].

Anterior oblique images may be done where useful SPECT is unavailable [28].

Sensitivity is increased with the use of SPECT (or SPECT/ CT), because some parathyroid adenomas have rapid washout of Tc-99m MIBI an early SPECT is done. The SPECT acquisition alone takes, approximately 25 minutes [29,30].

Lesion localization and attenuation correction is done by the CT component of the examination., CT parameters such as the optimal slice thickness, acquisition time, mAs and kVp is determined by individuals or by the manufacturer to maximize quality of image and radiation exposure minimization to the patient [31].

Within these CT parameters, the spatial resolution of the highest quality should be sought in setting up the imaging protocol. Parameters typically applied are a tube current ranging from 100 -200 mAs and a voltage ranging from 100 -140 kVp.

Intravenous contrast enhancement may be useful or justifiable in selected cases but is not usually applied.

Displaying of the image sets optimally includes SPECT, CT, and hybrid (SPECT/CT) images which are reconstructed in 3 projections (axial, coronal, and sagittal). All 3 sets should be preferably co-registered so that the same body region is displayed on any one of the numbered slices of any given projection. Co-registration allows for a comparison that is reliable between the anatomic/morphological and functional correlation [31,32].

Parathyroid imaging using Tc-99m MIBI in two phases uses the differential washout technique; this washout is seen between the thyroid and parathyroid glands. This method involves the rationale that Tc-99m MIBI washes out earlier in thyroid tissue and washout is delayed in parathyroid adenoma hence the term dual phase involving early and delayed imaging. Tc-99m MIBI washout from the parathyroid glands must be slower than from thyroid gland [33]. Tc-99m MIBI imaging is useful in patients with PHPT and these patients when patients are for parathyroidectomy [33].

It is used:

1. Parathyroid adenoma localization before surgery is initiated.
2. In PHPT and secondary hyperparathyroidism it detects adenomas that are recurring in the parathyroid or disease involving parathyroid glands that is not improving.

Patients need not be specially prepared for parathyroid scintigraphy. Tc-99m MIBI is the preferred agent for dual phase parathyroid scanning in nuclear medicine, recommended dose is ~600 MBq (16mCi) intravenously injected. The tracer is taken up in both the normally functioning thyroid tissue and is also taken up in parathyroid glands that are hyper active however there is faster washout from normal thyroid tissue. 99mTc-tetrofosmin does not have an effective differential washout as compared to Tc-99m MIBI [33].

Using Tc-99m tetrofosmin is another method in parathyroid scintigraphy however it is not advised and Tc-99m MIBI remains the tracer of choice [33].

Some techniques for improved quality include SPECT, SPECT/CT and pinhole these are more likely to locate parathyroid glands that are hyperfunctioning with accuracy and can also assist in finding smaller than usual adenomas. Static images using a certain matrix ideally equal to or more than 128×128. The collimator should be of high resolution and of low-energy, due to the low energy of the Tc-99m (140 Kev) that is used with the MIBI. The camera used is usually a dual head however a single-headed camera can be used because only anterior views are acquired and there is no need for posterior views.

Further delayed static images at 4 hours post tracer injection are acquired when there is poor washout from thyroid gland.

Single Photon Emission Tomography imaging offers increased specificity and sensitivity, parathyroid glands localization with a better delineation of parathyroid glands outside the normal anatomical location. SPECT is acquired post static acquisitions to avoid parathyroid adenomas with rapid washout which leads to false-negative results[36] the patient should not be moved from his/her position, and a matrix of 128×128 for 120 projections every 3° should be applied. Fusing functional and morphological/anatomical techniques considerably improves the overall scan findings, and this is achieved by hybrid SPECT/CT [36,37].

1.3. Problem statement

Primary hyperparathyroidism patients referred to our institution are subject to a dual phase (meaning early and delayed, to assess for washout) Tc-99m sestamibi imaging, which always includes dynamic study and always a SPECT/CT study.

- We acquire the dynamic study over 1 minute in CMJAH and over 3 minutes in CHBAH, eliminating this part could save some time on the radiographer and patient side as the gamma camera can be used to image other patients still awaiting scans.

- SPECT/CT is usually 45 minutes long and SPECT alone without the CT portion decreases the imaging time by 10-20 minutes depending on the slice thickness of the CT. This will cause unnecessary technical issues, increasing length of procedure eventually leading to unnecessary costs and increased radiation burden to patient.

Hence CT adds unnecessary radiation to patients and also subjects patients to more time under the camera with prolonged techniques and added technical procedures, leading to unnecessary, radiation.

2. CHAPTER 2: Materials and methods

2.1. Study design

This is a retrospective study of 99mTc-sestamibi studies performed in patients with primary hyperparathyroidism who were referred to the nuclear medicine at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital.

The images of all patients who were done in both our departments (Charlotte Maxeke Academic Hospital (CMJAH) and Chris Hani Baragwanath Hospital (CHBAH)) over the past 8 years from 01 January 2010 up until 31 December 2014.

The data then determines the trend and outcome in reporting with regards to the contribution of SPECT/CT vs SPECT alone and especially the dynamic phase of the study and how this contributes to patient management and also if it adds value. The archived images and serology results (PTH and Corrected Calcium) where available and were systematically reviewed in all patients referred. Tc-99m MIBI images and serology results were carefully reviewed and an independent reader reported on the images. This was then compared to original reports for discordance.

2.2. Study objectives

1. To determine the value of a dynamic (flow) phase and SPECT fused with CT (SPECT/CT) in that are referred for PHPT.
2. To evaluate impact: SPECT/CT vs SPECT alone on the diagnosis.

2.3. Sample size

A total of 273 patients referred for parathyroid scintigraphy at our two institutions (Charlotte Maxeke Johannesburg Academic and Chris Hani Baragwanath Hospitals) from 2010 to 2014 were eligible for inclusion. Images of all 273 patients were retrieved to assess the data.

2.4. Eligibility criteria

2.4.1. Inclusion criteria

1. All patients referred for parathyroid scintigraphy for suspected parathyroid adenoma
2. All ages were included
3. Patients who had a dynamic phase (flow) and a SPECT/CT as part of their diagnoses.

2.4.2. Exclusion criteria

Patients with dual isotope studies were excluded from the study.

2.5. Data collection

Names of patients who had been referred for parathyroid imaging for primary hyperparathyroidism were collected from both hospitals (CMJAH and CHBAH). With the help of Mr Mokemane (radiographer) archived images were retrieved from CD's these were patients from 2010 January up until 2014 December. From CHBAH Ms Marlini (radiographer) assisted with the archived images from CHBAH these images were also retrieved from CD's, for patients from 2010 January up until December 2014.

Prior to reader reporting the images it was necessary to ensure that each and every single patient in our study had both initial images and final report. Where patients did not have both images and reports available they were disqualified from the study/ not considered for the study.

All reports were printed out and the names used on the reports were changed to numbers for privacy and to avoid bias on the reporting, similarly the reports and images of each patient was given the same number. Patients reports and images were named from 1-273. Reports were kept separate from the images.

The final report for the patient (on our system) was used as the Gold standard.

The reader who had more than five years of experience reported the images without seeing final reports as follows:

- Planar statics with flow
- Planar statics without flow
- Delayed static images at 3 hours and SPECT without CT
- Delayed static images at 3 hours and SPECT with CT (hybrid SPECT/CT)

In other words each study was read individually (Flow, Planar at 20 minutes, Planar at 3 hours, SPECT alone and SPECT fused with CT (SPECT/CT). Studies were also read as paired sets for example, Dynamic/Flow with planar images at 20 minutes, planar images at 20 minutes with planar images at 3 hours, planar at 20 minutes with SPECT, planar at 20 minutes with SPECT/CT.

Images of the studies were interpreted without looking at the final report which was considered as a gold standard (because the report is usually finalised by consensus among more than one consultant and registrars).

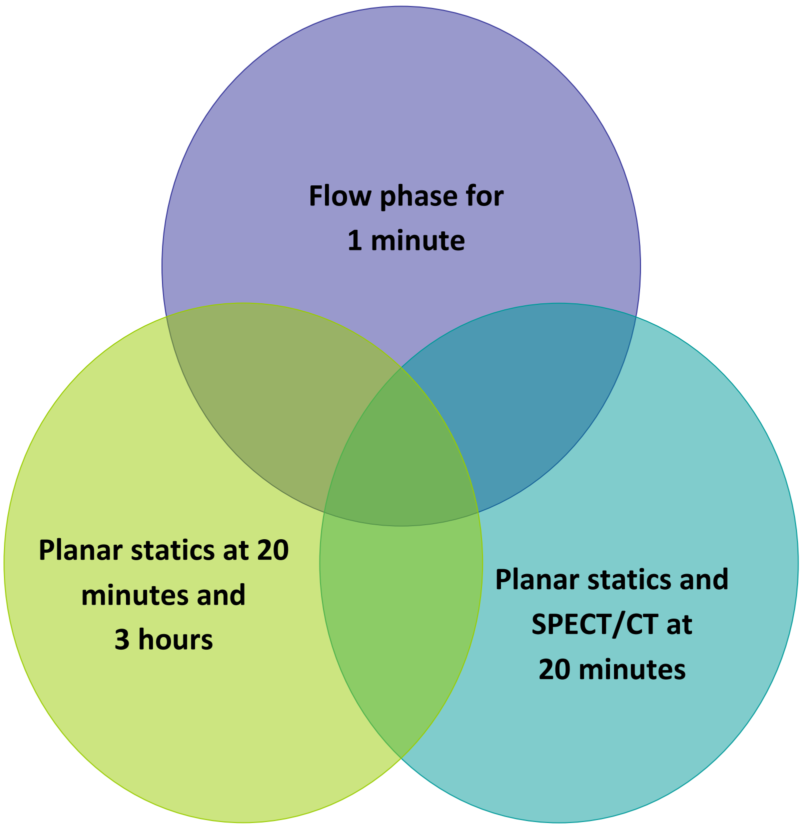

Figure 2.1: Imaging procedure

We then correlated the findings of the reader with the final results that were reported for each patient. We evaluated whether the addition of flow or addition of CT to SPECT (SPECT/CT) changed the outcome of our report.

Masked image sets were interpreted by a reader who was blinded to the original final reports of the Tc-99m MIBI parathyroid scans. The image findings were scored as either parathyroid adenoma present or parathyroid adenoma absent. The final result given by the reader was recorded in an Excel (Microsoft) spread sheet.

2.5.1. Data capture sheet

A data capture sheet was used to record information on age, gender, the hospital, biochemistry and scintigraphic imaging as shown in Appendix

2.6. Ethical considerations

This study was conducted subsequent to submission of a research protocol to the Human research ethics committee (medical), University of Witwatersrand. The proposed study received ethics approval from the committee and a clearance certificate was issued, Reference M160206 (APPENDIX A-E). Permission was obtained from the CMJAH chief executive officer (CEO) and CHBAH CEO. Confidentiality was maintained by assigning number to each patient for identification.

2.7. Imaging

2.7.1. Imaging techniques

a. Planar Imaging

Planar imaging in nuclear medicine forms part of the simplest protocol. With this form of imaging, the detector of the camera stays stationary over the parathyroid glands and chest region. The camera acquires data only from this one specific angle. The image created with this type of acquisition is similar to an X-ray image.

b. Dynamic/flow study

As discussed above the camera in a planar study remains at a fixed position, however with flow study one can trace the motion of the tracer during injection of the radiopharmaceutical.

Data is summed up over a certain short period of time approximately 1-10 seconds and this creates an animation where an interpreter can analyse the data

c. SPECT acquisition

This technique images the tracer at a variety of angles, the acquisition then creates a 3 Dimensional image from a 2 dimensional acquisition.

d. SPECT/CT acquisition

Fusing SPECT and CT to form a hybrid SPECT/CT image allows both anatomic and physiological images to be fused in one imaging session.

Adding CT to SPECT has led to increased patient radiation dose and increased length of imaging time. Correlating lesions found on SPECT with CT has been argued by some as a better way to visualize parathyroid lesions/adenomas. However there is still no consensus on whether addition of CT will increase sensitivity of scintigraphy findings [38].

2.7.2. Image interpretation

The images acquired at two different time intervals were visually assessed for each patient. Areas of focal increased tracer uptake either progressively increasing or persisting on the 3 hour image was worrisome of parathyroid pathology and this could be either be considered as a hyperfunctioning parathyroid adenoma [39].

The flow and planar images did not need any processing for planar images however processing for SPECT alone and SPECT fused with CT is always performed [40,41].

It is believed that both SPECT and/or SPECT/CT images of the parathyroid can correctly locate and position the parathyroid glands that are hyperfunctioning [42].

Tc-99m sestamibi scan findings were considered positive when there was no washout on the delayed images [43].

2.8. Data analysis

a. Images were selected according to the referral of primary hyperparathyroidism.
b. The reader reviewed the images of these cases with and without a dynamic flow to determine whether the flow added any additional information.
c. Images where reviewed with SPECT and the same images with SPECT fused with CT (SPECT/CT) and the CT component was assessed to see whether it is of any value.
d. Results obtained where compared to the actual final report/results.
e. The results of the data collected was analysed by both descriptive statistics and inferential statistics.
f. Measures of central tendencies of mean, standard deviation and frequency was used to reduce and summarize the data.
g. The test that was used to determine the association between the clinical tests and the presence or absence of parathyroid tumours was Chi-square test.
h. Measure of agreement between the clinical tests was tested by reporting the kappa statistics.
i. Calculation of the sensitivity, specificity, positive predictive value and negative predictive value of the tests were done.

j. The value of $p<0.05$ was set as the significant set. All data was analysed using IBM SPSS 23.0 ®

3. CHAPTER 3: Results

3.1. Demographics

This study had a total of 273 patients' images. The ages of the patients ranged from 3-90 years (median – 58) and there were 85.7% of females. The youngest patient was 3 years and the oldest patient was 90 years old see figure 3.1. The figure 3.2 below shows the age distribution categorised in decade intervals and gender distribution respectively.

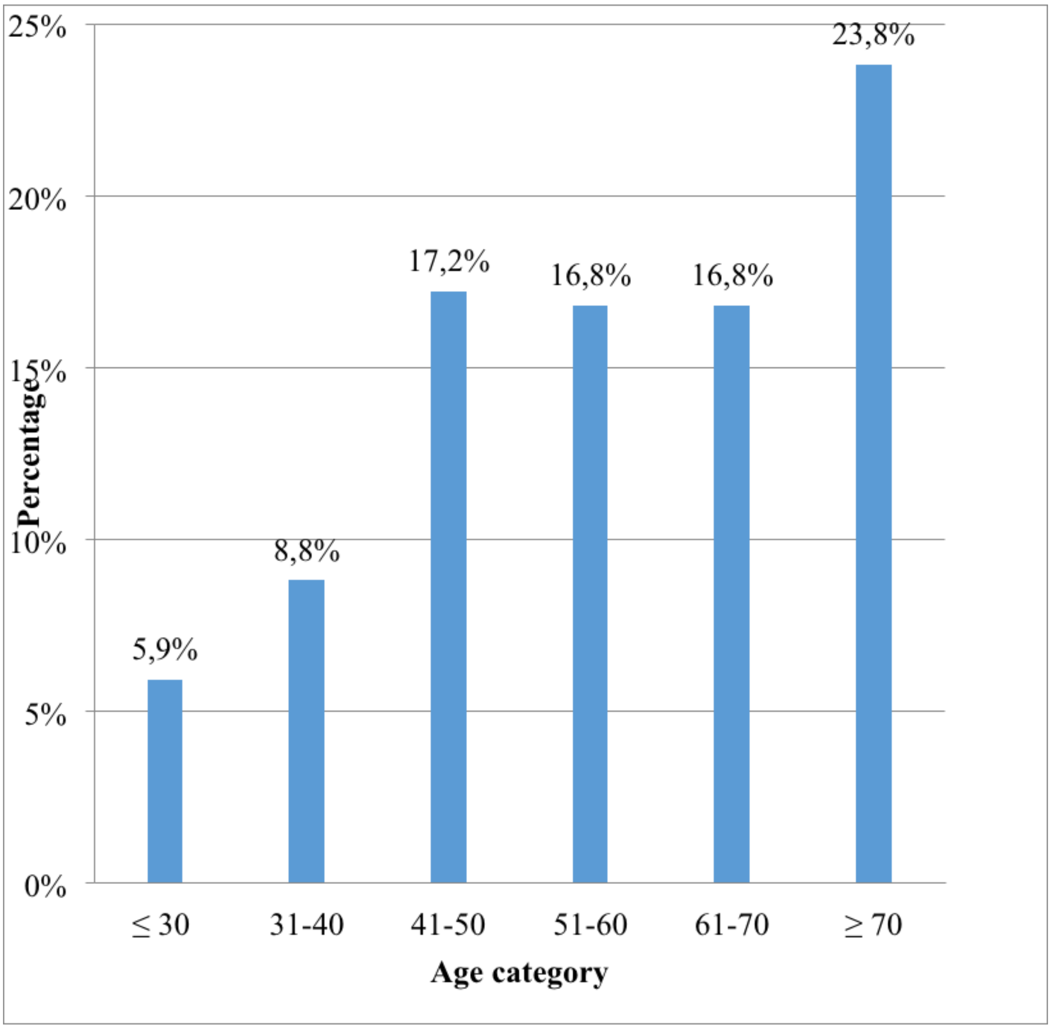

Figure 3.1: Age distribution of the patients

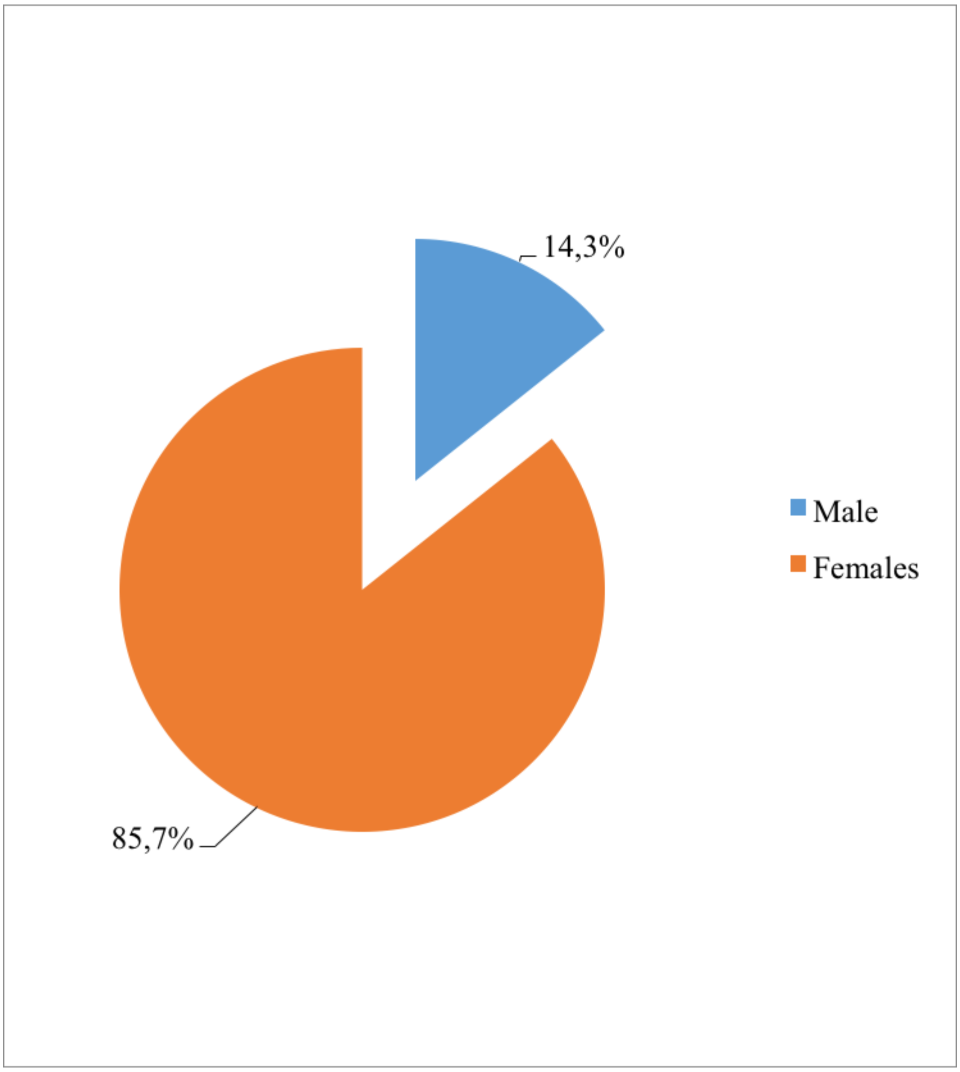

Figure 3.2: Gender distribution of the patients

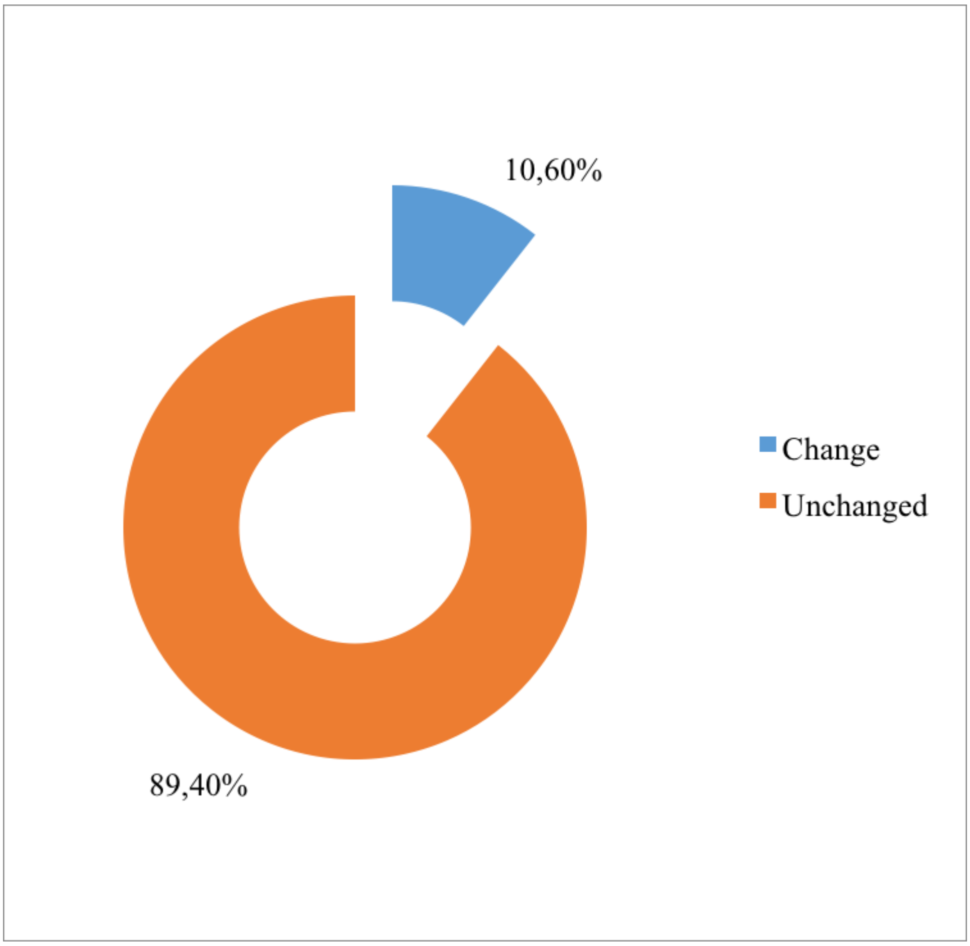

Figure 3.3: Diagnosis

Figure 3.1 shows that the majority of patients were between ages 41 and 70 years, which accounts for 50.8% of the overall patients between the duration of observation. Also, as illustrated in Figure 3.2, 85.7% of the patients were females.

3.2. Imaging techniques results

Table 3.1:

Procedure (N=273)	**N**	**%**
Dynamic phase		
Positive	34	12.5
Negative	125	45.8
Not acquired	100	36.6
Acquired not reported	14	5.1
Planar		
Positive	133	48.7
Negative	140	51.3
SPECT		
Positive	133	48.7
Negative	140	51.3
SPECT/CT		
Positive	138	50.5
Negative	125	49.5
Overall parathyroid adenoma		
Positive	266	97.4
Negative	7	2.6

We found 133 positive lesions (48,7%) on planar images and this number was not changed adding SPECT alone. However, when SPECT/CT was added additional 5 lesions (3.6%) were found. Only 159 (58.2%) of participants underwent a dynamic phase. Interestingly all these 34 patients also showed lesion on planar and SPECT on later images.

Due to 114 of cases on the flow phase not either not acquired or not reported it is difficult to directly compare change in diagnosis with SPECT or planar. However, only 34 cases were positive using the dynamic flow (see Table 3.1).

3.3. Association between imaging techniques and parathyroid tumours

Table 3.2: Association between the Imaging techniques and diagnosis

Tests	**X^2 (p-value)**
Dynamic phase (flow)	1.99 (0.57)
	Fischer's Exact Test
Planar	0.00**
SPECT	0.01*
SPECT/CT	0.00**

Significance* $p<0.05$, **$p<0.01$

Using the Fischer's exact test, there was a significant association between the ectopic gland tests and the change in the diagnosis of parathyroid tumours ($p<0.001$). There was no significant association between the biochemistry results and the change in the diagnosis to parathyroid tumour ($p=0.38$) as shown in Table 3.2.

The results of the association between the imaging techniques and the diagnosis showed that the dynamic phase had no significant association with the diagnosis, $p>0.05$. Planar, SPECT and the SPECT/CT showed significant association with the change in the diagnosis of primary hyperparathyroidism, $p<0.05$.

3.4. Diagnostic accuracy of the imaging techniques

Table 3.3: Sensitivity and specificity analysis

	Sensitivity	Specificity	AUC %	PPV	NPV	95%CI
Planar	75.9%	54.5%	56%	16.5%	95%	0.49-0.63
SPECT	72.4%	54.1%	63%	15.8%	94.3%	0.53-0.74
SPECT/CT	93.1%	54.5%	74%	19.6%	98.5%	0.66-0.82

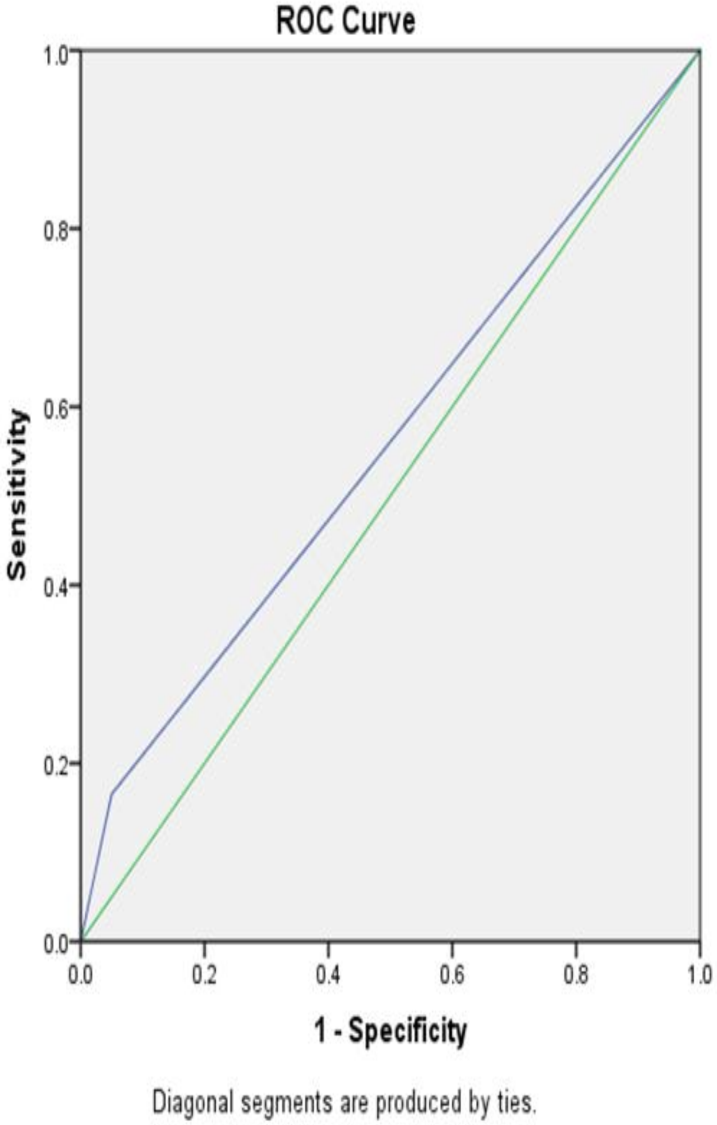

Figure 3.4: ROC curve for Planar

Figure 3.5 ROC curve for Planar with SPECT

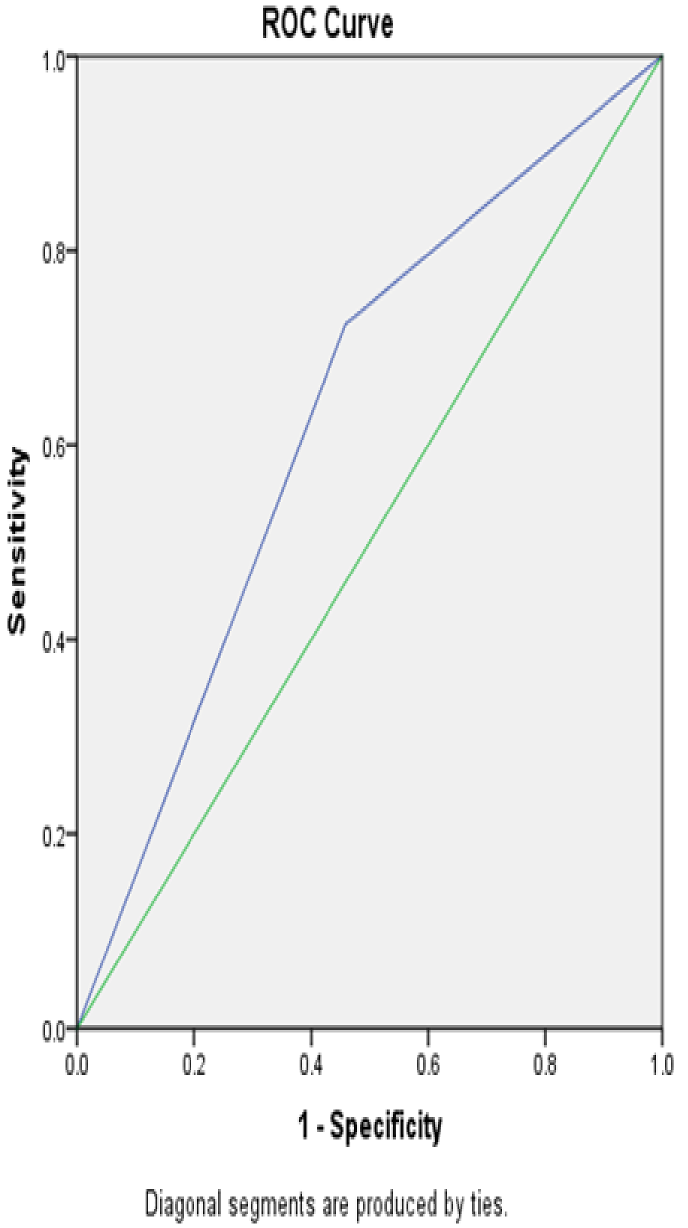

Figure 3.5: ROC curve for SPECT

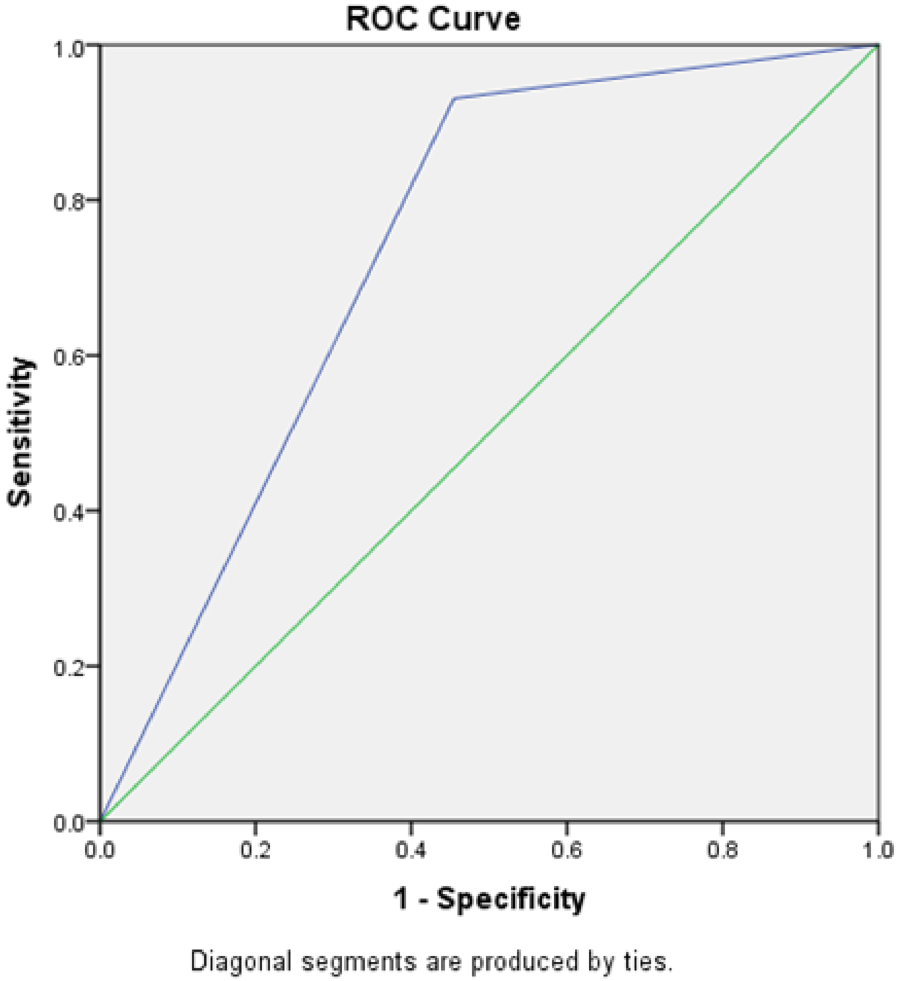

Figure 3.6: ROC curve for SPECT/CT

Table 3.4: Measurement of Agreement between the different tests

	k-coefficient
Dynamic flow versus planar	0.09
SPECT versus SPECT/CT	0.93

The diagnostic accuracy of the imaging techniques showed that SPECT/CT has 93.1% sensitivity in the diagnosis parathyroid tumour in the presence of a tumour while SPECT alone showed 72.4% sensitivity. The area under curve showed that SPECT/CT has good diagnostic accuracy of 74%. The SPECT/CT has a higher positive predictive value, 19.6% in changing the diagnosis of parathyroid tumour while SPECT alone has a 15.8% positive predictive test in changing the diagnosis of tumour. The measure of agreement between the imaging techniques and the change in the diagnosis of parathyroid tumour was poor in all the tests, kappa coefficient ranged from 0.1-0.20. Figures 3.4, 3.5 and 3.6 showed the diagnostic accuracy of the imaging techniques by using the ROC curves.

As shown in Table 3.4 above, the measurement of agreement between the radiological tests showed that the SPECT/CT and the SPECT alone showed a very good agreement (k-0.93, p<0.001) as well as with planar.

4. CHAPTER 4: DISCUSSION AND CONCLUSION

4.1. Discussion

The aim of our study was to determine the value of the various imaging techniques used in the diagnoses of parathyroid tumour. Our study showed that the dynamic (flow), planar, SPECT and SPECT fused with CT (hybrid SPECT/CT) were used mainly to diagnose parathyroid tumours in all the patients. However there is no literature describing the value of dynamic phase and SPECT/CT in literature is only recommended for some of the patients and not all warrant SPECT/CT, SPECT alone is sufficient.

An endocrine disorder such as primary hyperparathyroidism has a high prevalence, in most cases it is caused by a parathyroid adenoma which is usually solitary [43].

Currently the trend for removal of parathyroid lesions favours minimally invasive surgery of the parathyroid glands. These glands require accurate localization.

Presurgical scintigraphy localizes the exact position of a parathyroid adenoma which is essential for surgery involving minimally invasive surgery.

The planar, SPECT and the SPECT/CT were positive for parathyroid tumours in at least 48.7% of the patients. However, using the dynamic flow alone, only 12.5% of the patients were positive. It should be noted that in as much as 41.8% of the overall sample, the dynamic flow was either not acquired or not reported. There was no literature found to compare the results of the dynamic flow phase with.

The diagnosis of parathyroid tumour between the imaging techniques showed that only 10.6% of the patients had a change in diagnosis after the use of SPECT/CT.

As outlined above, 12.5% of the patients showed positive images for parathyroid adenoma and the dynamic phase was not acquired in 36.6% of the patients. Planar and planar-SPECT showed similar results. 48.7% of the patients showed positive images for parathyroid adenoma for both the planar and the planar-SPECT. However, planar-SPECT/CT showed a positive image of parathyroid adenoma in 50.5% of the patients. Of these, 97.4% of the positive radiological images were found in the ectopic gland. Biochemistry result was positive in 94.5% of the patients assessed [44-45].

Imaging with Tc-99m detects all abnormal parathyroid glands and indicates their exact position [46].

At times thyroid nodules may require concurrent surgical resection and reporting on these nodules is paramount [47-48].

There is no literature that mentions flow phase for parathyroid scinitgraphy so its relevance could not be assessed as we are the only centre that does flow with Tc-99m MIBI.

Luke Harris et al conducted a study of 23 patients with 66 years as the median age, using SPECT/CT they managed to correctly localize 16 of the 18 cases of individual adenomas, 1 out of 2 cases of double adenomas and none of the 3 cases of MGD. This study however had fewer patients (23) when compared to ours with 273 patients and this could increase the sensitivity of their study. In this study the impact of adding CT to SPECT was not fully explained and this study by Luke Harris et al was inconclusive.

Studies of SPECT alone without fused CT have reported sensitivities for parathyroid adenoma ranging from 90-95% [45]. Addition of CT component to SPECT (SPECT/CT) in most studies is not necessary when a lesion is demonstrated on SPECT alone.

SPECT-CT is useful in localizing ectopic lesions but its clinical value in localizing normally located parathyroid adenomas has been contested [46].

A study conducted with a total patient population of 92, Moka et al [42] patients had diagnosis of PHPT. Subtraction scintigraphy using planar technetium 99m-pertechnetate/ technetium 99m-MIBI identified and exactly localized adenomas in 87% of patients. The addition of SPECT increased sensitivity to 95%. Adenomas were exactly localized to the exact quadrant position 88% (41).This study shows us that SPECT alone can localize adenomas with a high sensitivity. The only patients that warranted SPECT/CT in this study where those with ectopic adenomas, to accurately localized the ectopic site. This study finding was also similar to our study findings and shows that CT component is not ideal for all patients but this study by Moka et al had less number of patients, 92 patients vs ours with 273 patients.

It was also demonstrated in one study where 44 Tc-99m MIBI studies were performed from patients, Billotey et al [43] the studied patients where biochemically hyperparathyroidal. In all patients, 86% were correctly picked/ detected by Tc-99m MIBI. Additional use of SPECT increases the sensitivity of static views from 86% to 90.5% . SPECT plays an important role in patients undergoing reoperation, it increases sensitivity from 79.5% to 87%. In this study SPECT alone was useful in patients for re-operation and no SPECT/CT was added to any of the patients.

SPECT alone adds no extra radiation to patient, however addition of CT component to SPECT during parathyroid imaging adds significant radiation dose to patients [49,50].

Not enough studies with significant number of patients such as ours have been done comparing SPECT vs SPECT/CT.

Limitations

This study had several limitations, which might have influenced the outcome of some of the results.

a. Lack of literature and studies has of parathyroid imaging done with addition of a flow/dynamic phase.

b. The study being retrospective, some patients referred for scintigraphy may not undergo the dynamic or SPECT/CT due to technical reasons. This influenced the sample size as these patients were excluded from the analysis.

c. Missing medical records might have affected outcome with regards to ascertaining the initial diagnosis on the final report.

d. The exact effective absorbed dose received by each patient post SPECT/CT was not calculated.

Conclusion and recommendations

Flow/Dynamic phase:

There is no literature/ studies done with flow/dynamic phase, most centres do not perform flow studies for parathyroid scintigraphy.

The poor agreement between the dynamic phase (flow) and the planar imaging indicates that there may be no significant value to add the early dynamic phase in the diagnoses of parathyroid adenoma thus the usage of this procedure in the hospital should re-evaluated.

Addition of CT to SPECT:

SPECT alone adds no extra radiation to patient, however addition of CT component to SPECT during parathyroid imaging adds significant radiation dose to patients.

Our study has shown that the measured agreement between the SPECT/CT and the SPECT alone was very good. Therefore, SPECT acquisitions can be obtained without exposing the patient to any additional radiation from the CT component. SPECT/CT seems to add value in clinical settings of high suspicion of disease and the planar imaging is negative. The performance of SPECT/CT in such situation may assist to localise ectopic parathyroid adenomas. In view of the radiation burden and minimal added value of SPECT/CT not all patients may require the addition of SPECT/CT imaging.

Our study therefore demonstrated that during parathyroid imaging for primary hyperparathyroidism dynamic phase and addition of CT component to SPECT is of no significant value.

Addition of dynamic phase increases the imaging time and addition of CT increases unwanted extra radiation.

The recommended protocol in these studies would be flow should be completely omitted and CT only added to patients where an ectopic lesion is suspected.

This then poses a question, of whether it would not be appropriate, based on the findings of this study, together with a strong published literature base, to change the acquisition protocol in our institution to limit acquisition of parathyroid adenomas to exclude the dynamic phase and only do planar statics and SPECT with CT to only the patients that have a suspicion of ectopic parathyroid adenoma.

This position however needs to be validated by a prospective study.

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Appendices

Appendix A Memorandum-Human Research Ethics Committee

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: PV Tobias Building Room 2nd Floor. Tel +27 (0)11-717-2700
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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Office of the Deputy Vice-Chancellor Research & Post Graduate Affairs

MEMORANDUM

TO: **Dr Ntanganedzeni Muambadzi**
Department of Nuclear Medicine
E-mail: nmuambadzi@yahoo.com

FROM: **Ms Zanele Ndlovu**
Administrative Officer: Human Research Ethics Committee (Medical)
Tel: 011 717-1252
e-mail: zanele.ndlovu@wits.ac.za

DATE: 29 February 2016

REF: ***R14/49***

PROTOCOL NO: M160206 *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

The protocol below was considered at a meeting of the Human Research Ethics Committee (Medical) **on Friday 26 February 2016.** The Committee requires the following amendments/corrections/information from you before your application can be approved.

Project Title: Value of dynamic phase and SPECT/CT during parathyroid imaging of primary hypoparathyroidism: impact on reporting and radiation exposure

Conditions: Approved subject to:

- Providing written permission to conduct the study from the CEO of CMJAH

NB:

1. **This memo is not a clearance certificate, no research should commence prior to obtaining a clearance certificate.**
2. **Please submit a covering letter (list all the conditions above and write your response below the each condition and attach relevant documentation), highlight any changes made and send two hard copy to this office. The default for submission is hardcopies – Amendments send by email will not be considered.**
3. **Amendments must be delivered at Faculty of Health Sciences, Phillip Tobias Building, second floor, Cnr York Road and Princess of Wales Terrance**

Appendix B Approval of Topic

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
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Reference: Ms Thokozile Nhlapo
E-mail: thokozile.nhlapo@wits.ac.za

12 January 2016
Person No: 736194
PAG

Dr N Muambadzi
PO Box 176
Kelvin
Sandton
2054
South Africa

Dear Dr Muambadzi

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Value of dynamic phase and SPECT/CT during Parathyroid imaging of primary hyperparathyroidism: impact on report and radiation exposure* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix C Medical Clearance Certificate

R14/49 Dr Ntanganedzeni Muambadzi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160206

NAME: (Principal Investigator) Dr Ntanganedzeni Muambadzi

DEPARTMENT: Nuclear Medicine
Charlotte Maxeke Johannesburg Academic Hospital

PROJECT TITLE: Value of Dynamic Phase and SPECT/CT during Parathyroid Imaging of Primary Hyperparathyroidism: Impact on Reporting and Radiation Exposure

DATE CONSIDERED: 26/02/2016

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Mboyo-Di-Tamba Vangu

APPROVED BY: ______________________
Professor P. Cleaton-Jones,Chairperson, HREC (Medical)

DATE OF APPROVAL: 23/03/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

______________________ ______________________
Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D CHBAH CEO Approval letter

GAUTENG PROVINCE

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 9 Dec 2016

TITLE OF PROJECT: Value of dynamic phase and SPECT/CT during parathyroid imaging of primary hyperparathyroidism: impact on reporting and radiation exposure

Received by:
Date:

UNIVERSITY: Witwatersrand

Principal Investigator: N Mnambadzi

Department: Nuclear Medicine

Supervisor (If relevant): MD Vangu

Permission Head Department (where research conducted): Yes

Date of start of proposed study: Dec 2016
Date of completion of data collection: Dec 2018

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

Recommended
(On behalf of the MAC)
Date: 09 December 2016

Approved/Not Approved
Hospital Management
Date: 13/12/16

Appendix E Data Capture Sheet

Patient ID	Age	Gender	Hospital	Dynamic flow	Planar	SPECT	SPECT/CT	Biochemistry