ADDED VALUE OF ^{99m}TC-SESTAMIBI SPECT/CT OVER DUAL PHASE PLANAR SCINTIGRAPHY IN PATIENTS WITH HYPERPARATHYROIDISM IN HOSPITAL PULAU PINANG

BY

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries, which have been duly acknowledged. I declare that I have no financial interest in the instruments or materials used in this study.

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"Verily, with hardship comes ease." –Holy Quran, 94:5.

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LIST OF ABBREVIATIONS

Abbreviations	
CaSR	Calcium-sensing receptor
CT	Computed tomography
HPP	Hospital Pulau Pinang
HPT	Hyperparathyroidism
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PHPT	Primary hyperparathyroidism
PPV	Positive predictive value
PTH	Parathyroid hormone
SHPT	Secondary hyperparathyroidism
SPECT	Single photon emission computed tomography
SPECT/CT	Single photon emission computed tomography/Computed tomography
US	Ultrasonography

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ABSTRAK

Latar belakang: Kajian ini adalah bertujuan untuk membandingkan kelebihan ^{99m}Tc-Sestamibi planar, SPECT dan SPECT/CT dalam lokalisasi kelenjar paratiroid yang berhiperfungsi sebelum pembedahan.

Metodologi: Kajian ini melibatkan analisisasi data retrospektif yang dijalankan terhadap 22 orang pesakit yang layak dengan bukti hiperparatiroidisme secara biokimia dan menjalani ^{99m}Tc-Sestamibi SPECT/CT dari 1 September 2019 sehingga 31 Mac 2021 di Hospital Pulau Pinang. Sensitiviti, spesifikasi, nilai ramalan positif (NRP) dan nilai ramalan negatif (NRN) dikira mengikut formula standard. Keselarasan prestasi diagnostik antara planar, SPECT dan SPECT/CT dianalisis menggunakan ujian Fleiss' kappa.

Keputusan: Sensitiviti, NRP dan NRN adalah tertinggi bagi SPECT/CT; 100%, 90.4% dan 100% mengikut turutan masing-masing, diikuti dengan SPECT (sensitiviti 89.5%, NRP 89.5% dan NRN 33.3%) dan paling rendah bagi planar (sensitiviti 84.2%, NRP 88.8% dan NRN 25.0%). Semua teknik penggambaran menunjukkan spesifikasi yang sama iaitu 33.3%. Analisis Fleiss kappa menunjukkan terdapat keselarasan sederhana bagi prestasi diagnostik antara planar, SPECT dan SPECT/CT, $\kappa=0.573$ (95% CI, 0.332 to 0.815), $p < 0.001$.

Konklusi: SPECT dan SPECT/CT menunjukkan kelebihan yang signifikan dalam kelenjar paratiroid yang berhiperfungsi sebelum pembedahan, terutamanya bagi kelenjar yang berada lebih belakang. SPECT/CT juga menunjukkan kelebihan tambahan bagi kes yang perlahan dalam pembasuhan tiroid dan terutamanya penting dalam perancangan pembedahan.

ABSTRACT

Purpose: This study aims to investigate the added value of ^{99m}Tc-Sestamibi SPECT and SPECT/CT for pre-operative localisation of hyperfunctioning parathyroid glands.

Methods: Retrospective data analysis was performed on 22 eligible patients with biochemical evidence of hyperparathyroidism who underwent ^{99m}Tc-Sestamibi SPECT/CT from 1st September 2019 to 31st March 2021 in Hospital Pulau Pinang and had a histopathological diagnosis of surgically excised lesions. The imaging findings were compared to histopathological examination as reference standard. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated according to standard formulas. Agreement of diagnostic performance between planar, SPECT and SPECT/CT was analysed by Fleiss kappa test.

Results: Sensitivity, PPV, and NPV were the highest in SPECT/CT; 100%, 90.4% and 100% respectively, followed by SPECT (sensitivity 89.5%, PPV 89.5% and NPV 33.3%) and the lowest in planar (sensitivity 84.2%, PPV 88.8% and NPV 25.0%). All imaging techniques showed the same specificity (33.3%). Fleiss' kappa analysis showed that there was a moderate overall agreement of diagnostic performance between planar, planar with SPECT and planar with SPECT/CT, $\kappa=0.573$ (95% CI, 0.332 to 0.815), $p < 0.001$.

Conclusion: SPECT and SPECT/CT have significant incremental diagnostic value over planar scintigraphy in the pre-operative localisation of hyperfunctioning parathyroid glands, particularly in posteriorly located glands. SPECT/CT has also shown additional benefit in cases with slow thyroidal washout and especially crucial for surgical planning.

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

9.1 Overview of parathyroid gland

Parathyroid hormone (PTH) is essential for controlling the homeostasis of ionised calcium and phosphate. It is synthesised, stored, and secreted by the chief cells of the parathyroid gland.

Classically, there are superior and inferior parathyroid glands bilaterally, each measuring roughly 6 × 3 mm and weighing around 35 to 40 mg. They are commonly located along both thyroid lobes. Embryologically, the superior parathyroid glands descend alongside the thyroid from the dorsal aspect of the fourth pharyngeal pouch. Approximately 75% of the superior parathyroid glands are located posterior to the thyroid midpoles and 25% posterior to the upper poles of the thyroid, and superior to the inferior thyroid artery. The inferior glands migrate caudally with the thymus after developing from the third pharyngeal pouch's dorsal side. Compared to the superior glands, the inferior glands' final location is more diverse because of their protracted descent. Along the descent pathway, they might be found anywhere in the neck or mediastinum (Taterra et al., 2019). They are most frequently located adjacent to the lower pole of the thyroid. The superior and inferior parathyroid glands can be distinguished by their relation to the recurrent laryngeal nerve. The inferior glands are located anteriorly while the superior glands are located posteriorly to the recurrent laryngeal nerve. Supernumerary glands exist in 13% of the general population, in which they may have between 5 to 8 parathyroid glands. Some individuals may have only 3 parathyroid glands, which occur in less than 3% of cases (Petranović Ovčariček et al., 2021).

The term “ectopic parathyroid gland” is used for aberrant parathyroid glands that descend to an unusual location (O’Malley and Ziessman, 2021). It is estimated that up to 20% of the general population has ectopic parathyroid glands (Patrinos et al., 2019; Phitayakorn and McHenry, 2006). They can be found anywhere along the migratory route from the bifurcation of carotid artery to the pericardium. The most common locations for ectopic superior parathyroid gland are along the tracheoesophageal groove, retroesophageal area or in the posterior mediastinum. The ectopic inferior parathyroid glands are most commonly located intrathymus, followed by the anterior mediastinum and intrathyroidal location (Phitayakorn and McHenry, 2006).

The parathyroid glands are supplied mainly via the inferior thyroid artery and drain into the thyroid plexuses. The lymphatic drainage is to the paratracheal or deep cervical nodes. They receive innervation from branches of the cervical ganglia (Chen et al., 2013).

The parathyroid gland is made up predominantly of chief cells, oxyphil cells and rarely, water-clear cells. The calcium-sensing receptor (CaSR) on the surface of the cell membrane of the main cells plays an important function in calcium homeostasis by "sensing" the extracellular calcium concentration, and consequently alters the release of PTH (Tfelt- Hansen and Brown, 2005). In response to various phases of the secretory cycle, they undergo morphologic alterations. The oxyphil cells are thought to evolved from the chief cells either as a result of ageing or metabolic derangement. They are abundant in mitochondria, and their function is yet unknown (Tudela et al., 2010). The function of water-clear cells is also not well understood. Their existence is linked to parathyroid hyperplasia or parathyroid adenoma and may indicate a hyperfunctioning gland (Chen et al., 2013).

9.2 Overview on hyperparathyroidism

PTH stimulates the specific receptor-mediated responses in cells in a variety of target organs which include the bones, kidneys, brain, and digestive tract, to maintain ionised calcium and phosphate within the normal range (van der Plas et al., 2020). In the event of low circulating ionised calcium, PTH is released into extracellular space and helps to restore the normal level of calcium concentration by 3 major functions:

- i Stimulation of bone resorption to release skeletal calcium into the bloodstream by binding on its receptor on osteoclasts
- ii Inhibits phosphate reabsorption in the proximal renal tubule and stimulates calcium reabsorption in the distal tubule
- iii Increases the activity of the renal 1-hydroxylase, which produces 1,25-dihidroxyvitamin D and boosts calcium and phosphorus absorption from the intestine.

The resulting increased serum calcium from these effects acts on the CaSR expressed by the chief cells of the parathyroid gland via a classic endocrine feedback loop, thus decreasing the secretion of PTH (Chen et al., 2013; Fraser, 2009; van der Plas et al., 2020).

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcaemia and the third most common endocrine disorder. In PHPT, one or more incompletely regulated parathyroid glands secrete excessive PTH in the absence of known external stimulus, resulting in hypercalcaemia. About 90% of cases are caused by a solitary parathyroid adenoma, with gland hyperplasia (about 6%) and multiple adenomas (about 4%) occurring less commonly. Parathyroid carcinoma accounts for < 1% of cases. Compared to men, women have a 2 to 3 times higher risk of being affected, and the incidence rises with age (Bunch and Kelly, 2018). Most patients are asymptomatic and detected to have incidental hypercalcaemia in other studies. Symptoms and clinical signs are often due to chronic hypercalcaemia rather than raised PTH. The most common presenting illness in 20 – 30% of patients with symptoms is nephrolithiasis (Fraser, 2009). The only definitive management is parathyroidectomy. It is indicated for symptomatic patients and should be considered for patients who are asymptomatic. Minimally invasive parathyroidectomy and bilateral exploration are both effective and appropriate surgeries (Wilhelm et al., 2016). However, minimally invasive parathyroidectomy is recommended since it is more efficient, less complication and safer (Sackett et al., 2002). For a successful minimally invasive parathyroidectomy, pre-operative imaging for localisation is a pre-requisite (Bunch and Kelly, 2018).

Secondary hyperparathyroidism (SHPT) occurs as a response to hypocalcaemia, where the CaSR acts by increasing the secretion of PTH. This state of relative or absolute SHPT is transient under normal circumstances. However, hypocalcemia can happen when the PTH can no longer correct plasma calcium due to organ failure or a decrease in the availability of serum calcium. At this point, patients may have symptoms and signs related to hypocalcaemia and longstanding raised PTH (Fraser, 2009). Chronic renal disease (CKD) is the most common cause of SHPT. In CKD, hyperphosphataemia occurs because of excretion failure in the proximal tubule and also due to failure of kidney to synthesise 1,25-dihidroxyvitamin D. The parathyroid glands synthesize and secrete more PTH in response to prolonged exposure to hyperphosphataemia, hypocalcaemia, and elevated levels of fibroblast growth factor (FGF)-23 brought on by compromised renal function. This results in hyperplastic parathyroid tissue that is initially polyclonal and then monoclonal (van der Plas et al., 2020). Management of SHPT is predominantly pharmaceutical with vitamin D supplements, phosphate binders and calcimimetics. Parathyroidectomy is reserved for patients with severe hyperparathyroidism who have not responded to medical treatment (Bak Leong Goh et al., 2018). Compared to parathyroidectomy for PHPT, pre-operative imaging is not a standard of care in SHPT.

Unfortunately, these patients have a significant rate of persistent or recurrent disease after parathyroidectomy. Early surgical failure with the persistent disease may occur in 5%–10% of patients, and at 5 years, recurrence rate reaches 20%–30% (Taïeb et al., 2013). The main reason for surgical failure is inadequate intraoperative identification and removal of all hyperplastic parathyroid glands. In such patients, preoperative imaging is paramount to correctly localize all parathyroid tissues prior to re-operation. Parathyroid scintigraphy, alone or in combination with neck ultrasound, may be useful for pre-operative localisation prior to initial parathyroidectomy in SHPT, according to several publications from both nephrologists and surgeons (De La Rosa et al., 2008; Fuster et al., 2006; Périé et al., 2005).

After prolonged SHPT, tertiary hyperparathyroidism develops when the parathyroid glands become independent and cease to respond to physiologically negative feedback from serum calcium levels. It is characterised by hypercalcaemic hyperparathyroidism, which is similar to PHPT. Tertiary hyperparathyroidism, unlike PHPT, occurs because of external stimulus, commonly due to chronic kidney disease. According to both "Kidney Disease—Improving Global Outcomes (KDIGO) Chronic Kidney Disease—Mineral Bone Disease" (CKD-MBD) (Ketteler et al., 2017) and 1st Malaysian Chronic Kidney Disease-Bone Mineral Disorder (CKD-BMD) and Parathyroidectomy (Bak Leong Goh et al., 2018) guidelines, parathyroidectomy is recommended in this case.

9.3 Overview of parathyroid imaging

The only goal of parathyroid imaging is to identify the hyperactive gland(s) before surgery. As hyperparathyroidism is diagnosed based on a biochemical profile, parathyroid imaging plays no part in either confirming or excluding the diagnosis (Morris et al., 2022). It is recommended by the American Head and Neck Society (AHNS) Endocrine Section for both operative (Zafereo et al., 2019) and re-operative (Stack et al., 2018) planning in PHPT. Patients who have negative or ambiguous parathyroid imaging results are often still candidates for surgery, but they most likely need bilateral neck exploration rather than minimally invasive procedure (Zafereo et al., 2019). The most widely used imaging techniques are neck ultrasound and radionuclide parathyroid imaging. The clear advantage of radionuclide parathyroid imaging over neck ultrasound is better identification of the ectopic parathyroid gland and posteriorly located upper parathyroid gland (Petranović Ovčariček et al., 2021).

According to recent American College of Radiology (ACR) appropriateness criteria, US parathyroid, multiphase CT neck (4DCT parathyroid), planar ^{99m}Tc-Sestamibi dual phase with and without SPECT or SPECT/CT as well as dual tracer parathyroid scintigraphy with SPECT or SPECT/CT neck are indicated in secondary and tertiary hyperparathyroidism as initial imaging to direct the surgical strategy (Zander et al., 2021).

In the recent European Association of Nuclear Medicine (EANM) parathyroid imaging guidelines, a combination of ^{99m}Tc-Sestamibi dual phase parathyroid scintigraphy with SPECT/CT and neck ultrasound by an experienced sonographer is accepted as a first-line strategy. Subtraction parathyroid scintigraphy is a good alternative option. F18-choline analogues PET imaging has shown superior diagnostic performance in small cohort studies and when it is accessible, may be taken into consideration as a viable alternative first-line approach. When first-line imaging yields negative or inconclusive results, second-line imaging procedures are recommended. These include 4DCT parathyroid, C11-Methionine PET imaging, MRI neck and a combination of F18-choline PET and 4DCT. Invasive diagnostic procedures such as selective venous sampling and arteriography should remain as last resort (Petranović Ovčariček et al., 2021).

This research is carried out in Hospital Pulau Pinang (HPP), a tertiary hospital in the Northern part of Malaysia. It is equipped with an endocrine surgery unit. All patients with hyperparathyroidism will undergo neck ultrasound and parathyroid scintigraphy as first-line imaging for pre-operative localisation. The routine protocol for parathyroid scintigraphy in HPP is a single tracer dual phase study using ^{99m}Tc-Sestamibi. A previous study in this centre comparing single tracer dual phase and dual tracer subtraction parathyroid scintigraphy has shown that single tracer dual phase protocol has better sensitivity (77.3%) than dual tracer subtraction protocol (sensitivity 27.3%) (Saburinah et al., 2015). The dual phase protocol has been adopted as routine since then as it is more sensitive, simpler, cost-effective and convenient for patients and staff.

9.4 ^{99m}Tc-Sestamibi dual phase parathyroid scintigraphy

^{99m}Tc-Sestamibi is a lipophilic cation member of the isonitrile family (Hexakis 2-methoxyisobutyl isonitrile) that localises and is retained in mitochondria. It accumulates more in parathyroid tissue owing to the mitochondrial-rich oxyphil cells, and the uptake is more avid with higher oxyphil cells content. Other factors influencing ^{99m}Tc-Sestamibi uptake and retention in parathyroid tissue include vascular supply and capillary permeability, cell cycle phase, serum calcium level, as well as expression of P- glycoprotein and multidrug resistance (MDR) protein. Parathyroid tissue has greater ^{99m}Tc-Sestamibi uptake and longer retention compared to thyroid tissue. These two criteria make ^{99m}Tc-Sestamibi a favourable tracer for dual-phase imaging. The conundrums of this technique are rapidly washout parathyroid adenoma which might be attributed to the expression of P-glycoprotein, and slow thyroidal washout, especially in concurrent thyroid pathology. The Society of Nuclear Medicine and Molecular Imaging (SNMMI) has suggested that early SPECT/CT may improve sensitivity in case of rapidly washout parathyroid adenoma (Greenspan et al., 2012). For slow thyroidal washout, the subtraction technique may be helpful.

The incorporation of SPECT/CT into parathyroid scintigraphy for pre-operative evaluation for primary hyperparathyroidism has been reported to have superior diagnostic performance in a few studies. In 24 patients with primary hyperparathyroidism, the effectiveness of SPECT/CT was compared with planar ^{99m}Tc-Sestamibi scintigraphy, SPECT, and conventional imaging (ultrasound and computer tomography) (Kim et al., 2012). SPECT/CT has shown significantly better sensitivity (100%) than planar, SPECT and conventional imaging (62.5%, 75% and 70.8%, respectively) in patient-based analysis in detecting parathyroid adenoma. Wong et al. reported in the meta-analysis on 1276 patients that SPECT/CT has estimated pooled sensitivity of 81% and superior to SPECT (74%) and planar (70%). SPECT/CT outperformed SPECT and planar imaging in detecting and localising ectopic parathyroid glands (Wong et al., 2015).

In 2019, Assante et al. compared the diagnostic performance of planar ^{99m}Tc-Sestamibi parathyroid scintigraphy and SPECT/CT on forty-six patients with primary hyperparathyroidism. They demonstrated that the addition of SPECT/CT has superior sensitivity compared to planar ^{99m}Tc-Sestamibi parathyroid scintigraphy (97% and 63%, respectively) (Assante et al., 2019).

In a study by Tawfik et al., 60 patients with primary hyperparathyroidism were subjected to both neck ultrasound and ^{99m}Tc-Sestamibi parathyroid scintigraphy with SPECT/CT for pre-operative localisation. SPECT/CT alone demonstrated 83% sensitivity which is higher compared to ultrasound alone (76%). In 48 patients with pathologically proven parathyroid adenoma, 8 cases were detected during surgery and missed by SPECT/CT, and 10 cases were missed by neck ultrasound. All 8 false negative SPECT/CT cases were attributed to small size adenoma. Comparatively, just 6 cases were missed with combination of both SPECT/CT parathyroid scintigraphy and neck ultrasonography. The addition of neck ultrasound was reported to be useful in cases with less tracer retention (Tawfik et al., 2019).

It is still uncertain when to perform SPECT/CT. All studies mentioned above were acquired with delayed-phase SPECT/CT. In a direct comparative study, Lavely et al. demonstrated that early SPECT/CT with a combination of any delayed method has the highest sensitivity (72-73%) and is superior to delayed SPECT/CT (Lavely et al., 2007). However, later studies have used SPECT/CT with higher specifications and demonstrated higher sensitivity (> 80%) with dual phase planar and delayed SPECT/CT (Assante et al., 2019; Tawfik et al., 2019; Wong et al., 2015). Delayed SPECT/CT imaging was also able to identify hyperfunctioning parathyroid tissue in 14 patients with concurrent thyroid disease and negative planar scintigraphy (Assante et al., 2019). A recent comparative study in 35 patients with any type of hyperparathyroidism has shown that dual-phase SPECT/CT in both early and delayed phases has the highest sensitivity (100%) compared to a single-phase SPECT/CT (either early or delayed) and dual-phase SPECT (Lee et al., 2020).

In context of secondary hyperparathyroidism, parathyroid scintigraphy is less sensitive. A meta-analysis by Caldarella et al. showed that the sensitivity of ^{99m}Tc-Sestamibi planar scintigraphy for detecting hyperplastic glands and diffuse or nodular hyperplasia in these patients was only 58%. They concluded that ^{99m}Tc-Sestamibi planar scintigraphy should not be used as the first diagnostic imaging technique for localisation of hyperplastic parathyroid glands before surgery in SHPT (Caldarella et al., 2012).

In 2016, a study by Yuan et al. on 60 end-stage renal failure patients who underwent pre-operative imaging with ^{99m}Tc-Sestamibi SPECT/CT and neck ultrasound showed that the combination of both imaging modalities has superior sensitivity (93%) than to SPECT/CT (85%) and neck ultrasound alone (81%) (Yuan et al., 2016). In a retrospective cohort study on 569 patients with secondary hyperparathyroidism, they compared the sensitivity, specificity and consistency of planar parathyroid scintigraphy and SPECT/CT. They concluded that SPECT/CT may improve the overall sensitivity (80.4% in SPECT/CT and 66.3% in planar) and consistency of pre-operative localisation of eutopic parathyroid glands, and it can detect ectopic parathyroid accurately without sensitivity improvement (Zeng et al., 2019).

Our region has not yet had a local consensus regarding the most appropriate imaging to use for pre-operative localisation in primary hyperparathyroidism. Regarding secondary hyperparathyroidism, the CKD-BMD and parathyroidectomy guidelines (Bak Leong Goh et al., 2018) did not include pre-operative imaging as a pre-operative assessment.

9.5 Problem statement

Although it has been demonstrated that the combination of SPECT and SPECT/CT to 99mTc-Sestamibi scintigraphy improves sensitivity in identifying parathyroid pathology, this procedure is not standard in nuclear medicine facilities in Malaysia. SPECT/CT is only recently added to the parathyroid scintigraphy protocol in HPP since September 2019 after a SPECT/CT scanner is available and is yet to be proven in local settings to offer additional value in pre-operative localisation for patients with hyperparathyroidism.

9.6 The rationale of this study

Incorporating SPECT/CT in routine parathyroid imaging will provide incremental value over planar parathyroid scintigraphy in the pre-operative localization of hyperfunctioning parathyroid tissue in patients with hyperparathyroidism. The improved sensitivity in parathyroid scintigraphy will allow better identification of parathyroid pathology. This information will be helpful to surgeons to perform successful parathyroidectomy for patients and minimising the likelihood of re-operation.

Characteristics of patients with hyperparathyroidism referred for parathyroid scintigraphy in our institution may differ from other study populations. Hence, the diagnostic performance of 99mTc-Sestamibi planar parathyroid scintigraphy, SPECT and SPECT/CT may also be different from other studies. Information regarding the diagnostic performance of a test is crucial to guide surgeons/clinicians in selecting appropriate imaging modalities for their patients.

CHAPTER TWO

OBJECTIVES

10.1 General Objective

To investigate the added value of ^{99m}Tc-Sestamibi SPECT and SPECT/CT compared to planar imaging for pre-operative localisation of hyperfunctioning parathyroid glands.

10.2 Specific Objectives

i To determine the diagnostic accuracy of planar, SPECT and SPECT/CT dual phase parathyroid scintigraphy for pre-operative localisation of hyperfunctioning parathyroid glands using histopathological examination as reference standard.

ii To assess the agreement between planar, SPECT and SPECT/CT in detecting hyperfunctioning parathyroid glands.

10.3 Alternative Hypothesis

There is good agreement between planar, SPECT and SPECT/CT in detecting hyperfunctioning parathyroid glands.

10.4 Null Hypothesis

There is no agreement between planar, SPECT and SPECT/CT in detecting hyperfunctioning parathyroid glands.