QUANTITATIVE EVALUATION OF ^{99M}TC MIBI PARATHYROID SPECT-CT: IN CORRELATION WITH DISEASE SEVERITY AND OUTCOME IN PRIMARY HYPERPARATHYROIDISM

BY

DR NIMALA BASKARAN

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF MEDICINE
(NUCLEAR MEDICINE)

ADVANCED MEDICAL AND DENTAL INSTITUTE
UNIVERSITI SAINS MALAYSIA

2022

DECLARATION

I hereby declare that this research has been sent to Universiti Sains Malaysia for the Degree of Master of Medicine (Nuclear Medicine). It is also not to be sent to other universities. With that, this research might be used for consultation and will be photocopied as reference.

Dr Nimala Baskaran

P-IPM0064/15

ACKNOWLEDGEMENT

First and foremost, I would like to thank the Almighty for the divine blessings bestowed upon me to complete this study.

It gives me great pleasure to acknowledge my supervisors Dr Khadijah binti Abdul Hamid, Associate Professor Dr Muhammad Nazri bin Md Shah and Dr Jeyakantha Retnasingam for their invaluable steadfast guidance and assistance throughout this study. The encouraging support I received from my supervisors is very much appreciated, not forgetting Professor Dr Sazilah binti Ahmad Sarji for her unwavering support throughout the course of my studies.

I would like to also extend my appreciation to the lecturers at the Advanced Medical and Dental Institute, Universiti Sains Malaysia particularly Dr Mahayuddin bin Abdul Manap and Dr Hazlin Hashim for their encouragement and support through my years of study at USM.

A special mention goes to all the specialists, radiographers and technologists, particularly Mr Prakash Kumar Sarkunam and En Mohammad Junaidin bin Jasa, physicists and other team members of the Nuclear Medicine Unit, Department of Biomedical Imaging, University Malaya Medical Centre as well as Dr Siti Zarina bin Amir Hassan and all at the Department of Nuclear Medicine, Hospital Kuala Lumpur. I am indeed grateful to my fellow colleagues, in particular Dr. Mohd Fazrin bin Mohd Rohani and Dr Piriatharisini Gopinathan for their valuable assistance during periods of the study. My sincere thanks and appreciation to the patients whose valuable data and findings without which the results of this study would not have materialised.

I would also like to extend my gratitude to Associate Professor Dr Karuthan Chinna who had been very generous with his help and teaching in the statistical analysis.

Last but not least, my pillars of support at home, my dearest husband Mr Sashi Vadivale my strongest pillar, my darling daughter who was my cheerleader in many ways, my dear parents, Mr (Ir) Baskaran Sambanthar and Professor Dr Loga Mahesan for their unwavering support by sorting out my home front more times that I could imagine as well as my brothers and my close friends who gave me the encouragement needed to push me forward during this study period.

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LIST OF SYMBOLS

g	gram
mg/ml	milligram per milliliter
mCi	millicurie
MBq	megabecquerel
cm/min	centimeter per minute
s	seconds
mAs	milliampere-seconds
kV	kilovoltage
mm	millimeter
ng/ml	nanogram per milliliter
g/ml	gram per milliliter
U/L	units per litre
kBq/ml	kilobecquerel per milliliter

LIST OF ABBREVIATIONS

AAES	American Association of Endocrine Surgeon
BMD	Bone mineral density
CT	Computed tomography
GFR	Glomerular filtration rate
kVp	Kilovoltage peak
IPS	Institut Pengajian Siswazah
mAs	Milliampereseconds
MGD	Multiglandular disease
MBq	Megabecquerel
mCi	Milicurie
MIP	Minimally invasive parathyroidectomy
MRI	Magnetic Resonance Imaging
PBRPL	Parathyroid adenoma to background ratio on parathyroid planar scan
PET	Positron emission tomography
pHPT	Primary hyperparathyroidism
Vp	Pathological volume
PTH	Parathyroid hormone
ROI	Region of interest
SPECT	Single photon emission computed tomography
SPSS	Statistical Package for the Social Sciences
^{99m}Tc MIBI	Technetium-99m- Sestamibi
UMMC	University Malaya Medical Centre
USG	Ultrasonography
USM	Universiti Sains Malaysia
Vm	Metabolic volume
VOI	Volume of interest

ABSTRAK

Tajuk: Penilaian kuantitatif ^{99m}Tc MIBI parathyroid SPECT-CT: korelasi dengan keterukan penyakit dan dapatan dalam hiperparatiroidisme primer.

Pengenalan: Hiperparatiroidisme primer ialah gangguan endokrin ketiga paling umum. Ia terhasil akibat rembesan hiper hormon paratiroid secara autonomi daripada kelenjar paratiroid yang abnormal dan sering kali berpunca akibat adenoma paratiroid. Sintigafi paratiroid telah terbukti sebagai modaliti pengimejan paling berkesan untuk penyetempatan adenoma paratiroid sebelum pembedahan paratiroid invasif minima. Namun begitu, potensi maksimum analisis kuantitatif ^{99m}Tc MIBI paratiroid SPECT-CT masih belum dipastikan secara menyeluruh.

Objektif: Untuk menilai kegunaan indeks kuantitatif sintigafi paratiroid dalam meningkatkan objektiviti dan kebolehpercayaan tafsiran kualitatif di dalam aplikasi diagnostik sintigafi paratiroid.

Subjek dan Kaedah: Rekod sebelas pesakit yang disyaki menghidapi hiperparatiroidisme primer dan telah menjalani ujian SPECT-CT paratiroid diperolehi secara retrospektif daripada pangkalan data imej (PACS) UMMC. Imbasan paratiroid planar dan SPECT-CT menggunakan ^{99m}Tc MIBI dilaksanakan mengikut protokol piawaian institusi. Penanda keterukan penyakit seperti kadar kalsium serum, hormon paratiroid (PTH) dan kreatinin serum diperolehi daripada rekod perubatan dalam talian/ bertulis. Pendekatan isokontur digunakan untuk mengukur isipadu metabolik (V_m) pada paratiroid SPECT-CT. Kadar penyerapan maksimum adenoma paratiroid dan kadar purata penyerapan tisu tiroid kontralateral disukat untuk menghitung nisbah

adenoma paratiroid kepada latar belakang di dalam SPECT-CT paratiroid (PBRSCT) dan imbasan planar (PBRPL). Isipadu patologi (V_p) adenoma diukur bagi pesakit yang telah menjalani paratiroidektomi. Hasil surogat untuk penanda keterukan penyakit turut dinilai sehingga 6 bulan selepas pembedahan.

Keputusan: PBRPL berkorelasi dengan signifikan dengan paras PTH serum (rho = 0.697; p = 0.017). Isipadu metabolik, Vm, menunjukkan korelasi signifikan yang kukuh dengan paras PTH serum (rho = 0.838; p = 0.001) dan korelasi signifikan yang sederhana dengan kalsium serum (rho = 0.687; p = 0.020). Untuk isipadu patologi, Vp, terdapat korelasi sederhana yang signifikan dengan paras kalsium serum (rho = 0.732; p = 0.010). PBRPL menunjukkan korelasi signifikan yang kukuh dengan PBRSCT (rho = 0.909; p < 0.001). Semua indeks kuantitatif yang diuji menunjukkan kesamaan dan kebolehpercayaan di antara pemerhati yang sangat baik. Perihal faktor yang mempengaruhi indeks kuantitatif di antara demografi pesakit, komorbiditi, dan penggunaan agen penurun kalsium, hanya faktor jantina mempengaruhi PBRSCT (p = 0.042). Bagi hasil surogat untuk penanda keterukan penyakit sebelum dan selepas pembedahan paratiroid, paras kalsium serum (p = 0.001) dan PTH serum (p = 0.003) menunjukkan perbezaan yang ketara.

Kesimpulan: Indeks kuantitatif SPECT-CT paratiroid berkolerasi secara signifikan dengan paras kalsium serum dan PTH serum. Terdapat kesamaan antara pemerhati yang amat baik bagi semua indeks kuantitatif yang diuji. Perbezaan ketara PBRSCT antara jantina yang bernilai turut menguatkan visi untuk meneroka epigenetik perbezaan berkaitan jantina dalam penilaian indeks kuantitatif ^{99m}Tc MIBI paratiroid SPECT-CT. Ini menunjukkan bahawa SPECT- CT paratiroid boleh diguna

untuk meningkatkan objektiviti dan kebolehpercayaan dalam menilai keterukan penyakit hiperparatiroidisme primer.

Kata kunci : SPECT-CT paratiroid, sintigafi paratiroid, hiperparatiroidisme, indeks kuantitatif, isipadu patologi.

ABSTRACT

Title: Quantitative evaluation of ^{99m}Tc MIBI parathyroid SPECT-CT: in correlation with disease severity and outcome in primary hyperparathyroidism.

Introduction: Primary hyperparathyroidism is the third most common endocrine disorder, caused by the autonomous hypersecretion of parathyroid hormone by abnormal parathyroid gland(s), most often due to presence of parathyroid adenoma. Parathyroid scintigraphy has been proven as the most effective imaging modality for preoperative localization of parathyroid adenomas prior to minimally invasive parathyroidectomy. However, the maximum potential of quantitative analysis of ^{99m}Tc MIBI Parathyroid SPECT-CT has yet to be fully established.

Objective: To employ the use of quantitative indices in parathyroid scintigraphy to add objectivity and reliability to qualitative interpretation in the diagnostic application of parathyroid scintigraphy.

Subjects and Methods: Records of 11 patients with primary hyperparathyroidism, positive parathyroid scintigraphy findings and histopathologically confirmed parathyroid lesion after undergoing parathyroid SPECT-CT were retrospectively retrieved from the PACS image database of UMMC. Our institutional standard protocols were followed when performing planar and SPECT-CT with ^{99m}Tc MIBI. Disease severity markers such as serum calcium, parathyroid hormone (PTH) and serum creatinine were obtained from online/written medical records. An isocontour approach was used to measure metabolic volume (VM) on parathyroid SPECT-CT. Maximum uptake of parathyroid adenoma and mean

uptake of contralateral thyroid tissue were measured to calculate the parathyroid adenoma-to-background ratio on parathyroid SPECT-CT (PBRSCT) and planar scan (PBRPL). Patients who had parathyroidectomy had their pathological volume (Vp) of the adenoma quantified. Surrogate outcome of disease severity markers, up to 6 months from the time of surgery was evaluated.

Results: PBRPL correlates significantly with serum PTH (rho = 0.697; p = 0.017). For metabolic volume, Vm, there was a significant strong correlation with serum PTH (rho = 0.838; p = 0.001) and a significant moderate correlation with serum calcium (rho = 0.687; p = 0.020). For pathological volume, Vp, there was a significant moderate correlation with serum calcium (rho = 0.732; p = 0.010). PBRPL shows a strong significant correlation with PBRSCT (rho = 0.909; $p < 0.001$). All the quantitative indices tested showed excellent interobserver agreement and reliability. Regarding the factors affecting quantitative indices in relation to patient demographics, comorbidities and use of calcium lowering agents, only gender was found to affect PBRSCT (p = 0.042). In terms of surrogate outcome, pre- and post-surgery disease severity marker was significantly different for serum calcium (p = 0.001) and serum PTH (p = 0.003).

Conclusion: Quantitative indices of parathyroid SPECT-CT significantly correlate with serum calcium and serum PTH. There is excellent interobserver agreement between all quantitative indices tested. The valuable significant difference of PBRSCT between genders also potentiates the vision of exploring the epigenetics of gender associated differences in the assessment of quantitative indices in ^{99m}Tc MIBI parathyroid scintigraphy, particularly pertaining to the pathogenesis of sporadic

parathyroid adenomas. Hence, this shows that parathyroid SPECT-CT can be utilized to increase objectivity and reliability in evaluating disease severity of primary hyperparathyroidism.

Key words: parathyroid SPECT-CT, parathyroid scintigraphy, hyperparathyroidism, quantitative indices, pathological volume.

CHAPTER 1

INTRODUCTION

1.1 Background and significance

Primary hyperparathyroidism (pHPT) was first described in the 1930s and is the third most common endocrine disorder (Wilhelm SM 2016). It is characterised by repeated elevations in total serum calcium levels accompanied by elevated PTH levels. It is caused by the autonomous hypersecretion of parathyroid hormone by abnormal parathyroid gland(s). pHPT is diagnosed biochemically. Whilst symptomatic pHPT patients have overt signs and symptoms that can be linked to the condition, such as nephrolithiasis, osteitis fibrosis cystica, peptic ulcers, and psychiatric/cognitive problems, patients with "asymptomatic" pHPT, on the other hand, have no disease-specific symptoms. Prior to the advent of regular serum calcium testing, most often than not, the clinical symptoms and signs were present prior to the diagnosis of pHPT. However, the current trend of detection in the diagnosis of pHPT precedes symptoms related to kidney and bone disease.

In both symptomatic and asymptomatic patients, pHPT is diagnosed biochemically. Primary hyperparathyroidism presents itself biochemically in two ways: hypercalcaemic pHPT and normocalcaemic pHPT. The former, the most commonly regarded manifestation of pHPT, is defined by serum calcium levels higher than the normal range with a concurrent abnormally raised PTH level. The "normocalcaemic pHPT" (NPHPT) form, on the other hand, is a new phenomenon described as incompletely defined variant with abnormally high PTH levels and normal total and ionised serum calcium levels (Sm *et al.*, 2016). The incidence of

NPHPT is unknown, but recent research suggests a low prevalence of 0.2-3.1 percent (Schini *et al.*, 2020).

1.2 Epidemiology

pHPT incidence increases with age, peaking between 50 and 60 years (Walker and Silverberg, 2018). However, it is known to occur at any age. Women are affected 3-4 times more than men. pHPT affects 50% of postmenopausal women, often in the first decade post menopause. The action of oestrogens on the skeletal system are known to counteract the hypercalcaemic effects of excess PTH in bone (Walker and Silverberg, 2018).

In many parts of the world, the way pHPT has been presented has altered over 50 years. Since the introduction of multichannel biochemical screening tests, the stage of pHPT diagnosis has evolved from symptomatic to asymptomatic, especially in the United States and Europe (Bilezikian *et al.*, 2014). The trend in the developed world and the developing world is quite different. While the former is experiencing an increase in incidence by four to fivefold as well as the appearance of asymptomatic disease, the latter is experiencing a shift in the disease spectrum from advanced symptomatic to less severe symptomatic disease (Bilezikian *et al.*, 2014).

An estimated 27.7 occurrences per 100,000 population in the United States arise annually, according to the latest available data. Females are three times more likely than males to be affected by the condition (Heath, 1991). pHPT is expected to affect 0.86 percent of the general population, according to prospective multicentred research conducted by Weber (Weber T 2013).

The prevalence of pHPT in Malaysia is only partially documented due to a scarcity of data. Roslani AC conducted a retrospective study involving 12 patients who

had parathyroidectomy for hyperparathyroidism between 2000 and 2005 (Roslani and Chang, 2006). Primary hyperparathyroidism was found in two of the twelve patients.

1.3 Management Of Primary Hyperparathyroidism

Hyperfunction in one or more parathyroid glands may lead to autonomous hormonal hypersecretion of pHPT, and it may stem from three possible distinct pathologic conditions: adenoma, hyperplasia, or carcinoma of the parathyroid glands. Single gland disease and multiglandular disease are the most convenient ways to categorise parathyroid pathology in a general way. Multiglandular disease (MGD) is collectively made up of double adenomas and hyperplastic glands. It has been stated that 6-33 percent of the population has MGD, and the weight of evidence shows that this rate is closer to 15 percent (Wilhelm SM 2016).

Pathophysiology of pHPT is associated with the loss of homeostatic control over the parathyroid hormone levels in the body. It is postulated that increased PTH production and secretion will result in increased PTH secretion by individual cells or enhanced parathyroid cell proliferation, despite the fact that each cell secretes the same amount of PTH. Parathyroid adenomas demonstrate lower than normal sensitivity to calcium's inhibitory impact, as opposed to the typical sensitivity of parathyroid gland to calcium (Walker and Silverberg, 2018).

Surgery is the only way to treat pHPT effectively. While a variety of medications can both increase bone mineral density and decrease calcium levels in the blood, none of them can do both. When it comes to increasing bone mineral density, lowering fracture risk, lowering the incidence of nephrolithiasis, and perhaps halting renal function loss, parathyroidectomy is a game changer. This game changer surgery

was performed successfully on a 34-year-old patient with osteitis fibrosa cystica by Felix Mandl way back in 1925 (Thompson, S, et al. 2015).

Asymptomatic patients with signs of subclinical end-organ involvement, as well as patients under the age of 50, are urged to have surgery under the current American Association of Endocrine Surgeons (AAES) guidelines (Sm *et al.*, 2016). According to the AAES guidelines, 85 percent of pHPT patients have a solitary adenoma that can be surgically removed resulting in a long-term cure. Parathyroid carcinoma, on the other hand, accounts for less than one percent of all instances (Sm *et al.*, 2016). Ruda et al., observed that solitary adenomas accounted for 88.9 percent of pHPT patients between 1995 and 2003, multiglandular disease accounted for 5.74 percent, double adenomas accounted for 4.14 percent, and parathyroid carcinomas accounted for 0.74 percent (Ruda JM 2005).

The pathogenesis of parathyroid adenoma stems from parathyroid hormone in surplus amounts, and is concentrated in the oxyphil cells of a parathyroid adenoma, which acts as the culprit lesion in 85 percent of cases in primary hyperparathyroidism. The question to be asked is, how is one to translate this quantitatively into pixel-based images, which can help the clinician on deciding on the ever-pertinent question: to resect or not to resect. To date, there is strong potential evidence on the value of quantitative indices and its association with disease severity markers which will be later iterated in the literature review section.

When removing the parathyroid gland, minimally invasive parathyroidectomy (MIP) is used. It requires a small incision (less than 2–3 cm in length) and gained popularity after preoperative imaging, particularly Sestamibi scintigraphy and ultrasound, was proven effective. MIP is defined by the following criteria, according to the AAES guidelines (Sm *et al.*, 2016):

- short incision length (for example, 3 cm)
- a focused extent of dissection (for example, typically only one gland is identified)
- employment of anaesthesia techniques (for example, local, regional, and/or general) that favour a brief hospital stay (for example, outpatient surgery)
- increased reliance on operative technology (for example, endoscopic) and adjuncts (for example, intra-operative PTH monitoring)
- and the routine use of preoperative imaging.

In this new age of minimally invasive surgery, the positive outcome of parathyroid surgery is contingent on the combination of a qualified surgeon and a sensitive and precise imaging tool. Parathyroid scintigraphy has a well-established role in separating functioning parathyroid tissue from other types of tissue, making it a useful imaging technique for the preoperative localisation of parathyroid adenomas. Conventional imaging techniques such as ultrasonography, CT, and magnetic resonance imaging (MRI) are still in use today, particularly in centres without nuclear medicine facilities. However, they have the limitation of being unable to distinguish between functional and non-functional tissue. Despite this, they produce images with exceptional resolution and contrast. Their accuracy generally varies from one modality to another. For example, ultrasound is operator-dependent and has a wide range of accuracy: sensitivities range from 36-76 percent; computed tomography is 46-76 percent; and magnetic resonance imaging (MRI) is 50-78 percent (Elgazzar, 2015). The radiopharmaceuticals ^{201}-thallium, ^{99m}Tc pertechnetate, ^{99m}Tc tetrofosmin, ^{99m}Tc MIBI, and ^{11}C-methionine positron emission tomography (PET) have all been

employed in nuclear medicine studies to date. However, ^{99m}Tc-MIBI SPECT- CT has extensively been studied to be superior to other modalities of imaging given the added value of functional imaging coupled with anatomical localisation. In a meta-analysis of 23 articles and 1236 patients, Treglia et al., reported an overall detection rate of 88 percent for both patient-based (95% CI = 84-92 percent) and lesion-based (95% CI= 82-92 percent) ^{99m}Tc-MIBI SPECT-CT for hyperfunctioning parathyroid glands in patients with pHPT (Treglia *et al.*, 2016).

1.4 Problem Statement

The maximum potential of ^{99m}Tc MIBI Parathyroid SPECT-CT is not fully utilised. Huang et al. (Im *et al.*, 2014) has demonstrated the usefulness of quantitative indices of parathyroid SPECT-CT in assessing disease severity of parathyroid adenoma. Subsequently, Cayir et al. (Çayir *et al.*, 2018) further ascertained positive correlations between disease severity markers of parathyroid adenoma with semiquantitative indices of ^{99m}Tc MIBI SPECT of dual phase parathyroid scintigraphy. Hitherto, no other study has reproduced any similar findings. In the local setting particularly, no study has looked beyond the anatomical localisation of parathyroid SPECT-CT, to provide additional quantitative measurements to the managing clinician.

1.5 Justification

With the advent of proposed quantitative indices in this study, parathyroid scintigraphy reporting can be fully utilised to add objectivity and reliability to qualitative interpretation in the diagnostic application of parathyroid scintigraphy.

Furthermore, correlations can be made between quantitative indices of parathyroid SPECT-CT and disease severity of primary hyperparathyroidism. Data collection of such kind in parathyroid scintigraphy SPECT-CT will be the first in Malaysia and South East Asia, utilising quantitative indices and disease severity to aid the management of pHPT. Furthermore, the data collected can be used to identify factors affecting quantitative indices in relation to the disease severity of pHPT. Thereby, these quantitative indices will increase the diagnostic confidence of nuclear medicine physicians in reporting parathyroid SPECT-CT scintigraphy.

CHAPTER 2

LITERATURE REVIEW

2.1 Normal Anatomy

The normal parathyroid gland weighs 20-50 mg (Sm *et al.*, 2016). The parathyroid glands are located behind the thyroid gland. In the pretracheal fascia, they are oval in shape and flattened.

The superior and inferior parathyroid glands derive from endodermal epithelial cells of the fourth and third pharyngeal pouches, respectively. Generally, patients have 4 parathyroid glands (2 superior and 2 inferior), however, in 13% of patients have extra glands. The position of the parathyroid glands varies depending on embryological descent.

Surrounding the cricothyroid junction, the superior glands are often embedded in the perithyroidal fascia or thyroid. Compared to superior glands, inferior glands tend have a lengthier embryological line of descent with more variability in their anatomical position. Minor parathyroids are located in the thyrothymic ligament and inferior parathyroids are located in the neck (undescended gland at carotid bulb) or mediastinum. In 1% of cases, intrathyroidal parathyroid glands are present.

The superior parathyroid glands are positioned posterior to the recurrent laryngeal nerve (RLN), most times 1-2 centimetres cranial to the junction of the RLN and the inferior thyroid artery, whereas the inferior parathyroid glands are anterior to the RLN.

Up to 22% of patients post parathyroidectomy, are found to have ectopic parathyroid glands, whereby embryonic migration causes them to be superior, inferior, or supernumerary in origin. However, ectopic anatomically includes the thymus, retro-

oesophageal, mediastinum, intrathyroidal, high cervical position, and carotid sheath (Sm *et al.*, 2016).

Abnormal supernumerary glands in adults, reported in up to 13% of cases, are usually surgically removed. The failure to precisely locate an ectopic parathyroid adenoma is the most common cause of a failed initial parathyroidectomy (Hindié *et al.*, 2021). Generally, parathyroid adenomas contain parathyroid chief cells and are encapsulated. Oxphilic or oncocytic adenomas are rare but it can cause pHPT (Petranović Ovčariček *et al.*, 2021).

2.2 Genetic Causes And Others

Genetic predisposition has been identified in 10% of pHPT cases, whereby they present themselves sporadically and hereditarily. Hereditary pHPT may arise in isolation or as part of a syndrome. The distinct feature of hereditary pHPT is early onset and higher rate of multiglandular involvement (Thakker RV, 2016). Autosomal dominant traits, namely CCND1 (cyclin D1) and MEN1 (menin) has been linked to sporadic parathyroid adenomas (Walker 2018). MEN1 tumour suppressor gene in multiple endocrine neoplasia type 1 syndrome and familial isolated primary hyperparathyroidism (FIHP); RET proto-oncogene in MEN 2A syndrome; CDKN1B in MEN 4 syndrome; inactivating mutations in CASR (which encodes the calcium-sensing receptor) in FIHP have all been associated genetically to pHPT.

Ionising radiation and chronic lithium use have been linked to pHPT. Radiation exposure is notably reported to increase the risk of pHPT when the source of exposure is during childhood. Lithium-associated pHPT is well documented in patients with bipolar disorders, whereby hypercalcaemia occurs in a quarter of patients (Ja, 2018).

Thereby it is justified for regular monitoring of hypercalcaemia in this subset of patients, of which the presentation is as a single adenoma or as multiglandular disease.

2.3 Pathophysiological Effects Of Excess Parathyroid Hormone

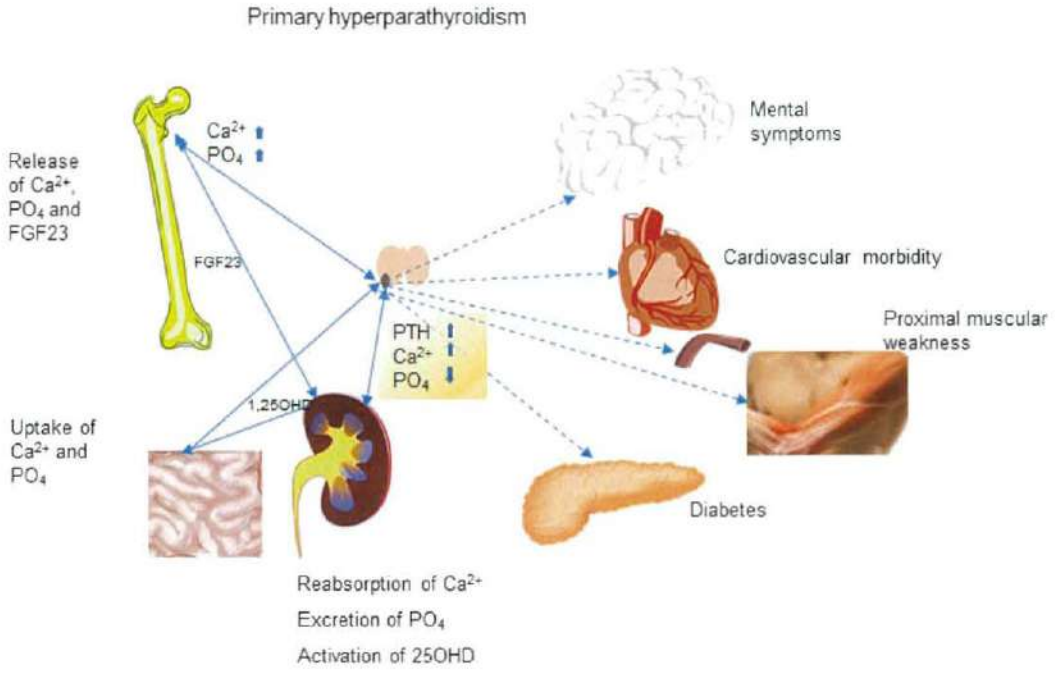

Figure 2.1 Pathophysiological effects of excess parathyroid hormone (PTH).

The dashed lines represent the less well-characterised relationships. Ca^{2+}: ionised calcium, PO_4^-: phosphate, 25OHD: inactive vitamin D, 1,25OH2D: activated vitamin D, FGF23: fibroblast growth factor-23. Journal of Internal Medicine, Volume: 285, Issue: 2, Pages: 149-164, First published: 05 October 2018, DOI: (10.1111/joim.12840)

The parathyroid glands are triggered by low serum calcium levels, by releasing the 84-amino acid peptide molecule parathyroid hormone. Calcium-sensing receptors (CASR) of parathyroid cells respond to serum calcium levels and are stimulated with a rise (hypocalcaemia) or fall (hypercalcaemia) of PTH. The direct action of PTH is on the bone and kidney, which leads to a rise in calcium levels. PTH acts on the osteoclasts to resorb bone, activating calcium and phosphorus influx into the

bloodstream. On the other hand, in the kidneys, PTH counteracts to reduce calcium clearance and triggers the production of 1,25-dihydroxyvitamin D, which thereafter causes a rise in the intestinal movement of calcium and phosphorus, as shown in Figure 2.1.

Normally functioning parathyroid glands act to keep a balanced homeostasis of the serum calcium levels within a tightly controlled range. They synthesise and store parathyroid hormone, which is triggered to be secreted when hypocalcaemia ensues in the body. Prolonged hypocalcaemia leads to cellular replication and further increased mass of the glands. There is an inherent negative feedback mechanism within the parathyroid glands to inhibit PTH release via calcium and 1,25-dihydroxyvitamin D. A solitary normal gland is sufficient to provide adequate levels of PTH and maintain the balance of normal calcium levels.

2.4 Secondary And Tertiary Hyperparathyroidism

On the other hand, secondary and tertiary hyperparathyroidism are biochemically distinct. Secondary hyperparathyroidism is characterised by increased PTH in response to hypocalcaemia and a low or normal serum calcium level usually caused by vitamin D deficiency, malabsorption, kidney disease or hypercalciuria. Some patients with secondary hyperparathyroidism have hypercalcaemia and are later diagnosed with pHPT after correcting the underlying condition, such as vitamin D deficiency. Tertiary hyperparathyroidism is prolonged, severe secondary hyperparathyroidism (as in end-stage renal disease) that advances into hypercalcaemia due to the autonomous functioning of hyperplastic parathyroid glands (Sm *et al.*, 2016).

2.5 Symptoms And Diagnosis

Clinical manifestations involving multiple systems are stated below (Ovčariček et al., Sm et al., 2016; Walker & Silverberg, 2018):

- Musculoskeletal: Bone disease & bone pain secondary to bone fractures weakened by osteopenia, osteoporosis or osteitis fibrosa cystica, Brown tumours/cysts, muscle aches, weakness, fatigue.
- Renal: Nephrocalcinosis, nephrolithiasis with attendant pain & obstructive uropathy, chronic renal insufficiency & renal function abnormalities leading to polyuria & secondary polydipsia.
- Gastrointestinal: Abdominal pain, constipation, nausea, vomiting, peptic ulcers, pancreatitis & gallstones.
- Neurocognitive: Depression, lethargy, seizure, anxiety, depression, cognitive dysfunction, nervousness, mild emotional disturbances, frank psychosis.
- Cardiac: Aortic &/or mitral valve calcifications, hypertension.

2.6 Disease Severity And Target Organ Effects

Disease severity is used as a term to characterise the impact that a disease process has on the utilisation of resources, comorbidities, and mortality (Gambert, 2013). In this study, disease severity markers, namely serum parathyroid hormone, serum corrected calcium and serum creatinine were used due to their distinct role in the pathophysiology of primary hyperparathyroidism. Previous literature supporting the use of these disease severity markers is explored further on in this chapter.

2.6.1 Renal Effects

Parathyroidectomy is warranted when distinct evidence of end-organ effects on the kidney surfaces. These renal end-organ effects comprise of renal calculi,

nephrocalcinosis and impaired renal function as evidenced by decreased GFR and concentrating capacity. The incidence of renal stones is reported to be between 20-50% (Sm *et al.*, 2016). Silent nephrolithiasis or nephrocalcinosis should also be kept in mind, which can be detected by renal imaging such as plain radiograph or ultrasound kidney, ureter, and bladder. A successful parathyroidectomy is associated with a decreased risk of developing new renal calculi. Albeit the fact that renal insufficiency and pre-existing nephrocalcinosis do not resolve, surgery may avert pHPT-related decline in GFR and lower the possibility of new renal calculi. The sustained impact of pHPT is ceased by surgery (Tassone *et al.*, 2015). Presence of renal complications of pHPT is a robust indication for parathyroidectomy. In addition, a decrease in GFR to <60 ml/min which accounts for derangement of renal function, are also an indication for surgical intervention (Sm *et al.*, 2016).

2.6.2 Skeletal Effects

Parathyroidectomy is also warranted when there is clear evidence of end-organ effects on the skeleton, typically causing a deterioration in BMD. This occurs mainly at the cortical bone sites, namely the distal third of radius. Increased cortical porosity has been reported on bone histomorphometry. Even mild pHPT adversely affect trabecular bone, as shown by high-resolution peripheral quantitative computed tomography and trabecular bone score (TBS) analysis of DXA lumbar spine images. Both symptomatic and asymptomatic patients benefit from parathyroidectomy in terms of bone mineral density, whereby the porosity of cortical bone is reversed and cancellous bone volume is increased (Sm *et al.*, 2016).

In a few controlled cohort studies, reduced fracture rates have been associated with curative parathyroidectomy. This advantage extends to not only those who have severe bone disease. A retrospective cohort study found the risk to be

reduced post parathyroidectomy regardless of the baseline bone morphometry, be it, normal, osteopenic or osteoporotic bone (VanderWalde, 2009). The evidence is clear that parathyroidectomy improves bone mineral density and bone microarchitecture. AAES guidelines recommend strongly with high quality evidence that all pHPT patients with a history of osteoporotic fracture (fragility fracture or vertebral compression fracture clinically or on vertebral imaging) or osteoporosis by BMD testing (defined as a T score < -2.5 at any site) should opt for parathyroidectomy (Sm *et al.*, 2016).

2.7 Outcome Of Parathyroidectomy

Outcomes or endpoints are defined as variables which are assessed during the course of a study to measure the impact of a particular intervention or exposure to the health of a given population (Ferreira and Patino, 2017). Some distinctive illustrations are clinical worsening of symptoms, cure and mortality.

Primary outcome is a patient-centred variable which is often looked at, as it involves the patient, such as quality of life and survival. There are also surrogate outcomes, which are typically biomarkers which are continuous variable that represent clinical outcome. Surrogate outcomes present themselves ahead of the clinical outcome, thus inadvertently reducing costs, study duration and size (Ferreira and Patino, 2017).

Parathyroidectomy is clearly the definitive therapy for pHPT. The majority of patients who are subject to parathyroidectomy are symptomatic. The dilemma is that those who are asymptomatic may not end up having definitive surgery. Zanocco et al. investigated the age of diagnosis and its impact on treatment decisions in sporadic asymptomatic pHPT cases whereby they compared treatment options of monitoring,

pharmacological therapy, and parathyroidectomy. They found that the optimal treatment strategy for life expectancies ranging from 6 months to 75 years. Patients with a predicted life expectancy of 5 years (outpatient parathyroidectomy) or 6.5 years (inpatient parathyroidectomy), parathyroidectomy was found to be more cost-effective. On the contrary, in patients with a shorter life expectancy, observation was the most cost-effective strategy. Interestingly, at any age modelled, pharmacological therapy was not found to be cost-effective (Zanocco K, 2008).

2.8 Role Of Biochemical Screening

On retesting of serum calcium, levels can sporadically fall into the normal range, still befitting the diagnosis of pHPT as long as a 'recurrent pattern' of hypercalcaemia is apparent. Inappropriately abnormal levels of PTH (>20 pg/ml) with hypercalcaemia is the typical feature of pHPT. On the contrary, non-parathyroid causes of hypercalcaemia (such as malignancy or granulomatous disease) are associated with suppressed levels of PTH.

An 'intact' second-generation PTH assay or a third-generation assay can be used to quantify PTH levels. Assays for PTH (1–84), PTH (7–84), and other long C terminal fragments are now available. Fragment contribution to PTH measurement is insignificant, other than in the case of renal failure. Unlike first-generation assays, intact assays can unfailingly differentiate pHPT from hypercalcaemia of malignancy. In addition to the main circulating form of PTH (1–84), the newer third-generation PTH assays detect a second PTH (1–84) molecule thought to have a post-translational modification.

2.9 Role Of Imaging

Preoperative imaging is critical prior to minimally invasive parathyroidectomy to avoid unnecessary exploration of all the parathyroid glands. To do so, the surgeon must work in tandem with the nuclear medicine physician and radiologist to identify the abnormal parathyroid lesion.

Ultrasound, four-dimensional computed tomography (4D-CT) and MRI are all options. The most cost-effective technique is 4D CT or sestamibi imaging (Petranović Ovčariček et al.,2021). The benefits of cervical ultrasound are low cost, no ionising radiation, and the ability to examine the thyroid for concomitant pathology, which the radiologist can conveniently do prior to surgery or by the surgeon during surgery. However, evaluating retro-oesophageal or mediastinal lesions is complex and is highly operator dependent.

^{99m}Tc-MIBI is the utmost frequently used radiopharmaceutical in parathyroid scintigraphy. Mediastinal or retro-oesophageal parathyroid glands can be detected using sestamibi and single photon emission computed tomography (SPECT). However, multiglandular disease sensitivity is low (Raruenrom *et al.*, 2018). 4D CT has improved sensitivity anatomic detail over traditional CT. Four gland hyperplasia should be investigated when more than a single parathyroid gland is enlarged. Venous sampling and MRI are options for cases requiring re-surgery or difficult localisation. Preoperative parathyroid fine-needle aspiration is rarely performed, as FNA biopsy can result in malignant-looking trabecular scarring, necessitating more extensive surgical resection.

At the moment, the preferred imaging modality in cases of false-negative SPECT parathyroid scintigraphy are new PET tracers as stated below (Petranović Ovčariček *et al.*, 2021):

- N – ^{18}F-fluoromethyl-2-hydroxy-N
- N-dimethylethanaminium (^{18}F-FCH or ^{18}F-fluorocholine) PET-CT
- L[methyl^{11}C] methionine (^{11}C-MET) PET-CT
- ^{11}C-2-hydroxy-N,N,N trimethylethanamium (^{11}C-CH) PET-CT
- 4D-CT
- MRI
- ^{18}F-fluorocholine PET-4D-CT
- ^{18}F-fluorocholine PET-MRI

False-negative results are frequently caused by small hyperfunctioning glands or a deficiency of oxyphil cells (Melloul M, 2001) parathyroid hyperplasia, multiglandular disease, and high expression of P-glycoprotein (Petranović Ovčariček *et al.*, 2021). Maximum standardised uptake values (SUVmax) and mean standardised uptake values (SUVmean) serve as distinct quantitative measures of parathyroid lesions detectability in PET imaging. However, disadvantages associated with these tracers include high expenses, availability due to a lack of on-site cyclotrons (especially with carbon-11 tracers), and probable uptake by inflammatory lymph nodes and thyroid nodules, which can present as false positive findings (Petranović Ovčariček *et al.*, 2021). Furthermore, the stark contrast between PET-CT and SPECT-CT technological advancements is notable, given that the present trend in molecular imaging is toward the use of PET-CT. Given the obvious cost and availability constraints, and the fact that not every molecular imaging centre has ready-to-use PET-

CT technology, the availability of SPECT-CT should be maximised to the best extent possible.

2.10 Management Of Primary Hyperparathyroidism

The goal of optimum medical therapy in pHPT is to normalise serum calcium and PTH levels, urine calcium excretion, enhance bone mineral density (BMD), and lower the risk of fractures and renal calculi. Approximately one-third of people who do not have surgery develop symptomatic pHPT. Patients who opt against surgery are recommended to undergo annual serum calcium, PTH, vitamin D, creatinine, glomerular filtration rate, 24-hour urine tests, and routine DEXA scans every 1–2 years with their endocrinologist or primary-care physician (Sm *et al.*, 2016). Because of the danger of aggravating hypercalcemia and hypercalciuria, calcium consumption is encouraged, and vitamin D replacement done with caution. The target is 25(OH)-vitamin D levels to rise to 20-30 ng/ml (50–75 nmol/l). Medications such as calcimimetics and bisphosphonates have been utilised to lower serum calcium and increase bone mineral density. Alendronate has been shown to improve BMD in the lumbar spine and hip while lowering bone turnover markers in those with pHPT. The use of calcimimetics and bisphosphonates in combination therapy appears to meet the goals of lowering serum calcium levels as well as stabilising BMD (Walker and Silverberg, 2018). Surgical management, however, is more effective and less expensive in the long run than pharmaceutical therapy, and it is still the preferred curative treatment.

2.11 Quantitative Based Parathyroid Imaging With SPECT-CT

To date, there are few aforementioned studies on the quantitative measurement of parathyroid nuclear imaging. One of the earliest studies in 2004 explored the idea

of quantitative measurement, whereby the concept of specific uptake size index (SUSI) for parathyroid adenoma quantification using subtraction methods of ^{123}I-iodide from MIBI images was explored (Fleming JS 2004). SUSI was defined as the specific uptake in the object divided by the concentration per unit volume (or area for 2D imaging) in the reference region (or average body concentration).

More recently, a valuable retrospective Korean study by Im et al. found parathyroid SPECT-CT using ^{99m}Tc MIBI to be helpful in the evaluation of underlying functional state and disease severity of parathyroid adenoma. It has shown parathyroid adenoma uptake to background ratio on parathyroid planar scan (PBRPL), parathyroid adenoma uptake to background ratio on parathyroid SPECT-CT (PBRSCT) and metabolic volume of parathyroid adenoma (Vm) on parathyroid SPECT-CT were found to be significantly correlated with serum iPTH and calcium levels. This paper is our primary reference for the quantitative indices (Im *et al.*, 2014). The reason being the protocol used by Im et al. for parathyroid SPECT-CT using ^{99m}Tc MIBI is similar to the protocol used in our centre.

Listewnik et al. conducted a prospective investigation including 40 patients in which the tumour to background ratios in the 10th and 120th minutes were determined (TBR10 and TBR120) using planar acquisition. The results were compared to the results of histological analysis (Listewnik *et al.*, 2017). TBR10 to TBR120 showed a high correlation coefficient in the parathyroid adenoma and parathyroid hyperplasia groups was observed with $r = 0.867$ and $r = 0.964$, respectively. PTH, ionised calcium and phosphate levels were measured and statistically significant correlation were found between medians of PTH concentration and parathyroid histopathological results ($p = 0.01$). Additionally, they discovered that parathyroid tumours had a higher TBR in semi-quantitative analysis. This study concluded that the washout technique

in ^{99m}Tc MIBI scintigraphy effectively detects parathyroid lesions (cancer, adenoma, hyperplasia, normal tissue of the parathyroid) pre-operatively (Listewnik *et al.*, 2017).

Cayir et al.(Çayir *et al.*, 2018) demonstrated in a retrospective study assessing the relationship of semiquantitative parameters from ^{99m}Tc MIBI dual-phase parathyroid SPECT images and disease severity in pHPT in 93 patients with histopathological confirmed parathyroid adenoma. In their study, there was a positive correlation between the weight of adenoma and serum PTH and serum calcium levels ($p < 0.001$), early parathyroid-thyroid counts (PT-T) and serum calcium ($p=0.027$), late parathyroid-thyroid counts (PT-T) with the weight of the adenoma ($p=0.04$) as well as parathyroid SPECT counts with serum calcium levels ($p = 0.046$). Moreover, their findings showed that serum calcium levels were significantly higher in patients with early parathyroid (PT) SPECT values above 116 (Çayir *et al.*, 2018).

Thereafter, two studies have evaluated the role of quantitative standardised uptake value (SUV) measurement of ^{99m}Tc MIBI in Parathyroid SPECT-CT. One retrospective study involving 39 patients, measured the max and mean SUV at 10 minutes (early) and 2 hours (delayed) post injection of ^{99m}Tc MIBI on SPECT-CT. Parathyroid adenoma was found to have significantly higher quantitative parameters (SUV) ($p < 0.0001$) than reference thyroid tissue in early and delayed phases of ^{99m}Tc MIBI SPECT-CT (Lee 2018).

Another retrospective study by Robin P et al. investigated the use early and delayed reconstructed SPECT-CT images with the maximum SUV of parathyroid adenomas and thyroid tissue. They calculated the washout rate of parathyroid adenomas and thyroid tissue. This quantitative analysis of 53 patients revealed a higher initial absolute uptake and slower rate of washout of MIBI in parathyroid adenomas than in thyroid tissue (Robin P 2019). However, these two studies did not correlate the

quantitative imaging measurements to primary hyperparathyroidism biochemical markers such as serum parathyroid hormone or serum calcium.

In this era of precision medicine, whereby patient-tailored treatment is key to managing diseases clinically, our study hopes to explore the quantitative parameters which can enhance the diagnostic accuracy and confidence in reporting by using an objective assessment method. The great advantage of molecular imaging in this form of personalised medicine is its ability to merge physiologic and metabolic data with clinical phenotypes and provide inestimable information guiding further management and treatment.

CHAPTER 3

OBJECTIVES

3.1 General objectives

To assess the value of quantitative indices of ^{99m}Tc MIBI parathyroid SPECT- CT, in relation to disease severity and outcome.

3.2 Specific objectives

a) To correlate between quantitative indices of parathyroid SPECT-CT and the disease severity in primary hyperparathyroidism.

b) To compare interobserver variation in measuring quantitative indices.

c) To identify if factors such as patient demographics, comorbidities and use of calcium lowering agents affect quantitative indices.

d) To assess the outcome of parathyroidectomy on disease severity markers by assessing the improvement of these parameters after an intervention.

3.3 Research Hypothesis

a) Null Hypothesis: There are no statistically significant differences between the quantitative indices of parathyroid SPECT-CT and the disease severity of primary hyperparathyroidism.

b) Alternative Hypothesis: There are statistically significant differences between the quantitative indices of parathyroid SPECT-CT and the disease severity of primary hyperparathyroidism.

CHAPTER 4

MATERIALS AND METHODS

4.1 Study Design

This retrospective cohort study was conducted in the Nuclear Medicine Unit, Department of Biomedical Imaging, University of Malaya Medical Centre (UMMC).

4.2 Study Duration And Location

The study population was derived from records of patients who had parathyroid SPECT-CT scans obtained from UMMC's picture archiving and communication system (PACS) image database. The study included records from patients above 18 years of age, who were referred for biochemically proven primary hyperparathyroidism with positive parathyroid scintigraphy findings.

4.3 Inclusion And Exclusion Criteria

4.3.1 Inclusion Criteria

a) Age > 18 years old

b) Clinical and biochemical evidence of primary hyperparathyroidism, according to the American Association of Endocrine Surgeons Guidelines (AAES) for Definitive Management of Primary Hyperparathyroidism (Strong Recommendation) (Sm *et al.*, 2016) with positive parathyroid scintigraphy findings and underwent surgery.

c) Underwent planar ^{99m}Tc MIBI parathyroid scan and SPECT-CT examination.