Optimising the Surgical Management of Secondary and Tertiary Hyperparathyroidism: A Meta-analysis and Examination of Management and Outcomes in the Western Sydney Local Health District (WSLHD)

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FRACS MBBS BMedSci

A thesis submitted in fulfilment of the requirements for the degree of Master of Philosophy

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2024

Statement of Originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work.

This thesis has not been submitted for any degree or other purposes.

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Abstract

Secondary hyperparathyroidism (SHPT) and tertiary hyperparathyroidism (THPT) are common sequalae of chronic kidney disease associated with significant morbidity and mortality, due to their metabolic and cardiovascular effects. When refractory to medical treatment, surgical parathyroidectomy is the treatment of choice. Due to their multi-gland disease nature, success in surgery can be challenging. Failure to identify and remove all pathological parathyroid glands may result in persistent or recurrent hyperparathyroidism, which is difficult to manage. Reoperative surgery is challenging due to increased perioperative morbidity. Preoperative localisation imaging help identify locations of pathological parathyroid glands. However, there is no strong evidence for the diagnostic test accuracy (DTA) of localisation imaging for SHPT and THPT to guide clinical decision-making.

WSLHD serves a large cohort of renal dialysis and renal transplant patients and the referral for parathyroidectomy for SHPT and THPT are centralised to two of the major hospitals within the health district. There are currently no local guidelines for the indications and timing of referral for parathyroidectomy. There have also been no studies assessing the local performance of preoperative localisation imaging, rate of persistent or recurrent disease and other surgical outcomes. An understanding of the WSLHD experience in surgical management and outcomes would provide insight into how we can optimise the quality of care for SHPT and THPT patients in WSLHD.

The aim of this thesis is to systematically review and meta-analyse the DTA of preoperative localisation imaging for SHPT and THPT, and to provide evidence for the clinical choice of preoperative localisation imaging.

We also aim to evaluate the WSLHD experience of referral practice, choice and performance of preoperative localisation imaging, and other aspects of surgical management and outcomes for patients with SHPT and THPT.

Acknowledgement

I would like to thank my supervisors Professor Henry Pleass and Associate Professor Tony Pang for their time, patience and advice. I would not have been able to complete this thesis without their support.

I would like to acknowledge the co-review author Dr George Liang for working with me on the systematic review and meta-analysis portion of the thesis as a second author, extracting and validating data.

Funding

No funding was sought for the research presented in this thesis.

List of Abbreviations

AAES	American Association of Endocrine Surgeons
ALP	alkaline phosphatase
ATSI	Aboriginal and Torres Strait Islanders
BMD	bone mineral density
Ca	corrected serum calcium
CI	confidence interval
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease–mineral and bone disorder
Cr	creatinine
CaSR	calcium-sensing receptor
CT	computerised tomography
DTA	diagnostic test accuracy
eGFR	estimated glomerular filtration rate
ESRD	end stage renal disease
EVOLVE	Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events
FGF-23	fibroblast growth factor 23
FN	false negative
FP	false positive
HREC	Human Research Ethics Committee
ICG	indocyanine Green
ioPTH	intraoperative parathyroid hormone
IV	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LCA	latent class analysis
LOS	length of stay
MIBI	Technetium ^{99m}Tc sestamibi
MRI	magnetic resonance imaging
PBS	Pharmaceutical Benefits Scheme
PET	positron emission tomography
PHPT	primary hyperparathyroidism
PO4	Phosphate
PROSPERO	International Prospective Register of Systematic Reviews
PTH	parathyroid hormone
QUADAS 2	Quality Assessment Tool for Diagnostic Accuracy Studies 2
RLN	recurrent laryngeal nerve
SD	standard deviation
SHPT	secondary hyperparathyroidism
SPECT/CT	single proton emission computerised tomography/computerised tomography
SPTX	subtotal parathyroidectomy

SROC	summary receiver operating characteristic
THPT	tertiary hyperparathyroidism
TN	true negative
TP	true positive
TPTX	total parathyroidectomy
TPTX + AT	total parathyroidectomy with autotransplantation of parathyroid
US	ultrasound
WSLHD	Western Sydney Local Health District
4D CT	Four-dimensional computerised tomography

Chapter 1: Introduction

Secondary and tertiary hyperparathyroidism: Scope of the problem, national and in WSLHD

According to the Australian Institute of Health and Welfare, 1.1% of Australians of all ages (264,900 people) had kidney disease in 2020 – 2021. The prevalence increases significantly with age, with 2.6% in 65-74 years and 5.0% in 75 years and over. 77.8% of patients with kidney disease had at least one other comorbidity. Prevalence was highest amongst the socio-economically disadvantaged population groups, in particular Aboriginal and Torres Strait Islanders (ATSI).[1]

WSLHD is one of the largest health districts in Sydney, Australia (Population 1,144,280 in 2021) and services some of the most socio-economically disadvantaged populations in Sydney, 4% of whom are identified as ATSI in comparison to 1.7% in Greater Sydney. WSLHD services one of the largest cohorts of renal dialysis and renal transplant patients in Australia, including a significant proportion of socio-economically disadvantaged patients.[2]

Hyperparathyroidism is a common sequelae of chronic kidney disease (CKD). There are two types of hyperparathyroidism in CKD, namely secondary hyperparathyroidism (SHPT) and tertiary hyperparathyroidism (THPT). SHPT and THPT are present in about 50% of patients with Stage 3 or 4 CKD and more than 90% of patients with end stage renal disease (ESRD).[3] SHPT and THPT are associated with significant morbidity and mortality, due to their cardiovascular effects, effects on bone metabolism and other metabolic effects. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines 2017 recommend that patients with Stage 3 CKD undergo screening for SHPT, and parathyroidectomy is recommended for those with severe hyperparathyroidism refractory to medical or pharmacological therapy.[4] KDIGO also recommends that renal transplant candidates refractory to medical therapy should undergo parathyroidectomy before transplantation, and renal transplanted patients with THPT should follow the same principle of management as those with SHPT.[5] This is because parathyroidectomy has consistently been shown to improve the life expectancy and quality of life for CKD patients with SHPT and THPT who fail medical treatment.[6] [7]

Secondary and tertiary hyperparathyroidism: Aetiology

Normal calcium and phosphate homeostasis is maintained through the interactions of a few key hormones, including parathyroid hormone (PTH), 1,25-dihydroxycholecalciferol (calcitriol), and bone derived fibroblast growth factor 23 (FGF23). When serum calcium level falls, PTH is released from the parathyroid glands through the activation of the calcium-sensing receptor (CaSR). PTH restores calcium homeostasis through (1) increasing bone resorption, thus releasing calcium into the blood stream; (2) increasing the conversion of 25-hydroxyvitamin D to its active form 1,25-dihydroxyvitamin D in renal tubular cells by activating the renal CYB27B1 enzyme; (3) increasing the renal reabsorption of calcium and excretion of phosphate; (4) increasing gastrointestinal absorption of calcium and phosphate

secondary to the effect of calcitriol. When serum calcium level normalises, the CaSRs are silenced and PTH values normalise. When serum phosphate level increases in an individual with normal renal function, FGF-23 promotes renal excretion of phosphate by binding to the FGFR (FGF receptor)1-Klotho complex and decreases gastrointestinal absorption of phosphate by decreasing CYP27B1 activity and therefore calcitriol synthesis. FDG-23 also suppresses the synthesis of calcitriol in the kidney both in a Klotho-dependent fashion through the FGFR1-Klotho complex and in a Klotho-independent fashion through FGFR3 and FGFR4. PTH and FGF-23 interact through a negative feedback loop, where PTH stimulates FGF23 synthesis in bone and FGF23 supresses PTH production in the parathyroids through binding of an FGFR-Klotho complex and subsequent activation of the MAPK pathway or a calcineurin-dependent signalling pathway. [3 8]

In patients with CKD, the kidneys fail to excrete phosphate, leading to an increased serum phosphate level and subsequently FGF-23 level. This along with reduced production of calcitriol by the kidneys lead to hypocalcaemia, which then triggers the secretion of PTH by the parathyroid glands. The usual compensatory mechanism to reduce PTH level once calcium level normalises does not work well in CKD, in particular due to decreased kidney Klotho expression and resistance to FGF-23, and development of PTH resistance. Parathyroid glands therefore are under constant stimulation and become hyperplastic and enlarged.[3]

The development of parathyroid hyperplasia is characterised by four stages, as shown in Figure 1.

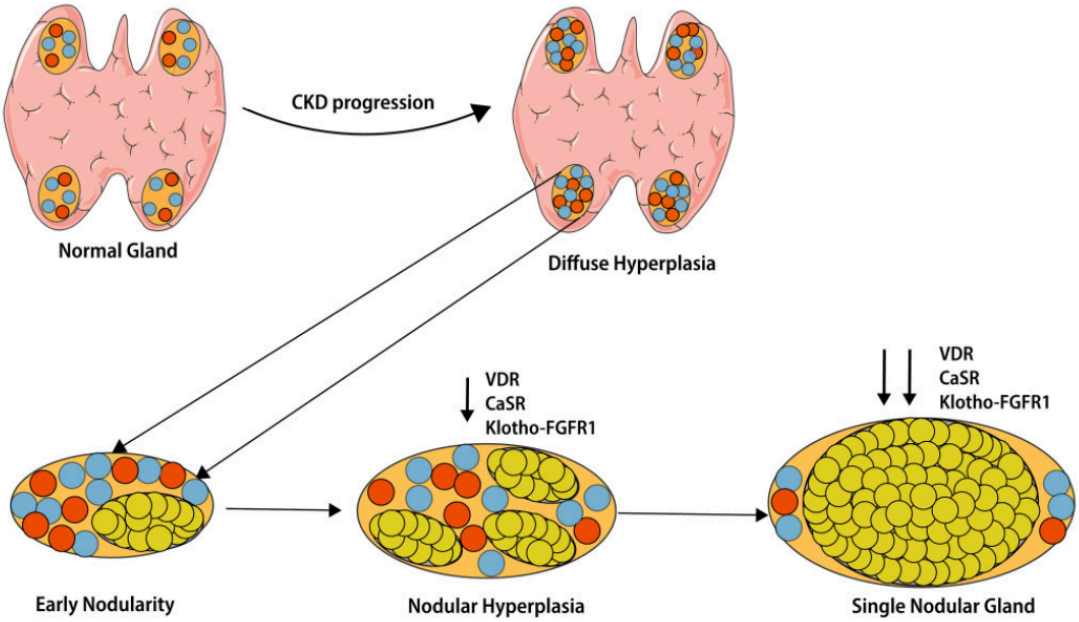

Figure 1 Four stages of parathyroid hyperplasia development in renal hyperparathyroidism: diffuse hyperplasia, early nodularity, nodular hyperplasia, and single nodular gland [3]

In patients that have had longstanding SHPT, the hyperplastic parathyroid glands can become nodular and become autonomous in PTH secretion. PTH levels remain high despite increasing serum calcium level, therefore leading to hypercalcaemia and THPT. THPT may also be considered by some clinicians as SHPT that persists after successful renal

transplantations. Regardless, both SHPT and THPT tend to be multi-glandular disease affecting all four parathyroid glands.[9]

Secondary and tertiary hyperparathyroidism: Complications

SHPT and THPT have significant metabolic consequences, including renal osteodystrophy and cardiovascular disease, that can lead to increased morbidity and mortality if left untreated.

Renal osteodystrophy in CKD is composed of a group of mineral and bone disorders due to mineral metabolism dysregulation. They can be either low turn-over bone disease such as osteomalacia or high bone turn-over bone disease such as osteitis fibrosis cystica. Clinically renal osteodystrophy can manifest as bone pain, pathological fractures, or symptomatic brown tumours. Brown tumours are localised regions of fibrous tissue formation in areas of bone loss secondary to longstanding bone resorption. They are often associated with significant pain and can lead to pathological fractures.[9] (Figure 2)

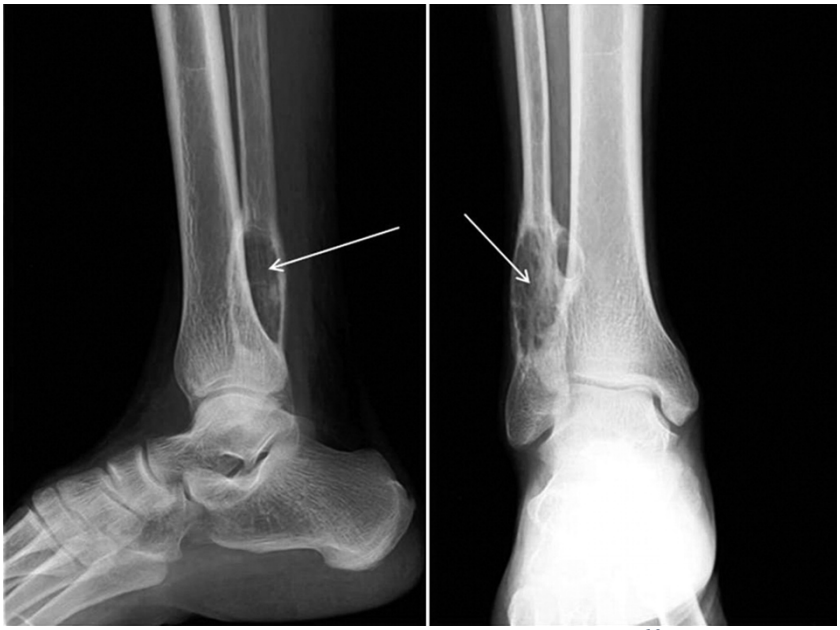

Figure 2 Xray of foot showing a brown tumour. [10]

The derangement in calcium and phosphate may also lead to vascular calcification in the macro- and micro-vascular system, including coronary arteries. Coronary vascular calcification increases risk of cardiovascular events and deaths.[9]

A rarer but devastating complication of SHPT is calciphylaxis, also known as calcific uremic arteriolopathy. This is characterised by painful skin lesions or soft tissue masses caused by arteriolar calcification leading to tissue ischaemia and infarction with or without ulceration. The damaged kidneys don't excrete phosphate properly, which results in a build-up of phosphate in the blood that combines with calcium. Serum calcium can also increase as a result of elevated PTH in SHPT, further contributing to the formation of calcification in small

vessels. Arteriolar calcification leads to thrombus formation, vascular occlusion, tissue ischaemia and subsequent infarction.[11] (Figures 3 and 4)

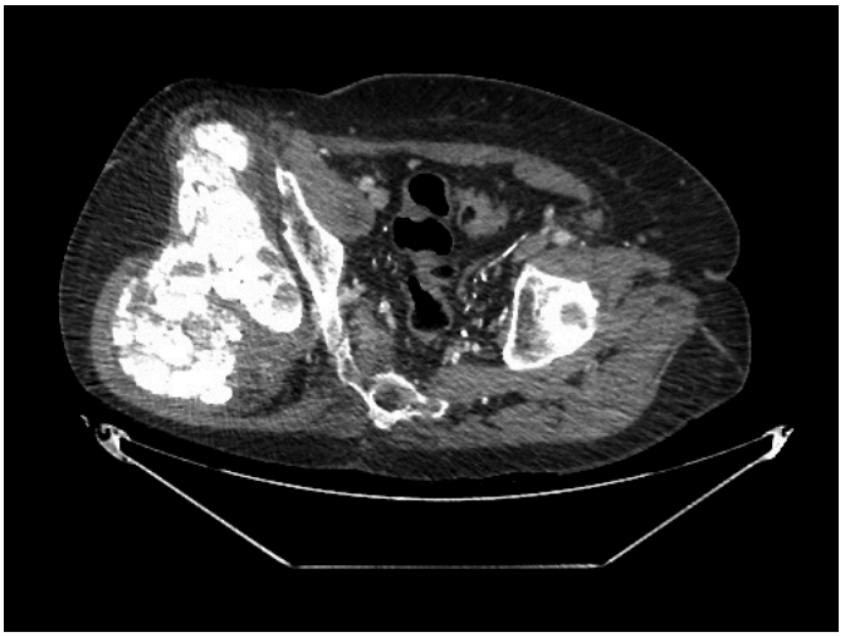

Figure 3 Radiograph of the right hip showing soft tissue tumoral calcinosis.[9]

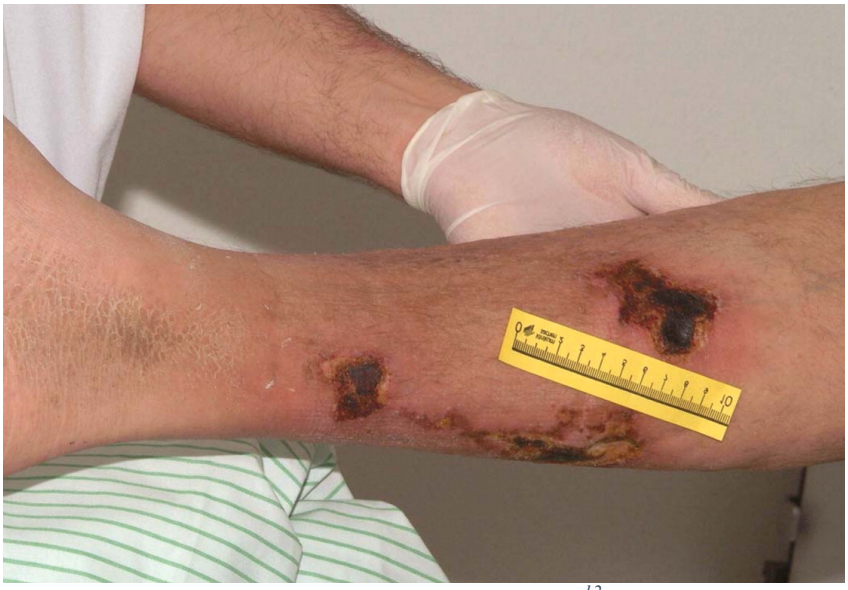

Figure 4 Cutaneous calciphylaxis. [12]

Markers for disease severity can also be broadly categorised into clinical, biochemical and radiological. Clinical markers include symptoms and signs such as pruritis, bone pain, pathological fractures, brown tumour, and calciphylaxis. Biochemical markers include corrected serum calcium, phosphate, alkaline phosphatase (ALP) and PTH level. Radiological markers include Bone Mineral Density (BMD), findings related to renal

osteodystrophy on other bone scans such as brown tumour, imaging findings of vascular calcifications or soft tissue tumoral calcinosis.

Secondary and tertiary hyperparathyroidism: Treatment options

Medical therapy

First line therapy for SHPT is medical, aiming to normalise serum phosphate and calcium levels through diet restrictions and medications.

Low phosphate diet and phosphate binders

The Western diet is rich in phosphate from meat, dairy products and phosphate additives. Patient education is important in helping them to avoid phosphate-rich foods.

Phosphate binders aim to reduce serum phosphate and PTH levels by binding to dietary phosphate and reducing absorption.

Vitamin D analogs

Treatment with Vitamin D supplement is often necessary as Vitamin D deficiency is a main drive behind PTH elevation in SHPT.

Calcimimetics

Cinacalcet is a calcimimetic agent that increases the sensitivity of parathyroid glands to extracellular calcium, and therefore suppresses PTH secretion. In 2012, the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial found that cinacalcet did not significantly reduce overall or cardiovascular mortality, and that it was less cost effective than surgical parathyroidectomy.[13] In Australia, cinacalcet was removed from the Pharmaceutical Benefits Scheme listing in August 2015 due to findings from the EVOLVE trial and relisted in February 2020. Jones et al. demonstrated an increase in the number of parathyroidectomies for CKD after the delisting of cinacalcet in comparison to the time prior to its delisting, associated with significant perioperative morbidity due to the older age and comorbid state of the local patient population.[14]

Surgical treatment

The indications for parathyroidectomy for SHPT and THPT have been described in recent international clinical guidelines. Parathyroidectomy can significantly improve patient symptoms, reduce all-cause mortality, and improve health-related quality of life. In patients with THPT, studies have shown that parathyroidectomy leads to lower rates of kidney graft failure than cinacalcet, therefore should be considered as the treatment of choice for

preservation of graft function.[8 15 16] The KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) recommends parathyroidectomy if SHPT or THPT is refractory to medical treatment. The American Association of Endocrine Surgeons (AAES) Guidelines for Definitive Surgical Management of Secondary and Tertiary Renal Hyperparathyroidism recommends referral for parathyroidectomy in patients with SHPT if they fail medical therapy, have complications due to hyperparathyroidism, or prefer surgery. AAES recommends parathyroidectomy for patients with THPT within 12 months post-kidney transplant or if there is hypercalcemic THPT.[4 5 8]

Surgical approaches

The three most common surgical approaches for parathyroidectomy in SHPT and THPT are total parathyroidectomy (TPTX) alone, TPTX with autotransplantation of parathyroid gland (TPTX + AT), and subtotal parathyroidectomy (SPTX). TPTX involves removing all four parathyroid glands. TPTX + AT involves removing all four parathyroid glands and autotransplanting a portion of the most normal appearing parathyroid gland. SPTX involves removal of 3.5 parathyroid glands, leaving half a gland in its usual anatomical position with intact vasculature.

Studies show comparable results between SPTX and TPTX + AT for treating hyperparathyroidism.[17] A network meta-analysis done by Hou et al. demonstrated that TPTX + AT and SPTX are superior to TPTX alone in terms of incidence of postoperative hypocalcaemia. Hou et al. also showed that there is a higher rate of recurrent hyperparathyroidism after SPTX compared to TPTX and TPTX + AT. SPTX may have a slightly lower risk of postoperative hypoparathyroidism compared to TPTX + AT in the immediate postoperative period, given the time required for the autotransplanted portion of the parathyroid gland to revascularize and become functional in TPTX + AT. Overall, TPTX + AT is the recommended surgical approach by Hou's group based on the network meta-analysis, with SPTX being a reasonable alternative.[18]

Transcervical thymectomy can be performed in conjunction with SPTX, TPTX + AT, or TPTX without AT. Reports show that 5-30% of patients with secondary or tertiary hyperparathyroidism have supernumerary parathyroid glands and 12% to 39.3% of patients have ectopic glands. Most commonly these supernumerary or ectopic glands reside in the thymus, as a potential location for persistent or recurrent disease. Some surgeons choose to perform bilateral transcervical thymectomy as a result, others perform ipsilateral transcervical thymectomy if an ipsilateral parathyroid gland is not identified intraoperatively.[8]

Surgical considerations

A four-gland exploration should be performed systematically to allow inspection of all four parathyroid glands and complete or partial resection of all enlarged glands depending on whether a TPTX or SPTX is pursued. This forms the basis of a successful surgery for SHPT and THPT. Embryologically the superior parathyroid glands descend from the fourth pharyngeal pouch along with the thyroid gland and the inferior parathyroid glands descend from the third pharyngeal pouch along with the thymus. Ectopic glands can therefore be

located anywhere along the median line of migration from the mandibular angle to the mediastinum. The inferior parathyroid glands have a greater likelihood to be found in ectopic locations due to their longer embryologic line of descent.

During a four-gland exploration, a midline incision is made along Langer's line followed by raising of superior and inferior subplatysmal flaps. The midline raphe of strap muscles is then opened, and strap muscles are retracted laterally to expose the thyroid gland. Medial and anterior rotation of the thyroid is required to allow exploration for the superior and inferior parathyroids. The middle thyroid vein usually needs to be divided during this step. The superior parathyroids are usually situated posterior to the superior pole of the thyroid gland, superior to the inferior thyroid artery, and posterolateral to the recurrent laryngeal nerve (RLN). The inferior parathyroids are usually located in close association to the inferior pole of the thyroid, inferior to the inferior thyroid artery and anteromedial to the RLN. If the parathyroids cannot be found in their usual location, further exploration of ectopic locations for the glands is performed, including the tracheoesophageal groove, paraesophageal space, retroesophageal space, carotid sheath, thyrothymic tract or cervical thymus. Other ectopic sites include within the thyroid, mediastinum, or undescended parathymus higher up in the neck. Cervical thymectomy can be considered if an ipsilateral parathyroid gland cannot be identified despite thorough exploration as mentioned previously. A hemithyroidectomy can be considered if there is suggestion of an intrathyroidal parathyroid gland on preoperative imaging, intraoperatively if a subcapsular intrathyroidal parathyroid gland is evident, or in selected cases where one or more ipsilateral parathyroid glands cannot be found. [19] [20]

Intraoperative adjuncts

Intraoperative adjuncts can be used to aid the identification of parathyroid tissue. Frozen section analysis is widely used intraoperatively for primary hyperparathyroidism (PHPT), SHPT and THPT to confirm the presence of parathyroid tissue. It does not always however discern adenoma from hyperplasia, or normal from abnormal parathyroid glands.[8] There can also be a delay in the return of results depending on the laboratory. Probe radioguidance with preoperative injection of Technetium 99-m as a radioisotope or fluorescence imaging for on-table direct visualisation of parathyroid tissue using near-infrared light, with or without injection of indocyanine green (ICG), are both useful for the intraoperative identification of parathyroid tissue, including in ectopic locations. Probe radioguidance has been shown to decrease overall operative time and have a high sensitivity making it a reliable substitute for frozen section analysis.[21] [22] Fluorescence imaging has also been shown to have a high sensitivity of 83% - 92%.[23] [24] [25] [26] Intraoperative PTH (ioPTH) monitoring has become a standard for parathyroidectomy for PHPT in many international centres to help with the confirmation of removal of the hyperfunctioning parathyroid adenoma/s. Currently there are mixed conclusions from studies regarding its usefulness in SHPT and THPT, particularly in terms of setting the appropriate threshold for ioPTH for predicting successful surgery. One major factor contributing to such limitations is the impaired metabolic clearance of PTH in patients with CKD.[8] [27]

Although the roles of the more novel intraoperative adjuncts in four-gland exploration for SHPT and THPT are not as well established as they are in PHPT, more studies are becoming available evaluating their potential benefits, especially given the challenges with identifying

and removing all pathological parathyroid glands in the context of the multiglandular disease process in SHPT and THPT.

Timing of referral from onset of dialysis

The disease process of SHPT and THPT usually starts once patients develop advanced CKD, with the commencement of dialysis being an appropriate surrogate marker. Despite the publication of international guidelines for the surgical management of SHPT and THPT, including indications, there is limited literature looking at the time to referral for surgical treatment from onset of dialysis, and its impact on disease severity and surgical outcomes. A survey by Zhang et al. of members of Dutch societies of nephrology, endocrinology, and surgeons with interest in endocrine surgery demonstrated considerable disagreement in treatment preferences, in terms of medical management versus surgical management, in a number of representative cases involving patients with variable age, PTH, serum calcium, phosphate, 25 (OH) Vitamin D levels, optimised by vitamin D supplementation and phosphate binders.[28] Understanding WSLHD's local experience of preoperative disease severity for patients undergoing parathyroidectomy for SHPT and THPT, time from dialysis to time of referral for surgical treatment, and potential correlations, may help identify areas for optimisation in terms of referral practice.

Preoperative localisation imaging

Role of preoperative localisation imaging

The role of preoperative localisation imaging in helping to identify adenomatous parathyroid gland/s prior to parathyroidectomy for PHPT has been well established. Systematic reviews and network meta-analysis have been done to compare the accuracy of various imaging modalities and provide evidence for choices of imaging modalities.[29] The role of preoperative localisation imaging, however, has not been well established for SHPT and THPT. Most clinicians would agree that it is necessary to perform preoperative imaging, usually in the form of a neck ultrasound, prior to four-gland surgical exploration for SHPT and THPT to exclude co-existing thyroid pathology that may need to be resected along with the parathyroids. However, the role for preoperative localisation imaging to identify and localise the hyperplastic parathyroid glands is more controversial. The rationale for not relying on preoperative localisation imaging was that SHPT and THPT were four-gland disease that would require four-gland exploration regardless of imaging findings, and there was little evidence regarding accuracy of various localisation imaging modalities in SHPT and THPT.

In the last decade, with the advancement of localisation imaging, more studies have become available in the literature evaluating the accuracy of localisation imaging modalities for SHPT and THPT, showing promising results. More importantly, more studies have shown that the incidence of supernumerary and ectopic glands in patients with SHPT and THPT is higher than previously thought and has been reported to be up to 37% and 45% respectively, which poses significant operative challenges in finding all four-glands and contributes to postoperative persistent and recurrent disease. [30] [31] [32] [33] [34] The incidence of persistent or

recurrent SHPT and THPT postoperatively can range between 10 to 30%.[35] Persistent or recurrent hyperparathyroidism in an already surgically explored neck and in a comorbid CKD patient can be very challenging to manage. Medical therapy is an option but often fails, and reoperative surgery is associated with higher morbidity, particularly the risk of RLN palsy. RLN palsy can lead to voice hoarseness and aspiration risks if unilateral, or requirement for tracheostomy if bilateral albeit a rare occurrence. Whilst there is no literature directly investigating the rate of RLN palsy for reoperative surgery in SHPT and THPT, Hiramitsu et al. demonstrated that during the index four-gland exploration for SHPT, patients with RLNs firmly adhered to parathyroid glands had a total RLN palsy rate, combining temporary and permanent palsies, of 17.6% compared to 5.3% in patients without adhesion.[36] As a reference, Jeannon et al. showed in a systematic review of RLN palsy post- initial thyroidectomy a temporary RLN palsy rate of 9.8% and a permanent RLN palsy rate of 2.3%, with a combined rate of 12.1%.[37]

With the advancement in the accuracy of preoperative localisation imaging modalities, they may be able to help identify not only the abnormal parathyroid glands in normal anatomical positions, but more importantly those in ectopic locations, and therefore help to guide surgical exploration. This may help reducing the incidence of persistent or recurrent disease, and their associated morbidity, mortality, and re-operative risks. A study by Andrade et al. demonstrated that preoperative Technetium ^{99}Tc Sestamibi scan identified 69.7% of ectopic parathyroid glands located in the mediastinal and thymic regions, which may otherwise not have been identified intraoperatively.[34] However, there is a lack of systematic review or meta-analysis of available literature to systematically evaluate and directly compare the accuracy of preoperative localisation imaging for SHPT and THPT and enable quality evidence-based practice when it comes to choosing the right imaging modality or modalities. There is also a gap in more recent literature evaluating the direct impact of preoperative localisation imaging on the surgical outcomes for SHPT and THPT, given most studies on DTA of preoperative localisation imaging are not designed to directly assess its impact on surgical success or outcomes, for example by comparing a patient group receiving preoperative localisation imaging to a control group with no imaging done prior to surgery.

Preoperative localisation imaging modalities

Ultrasound (US)

Ultrasound of the neck is often the initial modality used for localising parathyroid glands, in addition to excluding occult thyroid pathology. It is cost-effective and readily available. Parathyroid adenomas and hyperplasia tend to be homogeneously hypoechoic compared to the overlying thyroid gland. Ultrasound however has the limitation of not being able to assess for ectopic parathyroid glands in the mediastinum.[38]

Technetium ^{99}Tc Sestamibi (MIBI)

MIBI is a nuclear medicine two-dimensional planar imaging technique, often performed with a single-tracer dual-phase protocol. This involves the injection of a radioactive tracer (Technetium-99m sestamibi) with acquisition of early (15 minutes) and delayed (2 hours)

imaging of the neck and mediastinum. Hyperfunctioning parathyroid glands show high radiotracer uptake and persistent activity on delayed images, in contrast to the earlier tracer washout from thyroid tissue.[39]

Single Proton Emission Computerised Tomography/Computerised Tomography (SPECT/CT)

Fusion SPECT/CT include the multidimensional and maximum intensity projection images of the neck and mediastinum provided by SPECT, often performed with a single-tracer dual-phase protocol, combined with the anatomical images provided by non-contrast CT. The SPECT component provides more superior functional details of hyperfunctioning parathyroid glands compared to MIBI alone and the CT component provides important anatomical landmarks for improved tomographic assignment of parathyroid glands in relation to the neighbouring structures such as the thyroid gland, trachea, oesophagus, and great vessels.[39]

Computerised Tomography (CT)

CT scans can offer detailed anatomical information about the neck and surrounding structures, as well as the mediastinum. Contrast-enhanced CT scans can aid in localising enlarged parathyroid glands, including potential ectopic glands in the mediastinum.

Four-dimensional Computerised Tomography (4D CT)

4D CT combines CT imaging with dynamic data acquisition, including non-contrast, arterial and delayed phase image series, to provide not only detailed anatomical information of the neck and mediastinum, but also functional data. It can localise abnormal parathyroid glands based on their arterial blood supply and dynamic enhancement patterns, as they enhance in the arterial phase and wash out more rapidly in the delayed phase compared to thyroid tissue. 4D CT is more often used in the localisation of parathyroid adenomas in PHPT rather than SHPT or THPT due to the high intravenous (IV) contrast load required.[38]

Pharmaceutical Benefits Scheme (PBS) delisting of cinacalcet in Australia

Cinacalcet was first made available on Australian PBS in 2004. The introduction of cinacalcet, as a calcimimetic treatment, meant more SHPT and THPT patients were able to be treated medically with success, reducing the need for surgery. Cinacalcet was delisted from PBS in Australia in August 2015 due to new evidence from the EVOLVE trial demonstrating that there was no statistically significant difference in the primary outcome of time to death or non-fatal cardiovascular event, and a higher rate of adverse events with cinacalcet compared with placebo. A reduction in parathyroidectomy was the only benefit that was shown, therefore cinacalcet was overall not considered as being cost effective.[40]

Early studies post- delisting done in 2016 showed an increase in the number of parathyroidectomies for renal hyperparathyroid patients. Though cinacalcet has been relisted onto PBS since February 2020 due to a moderate unmet clinical need in the advanced CKD patient population in the absence of a suitable alternative PBS-listed calcimimetic medicine, a

more up to date evaluation of the impact of cinacalcet delisting on the demand for surgical management of SHPT and THPT is needed, to aid future decision-making regarding funding for the medication.[41]

Chapter 2: Comparison of Preoperative Imaging Modalities for Localisation of Secondary Hyperparathyroidism and Tertiary Hyperparathyroidism. A Systematic Review and Meta-analysis

Abstract

Background

Whilst diagnostic test accuracies of various modalities of preoperative localisation studies for primary hyperparathyroidism are well established, their accuracies and benefits for secondary and tertiary hyperparathyroidism remain unclear.

Objectives

To directly compare the performance of different preoperative imaging modalities for localisation of secondary and tertiary hyperparathyroidism, thereby identifying the ideal imaging modality and combination of modalities, by performing a systematic review of the literature and meta-analysis.

Search methods

International Prospective Register of Systematic Reviews (PROSPERO) was searched to ensure no similar systematic review or meta-analysis had been conducted prior to this study. Medline and Embase were searched from the earliest available indexing date through 7th June 2022.

Selection criteria

Studies evaluating preoperative imaging for localisation of secondary and/or tertiary hyperparathyroidism with the target condition being hyperplastic/adenomatous parathyroid gland/s identified on preoperative imaging, and reference standard being enlarged parathyroid gland/s identified and resected intra-operatively and subsequently confirmed to be hyperplastic or adenomatous parathyroid gland/s on histopathology.

Data collection and analysis

Two review authors independently reviewed the literature and extracted a standard set of data using a tailored data extraction form for each study. Risk of bias and applicability were assessed using Quality Assessment Tool for Diagnostic Accuracy Studies 2 (QUADAS 2). Studies whereby true positive (TP), false positive (FP), true negative (TN) and false negative (FN) values were provided or could be derived were selected for the meta-analysis. Meta-analysis was conducted with STATA software (SE14) using the meqrlogit statistics package, fitting the bivariate model with random effect in a frequentist environment, as recommended

by Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (DTA). A Summary Receiver Operating Characteristic (SROC) plot with summary point estimate of sensitivity and specificity and 95% confidence region was then obtained using Revman 5 software, based on the meta-analysis results for the preoperative imaging modalities to allow comparison.

Main results

19 studies comprising 1424 patients were included in this meta-analysis. These comprised of retrospective and prospective cohort studies evaluating the DTA of preoperative ultrasound (US), Technetium ^{99}Tc Sestamibi (MIBI) and Single Proton Emission Computerised Tomography/Computerised Tomography (SPECT/CT) for localisation of SHPT on a per lesion basis.

12 of the 19 studies evaluated accuracy of US, 14 evaluated MIBI, and 6 evaluated SPECT/CT. In meta-analyses, the summary sensitivity and specificity for US were 67% (95% CI 54% to 79%) and 65% (95% CI 44% to 81%), MIBI were 63% (95% CI 56% to 71%) and 81% (95% CI 64% to 91%), and SPECT/CT were 80% (95% CI 72% to 86%) and 78% (95% CI 57% to 91%) respectively.

Conclusions

SPECT/CT has demonstrated better DTA compared to US or MIBI in preoperative localisation of SHPT with a summary sensitivity of 80% (95% CI 72% to 86%) and specificity of 78% (95% CI 57% to 91%). Therefore, it should be considered as the preferred imaging modality for localisation of SHPT when single imaging modality is utilised. Combination imaging with US and SPECT/CT may have more superior performance in localisation than single imaging modalities however more studies are required for comparison.

Background

SHPT and THPT are common complications of CKD associated with significant morbidity and mortality due to their cardiovascular effects, effects on bone metabolism and other metabolic effects. The effectiveness of parathyroidectomy in preventing the complications of secondary and tertiary hyperparathyroidism has been well established in the international literature. Persistent or recurrent hyperparathyroidism in an already surgically explored neck and in a comorbid CKD patient can be very challenging to manage. Whilst diagnostic test accuracies of preoperative localisation imaging modalities for PHPT are well established, their performance and roles prior to parathyroidectomy for secondary and tertiary hyperparathyroidism remain unclear.

Target condition being diagnosed

Hyperplastic/adenomatous parathyroid gland/s identified on preoperative localisation imaging

Index tests

US
MIBI
SPECT/CT
CT
4D CT

Alternative tests

Magnetic resonance imaging (MRI) and Positron emission tomography (PET) can be alternative tests however are not commonly done as localisation imaging for hyperparathyroidism. They will not be included in the review.

Rationale

A preoperative localisation imaging modality which is readily accessible, affordable, and accurate is important to help with intraoperative identification of hyperplastic/adenomatous parathyroid gland/s, in particular ectopic glands, for SHPT and THPT, maximise the success of surgery and minimise the chance of disease persistence or recurrence.

Previously published systematic review and meta-analysis focused on the DTA of a single imaging modality i.e., MIBI in the preoperative localisation of SHPT. This demonstrated that MIBI had inadequate DTA for SHPT.[42] Systematic reviews and meta-analyses comparing different modalities of localisation imaging for secondary and tertiary hyperparathyroidism is lacking.

Objectives

To directly compare the performance of different preoperative imaging modalities for localisation of secondary and tertiary hyperparathyroidism, thereby identifying the ideal imaging modality and or combination of modalities, by performing a systematic review of the literature and meta-analysis.

Investigation of sources of heterogeneity

We planned to inspect forest plots and SROC plots to visually assess heterogeneity between study specific estimates of sensitivity and specificity.

Methods

Criteria for considering studies for this review

Types of studies

Studies sampling a consecutive series of patients, or a randomly selected series of patients were included. We included studies reported in English language only. For the meta-analysis, we included studies that presented sufficient data for us to extract or calculate absolute numbers of TP, FP, TN, and FN on a per lesion basis.

Participants

Patients with secondary and tertiary hyperparathyroidism that underwent preoperative localisation imaging prior to parathyroidectomy.

Index tests

US
MIBI
SPECT/CT
CT
4D CT

Comparator tests

We included studies regardless of whether they made comparisons with other preoperative localisation imaging modalities or not.

Target conditions

Hyperplastic/adenomatous parathyroid gland/s identified on preoperative localisation imaging.

Reference standards

Enlarged gland/s identified and resected intra-operatively, and subsequently confirmed to be hyperplastic/adenomatous parathyroid gland/s on histopathology.

Search methods for identification of studies

Electronic searches

PROSPERO was searched to ensure no similar systematic review or meta-analysis had been conducted prior to this study. The study protocol was registered with PROSPERO (CRD42022337915). Medline and Embase were searched from the earliest available indexing date through 4thJune 2022. We used a search algorithm based on a combination of these MeSH subject headings as keywords in Medline: *ultrasonography*; *technetium ^{99m}Tc sestamibi*; *tomography, x-ray computed*; *tomography, emission-computed, single-photon emission computed tomography*; *single photon emission computed tomography computed tomography*; *four-dimensional computed tomography*; *hyperparathyroidism, secondary*; and the keyword *tertiary hyperparathyroidism*. We used a search algorithm based on a combination of these subject headings as keywords in Embase: *echography*; *methoxy isobutyl isonitrile technetium ^{99m}Tc*; *CT scanner*; *single photon emission computed tomography*; *single photon emission computed tomography-computed tomography*; *four-dimensional computed tomography*; *secondary hyperparathyroidism*; *tertiary hyperparathyroidism*.

Data collection and analysis

Selection of studies

We included studies or subsets in studies evaluating the DTA of preoperative localisation imaging in patients with SHPT and THPT. Case reports, review articles, meta-analysis, systematic reviews, conference abstracts, and nonrelevant studies were excluded. Studies in non-English language were excluded. References of selected articles were screened to find additional eligible studies.

Studies that did not separate the data for primary and secondary hyperparathyroidism, primary and tertiary hyperparathyroidism or secondary and tertiary hyperparathyroidism were excluded. Studies with less than 10 SHPT or THPT patients were excluded.

For the systematic review, studies were excluded if sensitivity and specificity were not both available or could not be derived.

For the meta-analysis, studies were excluded if insufficient data was provided to allow extraction or calculation of TP, FP, TN, and FN. Studies done on a per patient basis were also excluded. This is because per lesion-based analysis of the accuracy of preoperative localisation imaging was more appropriate for inclusion given the multitude of pathological parathyroid glands in patients with secondary and tertiary hyperparathyroidism.

More than one modality of localisation imaging may be evaluated in each eligible study.

Data extraction and management

Two review authors independently extracted a standard set of data using a tailored data extraction form for each study including basic study characteristics and technical aspects of the imaging modalities. In cases of studies where only a subset of data met the inclusion criteria, we extracted and presented the eligible subset data.

Each study was analysed to retrieve the sensitivity and specificity of each localisation imaging modality. The absolute number of TP, FP, TN and, FN of localisation imaging in comparison to the histological examination were extracted or calculated from studies that provided sufficient data. Reverse engineering of TP, FP, TN and FN were based on values provided for sensitivity, specificity and or NPV, PPV or prevalence using formulas listed under Appendix A. NPV, PPV, accuracy and prevalence, if not already provided, were calculated based on available data of TP, FP, TN and FN. Same formula was used to check studies' calculation of sensitivity and specificity based on their TP, FP, FN and FN. Where there was inconsistency of data or calculated results, the corrected results were used for the study listed under Appendix B.

All eligible studies with available sensitivity and specificity were included in the systematic review. Only eligible studies with TP, FP, TN, and FN were included in the meta-analysis. A minimum number of four eligible studies is required to meta-analyse the DTA for a specific imaging modality.

Assessment of methodological quality

Two independent review authors evaluated the methodological quality of the selected studies using QUADAS 2. We answered each question on the checklist with a yes or no response or noted unclear if insufficient information was available in the study to enable a judgement. Disagreements were resolved by means of consensus.

Statistical analysis and data synthesis

Meta-analysis was conducted with STATA software (SE14) using the meqrlogit statistics package, fitting the bivariate model with random effects in a frequentist environment, as recommended by the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy version 2.0.[43] [44] [45] This enabled joint synthesis of sensitivity and specificity across studies, taking into account heterogeneity in study results. An SROC plot with a summary point estimate of sensitivity and specificity for each imaging modality, and a 95% confidence

region, was obtained using Revman 5 software, based on the meta-analysis results. The SROC plots of the imaging modalities were combined to allow comparison of their sensitivity and specificity for localisation of secondary and tertiary hyperparathyroidism.

Studies that allowed extraction of sensitivity and specificity values but not TP, FP, TN, and FN values were plotted against the combined SROC plot. This allowed us to compare and systematically review the distribution of sensitivity and specificity for relevant imaging modalities in studies not included in the meta-analysis.

Investigations of heterogeneity

We inspected the forest plots and SROC plots to visually assess heterogeneity between estimates of sensitivity and specificity.

Sensitivity analysis

Sensitivity analysis of the meta-analysis was performed by excluding an outlier study from each imaging modality to observe the impact on the summary point and 95% confidence region.

Results

Results of the search

438 records were obtained through Medline search, 682 records were obtained through Embase search, a total of 1120 records were screened. After exclusion of duplicate records, case reports, review articles, editorials, meta-analyses, systematic reviews, conference abstracts, nonrelevant studies, and non-English language studies, 82 studies were suitable for full-text review. An additional 5 studies were included after examining references of the suitable studies.

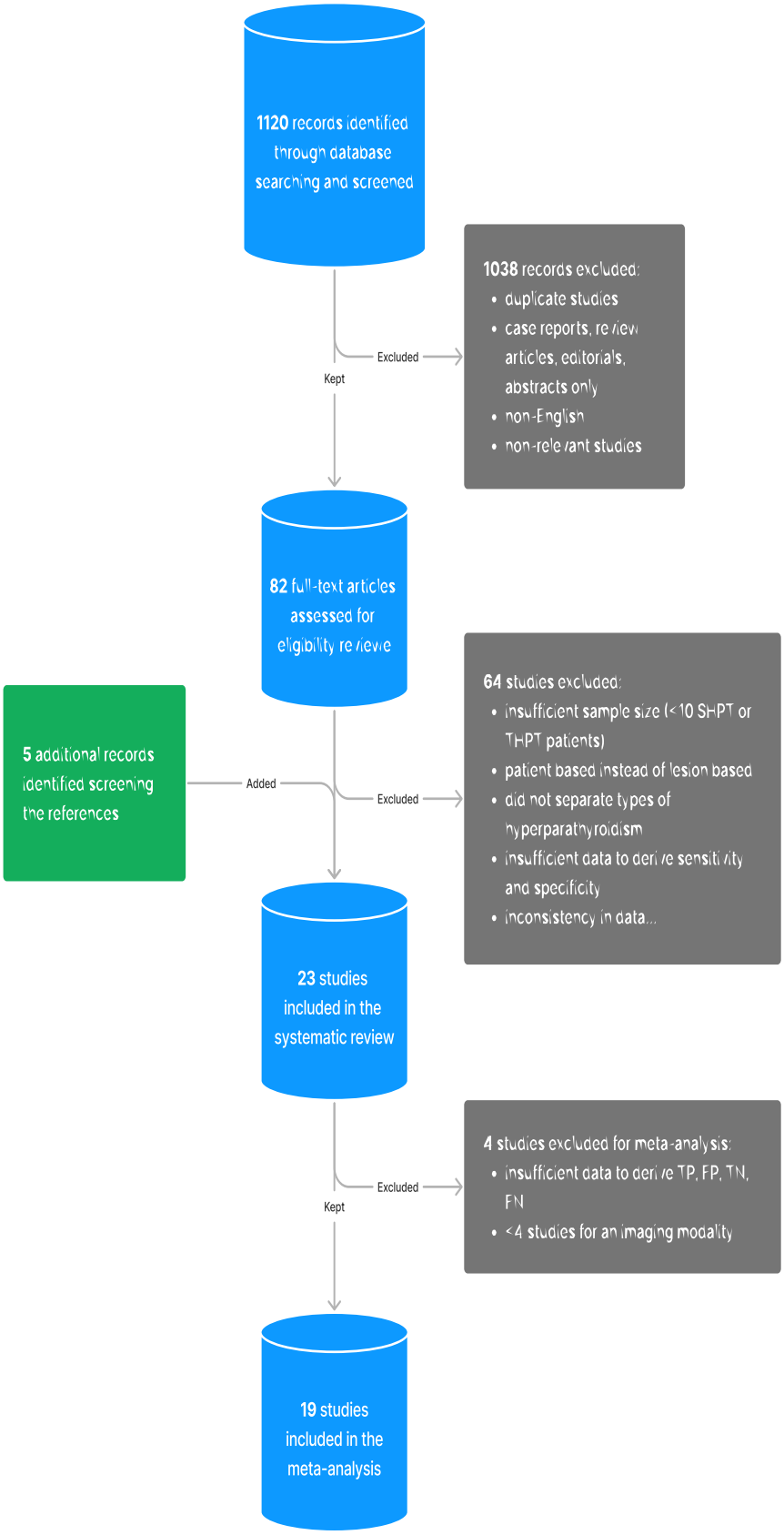

Figure 5 Flow chart of the search for eligible studies on the DTA of preoperative localisation imaging modalities in SHPT and THPT

After review of full article texts of the 87 studies, a further 64 studies were excluded. The excluded studies were done on a per patient basis instead of per lesion basis, did not separate data for primary and secondary hyperparathyroidism or tertiary hyperparathyroidism, had less than 10 SHPT or THPT patients, had duplication in patient population, or had discrepancies in key data points identified when validating or reverse-engineering sensitivity, specificity, TP, FP, TN or FN values. 1 study was excluded due to both TN and FP being 0 and therefore specificity could not be determined. The remaining 23 studies were included in the systematic review. Of note, only 1 eligible study was done for THPT.

For the meta-analysis, a further 4 studies were excluded from the 23 studies due to insufficient data provided for extraction or calculation of TP, FP, TN, and FN, or there being less than 4 studies for the imaging modality or combination of imaging modalities evaluated. 1 of the 4 excluded studies was the single study for THPT.

19 studies comprising 1424 patients were included in the meta-analysis. These comprised of retrospective and prospective cohort studies evaluating the DTA of preoperative US, MIBI or SPECT/CT for localisation of SHPT on a per lesion basis. See Figure 5 for a flow chart of search and eligibility results. Notably no study on 4D CT or CT qualified for the meta-analysis.

Tables 1 and 2 show the characteristics and Tables 3 to 8 show the technical aspects of the studies included in the meta-analysis and systematic review. A study may have data for a localisation imaging modality eligible for both meta-analysis and systematic review, and data for a different localisation imaging modality eligible for systematic review only. For example, Meola et al. looked at the DTA of US, MIBI, and the combination of US and MIBI in localising parathyroid glands preoperatively in SHPT patients. Data for US and data for MIBI were eligible for inclusion in both systematic review and meta-analysis. Data for the combination of US and MIBI was eligible for the systematic review component only as there were in total less than 4 studies examining the combination of US and MIBI, which is the minimum number of studies required to meta-analyse. For studies that evaluated early phase and delayed phase SPECT/CT separately, the one with the higher sensitivity was included for analysis.

Table 1 Characteristics of studies or subsets of studies included in the meta-analysis and systematic review. NR not reported.

Author	Year Published	Country	Type of Study	SHPT or THPT	Number of Patients	Mean Age	Localisation Imaging Modality
Liou et al.[46]	1996	Taiwan	Retrospective	SHPT	11	38	US
Pons et al.[47]	1997	Spain	Prospective	SHPT	20	48	US
							MIBI
Ishibashi et al.[48]	1998	Japan	Prospective	SHPT	17	47	US
							MIBI
Torregrosa et al.[49]	1998	Spain	Prospective	SHPT	22	NR	US
							MIBI
Jeanguillaume et al.[50]	1998	France	Prospective	SHPT	12	53	MIBI
Takebayashi et al.[51]	1999	Japan	Retrospective	SHPT	18	NR	MIBI
Olaizola et al.[52]	2000	France	Prospective	SHPT	21	57	MIBI
Arveschoug et al.[53]	2002	Denmark	Retrospective	SHPT	16	57	MIBI
Takeyama et al.[54]	2004	Japan	Prospective	SHPT	15	NR	US
							MIBI
Kawata et al.[55]	2009	Japan	Prospective	SHPT	44	50	US
Meola et al.[56]	2011	Italy	Prospective	SHPT	40	51	US
							MIBI
Saengsuda et al.[57]	2012	Thailand	Retrospective	SHPT	53	47	MIBI
Yang et al.[58]	2014	PR China	Prospective	SHPT	80	66	SPECT/CT
Yuan et al.[59]	2016	PR China	Prospective	SHPT	60	68	US
							SPECT/CT
Li et al.[60]	2017	PR China	Prospective	SHPT	50	51	US
							SPECT/CT
Hiramitsu et al.[61]	2019	Japan	Prospective	SHPT	298	56	US
							MIBI
Zeng et al.[62]	2019	PR China	Prospective	SHPT	569	46	MIBI
							SPECT/CT
Zhang et al.[63]	2020	PR China	Prospective	SHPT	60	48	US
							MIBI
							SPECT/CT
Li et al.[64]	2020	PR China	Prospective	SHPT	18	51	US
							MIBI
							SPECT/CT

Table 2 Characteristics of additional studies or subsets of studies included in the systematic review only.

Author	Year Published	Country	Type of Study	SHPT or THPT	Number of Patients	Mean Age	Localisation Imaging Modality
Chesser et al.[65]	1997	UK	Prospective	THPT	12	47	MIBI
Neumann et al.[66]	1998	USA	Prospective	SHPT	19	43	SPECT
Lomonte et al.[67]	2006	Italy	Prospective	SHPT	35	51	MIBI
Meola et al.[56]	2011	Italy	Prospective	SHPT	40	51	US + MIBI
Vulpio et al.[68]	2013	Italy	Prospective	SHPT	26	NR	US
Yuan et al.[59]	2016	PR China	Prospective	SHPT	60	68	US + SPECT/CT
Hiramitsu et al.[61]	2019	Japan	Prospective	SHPT	298	56	CT
							US + MIBI
							US + CT
							MIBI + CT
							US + MIBI + CT
Li et al.[64]	2020	PR China	Prospective	SHPT	18	51	US + MIBI
							US + SPECT/CT
							MIBI + SPECT/CT
							US + MIBI + SPECT/CT

*Table 3 Technical aspects of US studies included in the meta-analysis. NR not reported. *CEUS contrast-enhanced US*

US		
Author	**Frequency (MHz)**	**Other imaging methods**
Hiramitsu et al.[61]	NR	MIBI, CT
Ishibashi et al.[48]	7.5	MIBI, MRI
Kawata et al.[55]	7.5	CT
Li et al. 2017[60]	8 - 13	SPECT/CT
Li et al.2020[64]	5-9	CEUS, MIBI, SPECT/CT
Liou et al.[46]	7.5 or 10	^{201}Ti-^{99m}TC subtraction scan
Meola et al.[56]	9-10	MIBI
Pons et al.[47]	NR	MIBI
Takeyama et al.[54]	NR	MIBI
Torregrosa et al.[49]	7.5	MIBI
Yuan et al.[59]	7 - 12	SPECT/CT
Zhang et al.[63]	8.4 – 9	MIBI, SPECT/CT

Table 4 Technical aspects of MIBI studies included in the meta-analysis. NR not reported.

MIBI				
Author	**Activity (MBq)**	**Acquisition protocol**	**Thyroid imaging**	**Other imaging methods**
Arveschoug et al.[53]	750-900	Parallel-Hole and Pinhole	No	None
Hiramitsu et al.[61]	NR	NR	No	US, CT
Ishibashi et al.[48]	600	Parallel-Hole	No	US, MRI
Jeanguillaume et al.[50]	550	Parallel-Hole	I-123	US
Li et al. 2020[64]	740	NR	No	US, CEUS, SPECT/CT
Meola et al.[56]	740	Pinhole	No	US
Olaizola et al.[52]	700MBq/70kg body weight	NR	No	None
Pons et al.[47]	700MBq/70kg body weight	Parallel-Hole	No	US
Saengsuda et al.[57]	740	Parallel-Hole	No	None
Takebayashi et al.[51]	740	Parallel-Hole	No	None
Takeyama et al.[54]	NR	NR	NR	US
Torregrosa et al.[49]	740	Parallel-Hole	No	US
Zeng et al.[62]	740	NR	No	SPECT/CT
Zhang et al.[63]	555	NR	No	US, SPECT/CT

Table 5 Technical aspects of the SPECT/CT studies included in the meta-analysis. NR not reported.

SPECT/CT					
Author	**Activity (MBq)**	**Phase**	**Slice thickness (mm)**	**Slice increment (mm)**	**Other imaging methods**
Li et al. 2017[60]	740	Dual	3	2	US
Li et al. 2020[64]	740	Delayed	NR	NR	US, CEUS, MIBI
Yang et al.[58]	740	Early, delayed	3	2	None
Yuan et al.[59]	740	Dual	NR	NR	US
Zeng et al.[62]	740	Early	3.75	NR	MIBI
Zhang et al.[63]	555	Dual	2.55	NR	US, MIBI

Table 6 Technical aspects of the US study included in the systematic review only

US		
Author	**Frequency (MHz)**	**Other imaging methods**
Vulpio et al.[68]	7.5-15	None

Table 7 Technical aspects of the MIBI studies included in the systematic review only

MIBI				
Author	**Activity (MBq)**	**Acquisition Protocol**	**Thyroid imaging**	**Other imaging methods**
Chesser et al.[65]	450	Parallel-Hole	Pertechnetate	None
Lomonte et al.[67]	700MBq/70kg body weight	Parallel-Hole	No	None

Table 8 Technical aspects of the SPECT study included in the systematic review only

SPECT				
Author	**Activity (MBq)**	**Phase**	**Thyroid imaging**	**Other imaging methods**
Neumann et al.[66]	NR	Dual	^{123}I	None

Table 9 True-positive, true-negative, false-positive, false-negative values of 19 studies included in the meta-analysis

Author	**Localisation Imaging Modality**	**TP**	**TN**	**FP**	**FN**
Liou et al.[46]	US	12	6	1	25
Pons et al.[47]	US	25	17	2	36
	MIBI	33	17	2	28
Ishibashi et al.[48]	US	39	3	2	23
	MIBI	43	3	1	18
Torregrosa et al.[49]	US	25	17	2	36
	MIBI	33	17	2	28
Jeanguillaume et al.[50]	MIBI	41	0	1	9
Takebayashi et al.[51]	MIBI	49	17	2	10
Olaizola et al.[52]	MIBI	29	26	0	29
Arveschoug et al.[53]	MIBI	22	6	0	2
Takeyama et al.[54]	US	45	0	4	15
	MIBI	40	2	2	20
Kawata et al.[55]	US	112	7	27	30
Meola et al.[56]	US	107	6	2	37
	MIBI	86	1	7	58
Saengsuda et al.[57]	MIBI	116	36	3	57
Yang et al.[58]	SPECT/CT	220	38	0	58
Yuan et al.[59]	US	155	17	19	37
	SPECT/CT	163	21	15	29
Li et al. 2017[60]	US	86	12	3	97
	SPECT/CT	108	12	4	74
Hiramitsu et al.[61]	US	402	4	1	301
	MIBI	299	3	2	404
Zeng et al.[62]	MIBI	440	25	11	224
	SPECT/CT	1212	51	17	296
Zhang et al.[63]	US	175	11	3	54
	MIBI	114	12	2	115
	SPECT/CT	205	9	5	24
Li et al. 2020[64]	US	70	1	1	1
	MIBI	36	1	1	35
	SPECT/CT	56	1	1	15

Table 9 shows the true-positive, true-negative, false-positive and false-negative values for the localisation imaging modalities evaluated by the 19 studies included in the meta-analysis.

Methodological quality of included studies

Overall, the studies included in this meta-analysis have shown moderate methodological quality according to QUADAS 2. (Figures 6 and 7) The main methodological issue of the included studies is that the index test and the reference standard were often interpreted without blinding, therefore the surgeons had access to the preoperative localisation imaging at the time of surgery. It was not clear in a few studies whether consecutive patients were selected.

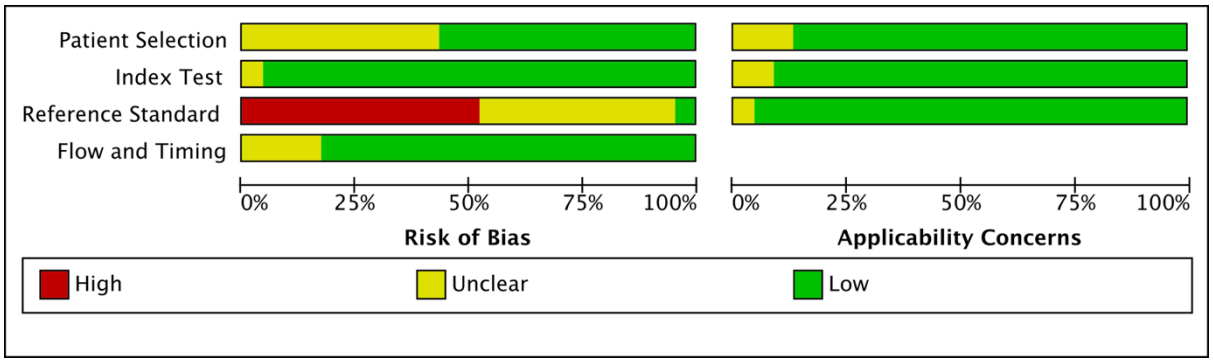

Figure 6 Risk of bias and applicability concerns graph

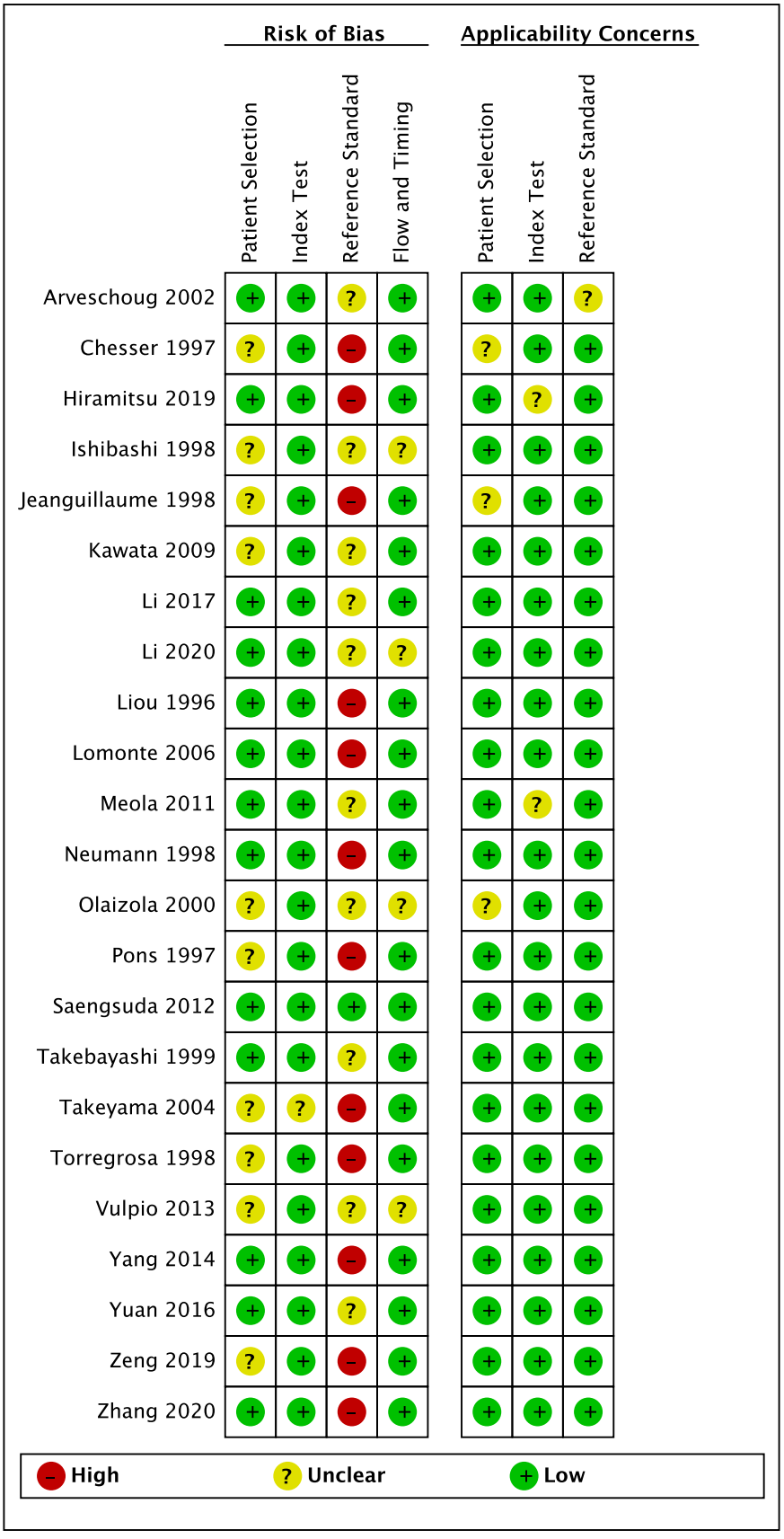

Figure 7 Risk of bias and applicability concerns summary

Meta-analysis

19 studies were eligible for the meta-analysis of accuracy of preoperative localisation imaging modalities for SHPT on a per lesion basis (Figure 8). 12 studies evaluated accuracy of US, 14 MIBI, and 6 SPECT/CT. No study on 4D CT or CT was eligible for the meta-analysis.

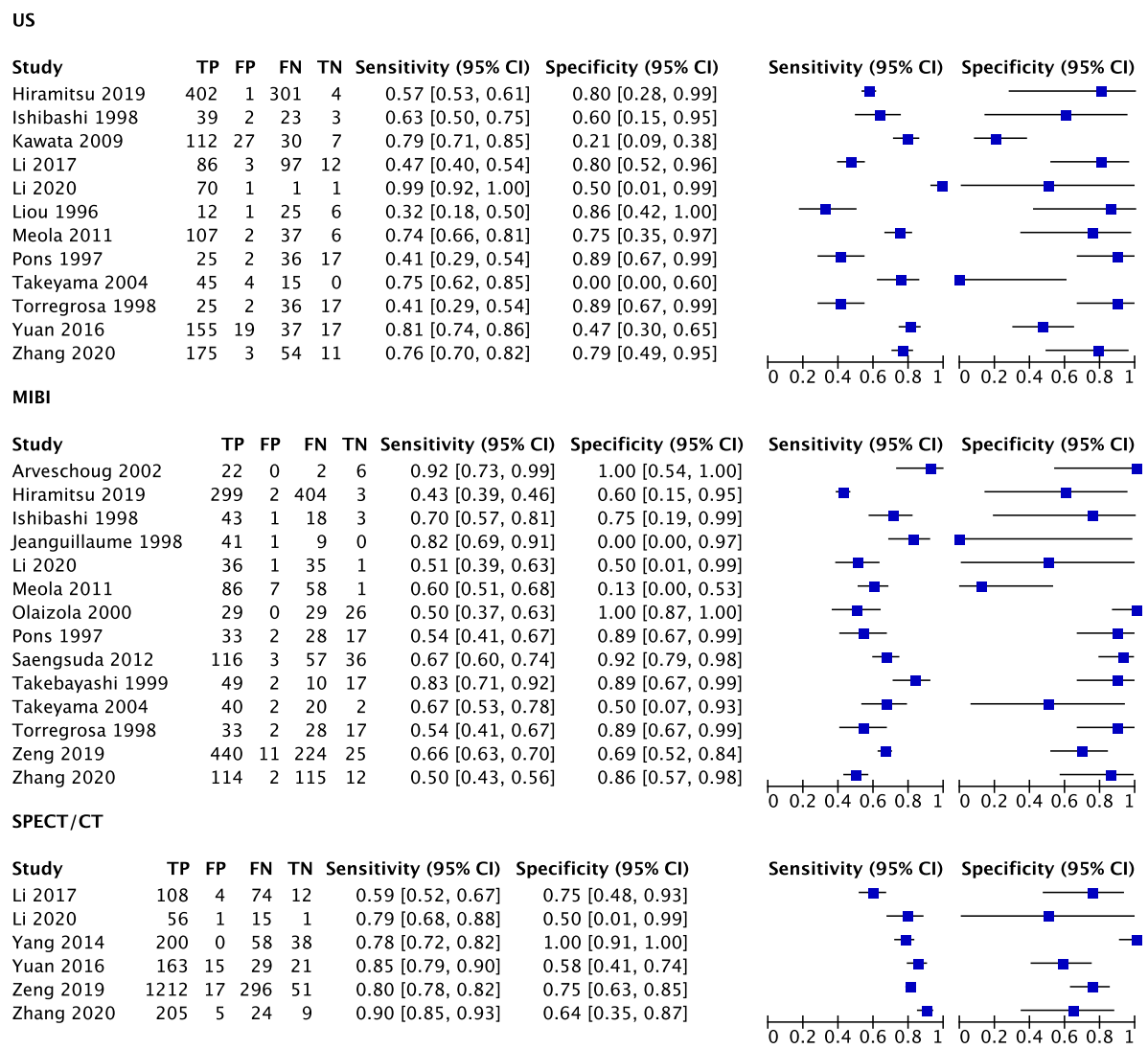

Figure 8 Forest plot of US, MIBI and SPECT/CT for preoperative localisation of SHPT.

For US, sensitivity reported by the included studies ranged from 32% to 92%, specificity ranged from 0% to 89%. For MIBI, sensitivity ranged from 43% to 99%, specificity ranged from 0% to 100%. For SPECT/CT, sensitivity ranged from 59% to 90%, specificity ranged from 50% to 100%. The sensitivity of each imaging modality reported in the studies represents the number of pathological parathyroid glands correctly localised in the preoperative localisation study and confirmed on histopathology as a percentage of the total number of pathological parathyroid glands in the patient cohort, which is four times the total number of patients as majority of patients would have four pathological parathyroid glands in SHPT. The specificity of each imaging modality represents the percentage of normal parathyroid glands that test negative on the preoperative localisation studies.

The summary sensitivity and specificity were 67% (95% CI 54% to 79%) and 65% (95% CI 44% to 81%) for US, 63% (95% CI 56% to 71%) and 81% (95% CI 64% to 91%) for MIBI, and 80% (95% CI 72% to 86%) and 78% (95% CI 57% to 91%) for SPECT/CT. We compared the summary sensitivity and specificity of the three imaging modalities in Figure 9. Few studies directly compared the imaging modalities therefore meta-analyses of comparative studies were not possible. The results from Zhang et al., the only study that compared US, MIBI and SPECT/CT directly, were consistent with the meta-analytic finding and demonstrated the highest sensitivity for SPECT/CT at 90%.

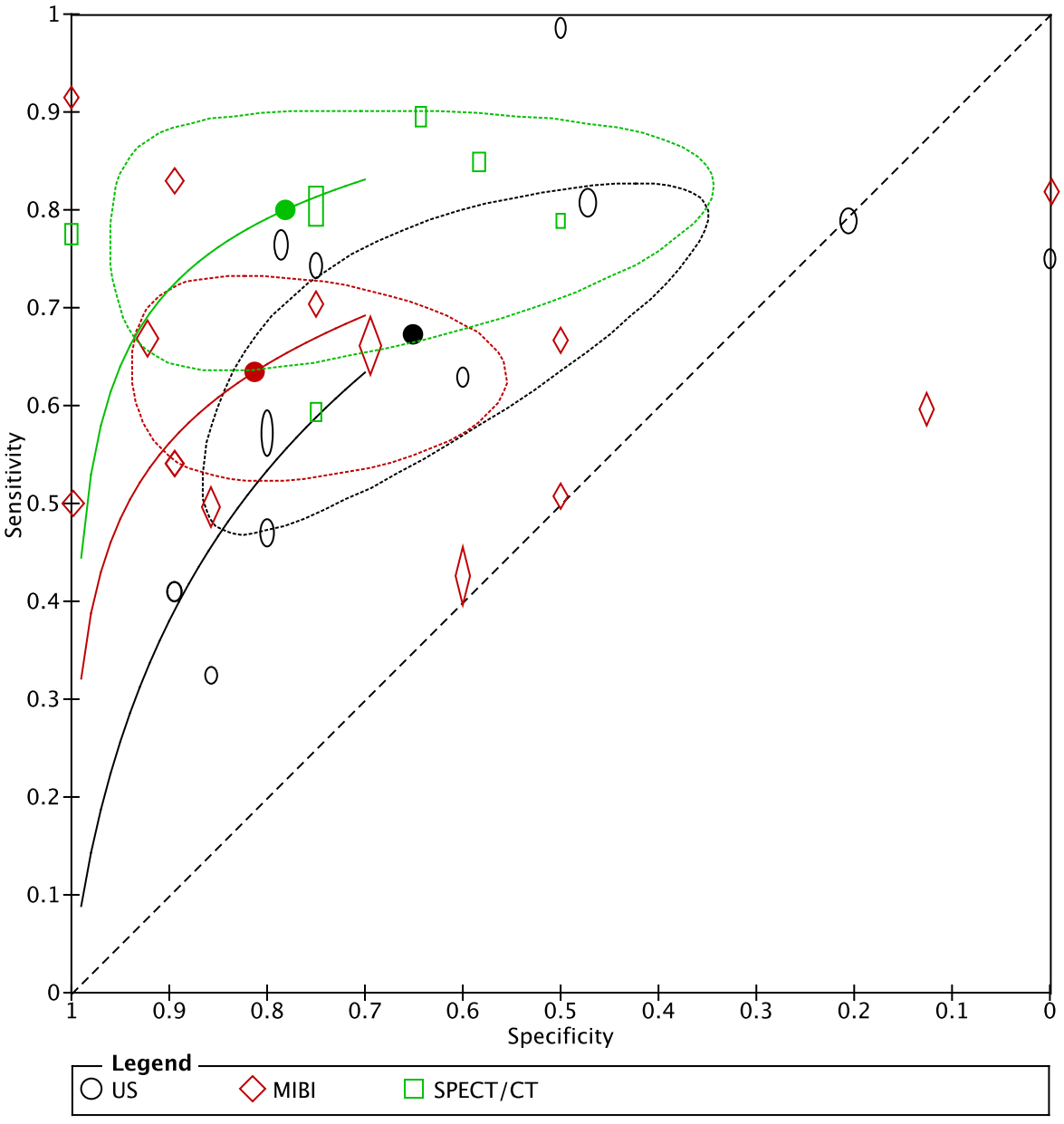

Figure 9 SROC plot with summary point of sensitivity and specificity with 95% confidence region for US, MIBI and SPECT/CT

Investigation of heterogeneity

The forest plot (Figure 8) suggests heterogeneity in the sensitivity and specificity estimates of US, and the specificity estimates of MIBI and SPECT/CT. The scattered distribution SROC plot data points for US also indicates heterogeneity. (Figure 9) The basic study characteristics and technical aspects of imaging of the studies were similar. (Tables 1, 3, 4, and 5)

Sensitivity analysis

The summary sensitivity and specificity for US and MIBI and the 95% confidence region did not shift significantly after exclusion of an outlier study. (Figures 10 and 11) Whilst there is a decrease in specificity for SPECT/CT after an outlier study was excluded, there was no significant shift in the summary sensitivity, and the 95% confidence region became smaller. (Figure 12) Overall, the sensitivity analysis showed that the summary sensitivity and specificity for US, MIBI and SPECT/CT were reliable.

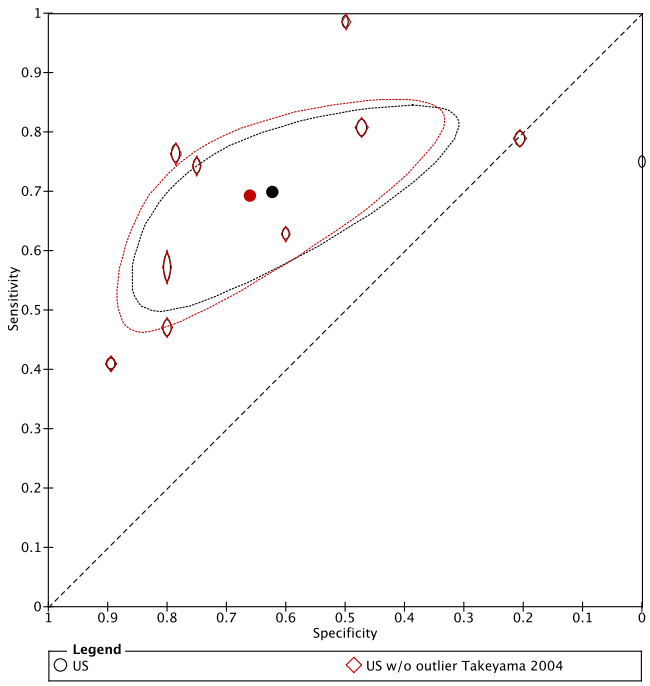

Figure 10 Sensitivity analysis of US comparing SROC plot with and without outlier study Takeyama et al. 2004

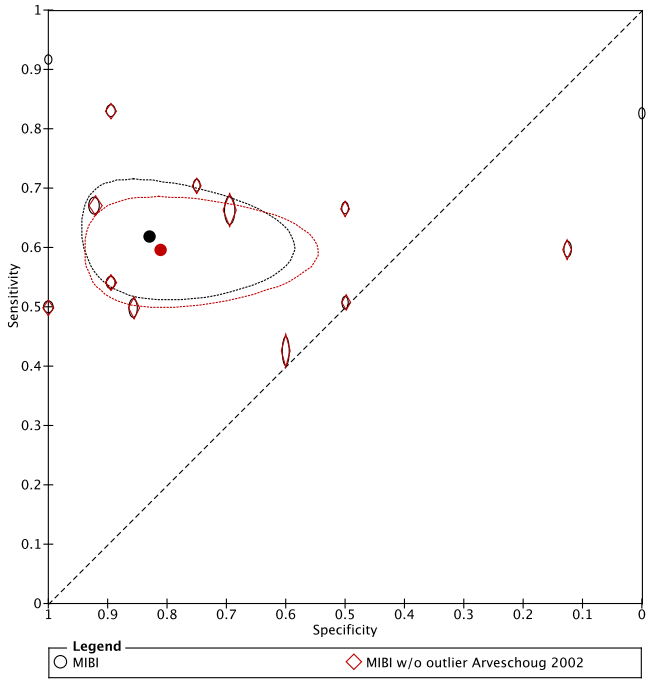

Figure 11 Sensitivity analysis of MIBI comparing SROC plot with and without outlier study Arveschoug et al. 2002

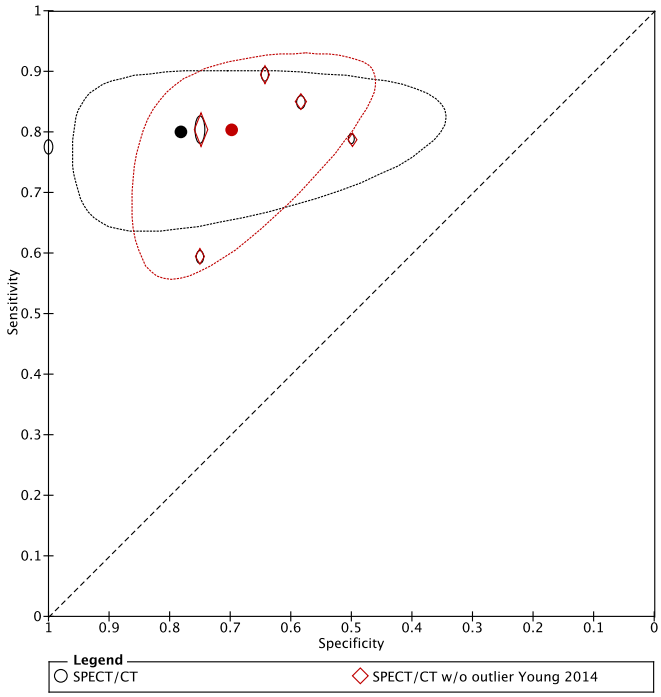

Figure 12 Sensitivity analysis of SPECT/CT comparing SROC plot with and without outlier study Young et al. 2014

Systematic review

4 additional studies and subsets of 4 studies included in the meta-analysis evaluated the sensitivity and specificity of US, MIBI, and SPECT/CT but were not appropriate for the meta-analysis (Table 2).

The sensitivity and specificity of US, MIBI, SPECT/CT and imaging combination of US, MIBI, and or SPECT/CT in these studies were plotted against the meta-analysis SROC plot to give a visual representation of the distribution of their sensitivity and specificity results compared to the meta-analysis results (Figure 13). Notably, the two studies (Yuan et al., Li et al. 2020) that evaluated the sensitivity and specificity of US + SPECT/CT showed more superior sensitivity between 90% to 100% compared to the summary sensitivity of 80% for SPECT/CT alone.

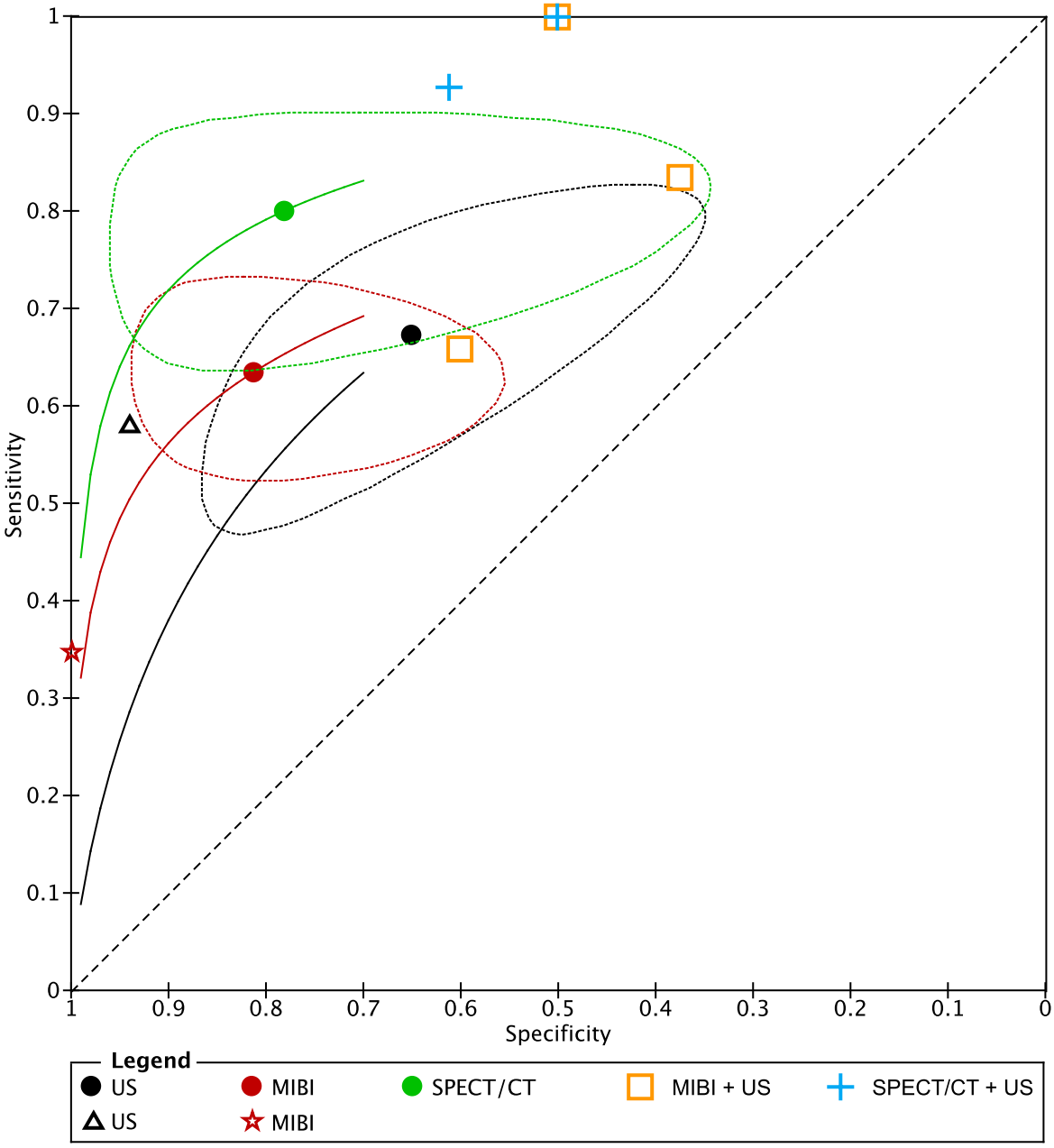

Figure 13 Sensitivity and specificity of studies suitable for systematic review but not meta-analysis plotted against the SROC plot from meta-analysis

Chesser et al. was the only eligible study that evaluated the DTA of preoperative localisation imaging modality in THPT patients. The sensitivity and specificity for MIBI were 82% and 0% respectively.

Discussion

Summary of main results

19 studies comprising 1424 patients were included in this meta-analysis. These comprised of retrospective and prospective cohort studies evaluating the DTA of preoperative US, MIBI and SPECT/CT for localisation of SHPT on a per lesion basis.

12 studies evaluated accuracy of US, 14 evaluated MIBI, and 6 evaluated SPECT/CT. In meta-analyses, summary sensitivity and specificity were 67% (95% CI 54% to 79%) and 65% (95% CI 44% to 81%) for US, 63% (95% CI 56% to 71%) and 81% (95% CI 64% to 91%) for MIBI, and 80% (95% CI 72% to 86%) and 78% (95% CI 57% to 91%) for SPECT/CT.

Systematic review of additional studies and subsets of studies in the meta-analysis not eligible for meta-analysis showed potentially improved sensitivity with the combination of US and SPECT/CT (sensitivity 90% - 100%).

Strengths and weaknesses of the review

Accuracy of the reference standard

In this analysis of DTA of preoperative localisation imaging modalities, our target conditions are hyperplastic/adenomatous parathyroid gland/s identified on preoperative localisation imaging. Our reference standards, as a representation of the true total number of pathological glands, are enlarged gland/s identified and resected intra-operatively, and subsequently confirmed to be hyperplastic/adenomatous parathyroid gland/s on histopathology. The true total number of pathological glands cannot be directly ascertained for any given cohort of parathyroidectomy patients in SHPT or THPT due to the multiplicity of diseased glands and inherent challenges of identifying and resecting all pathological parathyroid glands intraoperatively. The closer the reference standard is to the true total number of pathological parathyroid glands in a patient cohort, the more accurate the reference standard would be.

Majority of patients included in the studies had normalisation of PTH post-parathyroidectomy. Some of the studies excluded patients that had persistently elevated PTH postoperatively. This means that majority of patients included in the studies had all their pathological parathyroid glands removed. In these circumstances, the number of glands removed and confirmed on histopathology to be hyperplastic or adenomatous would be a near perfect reference standard or representation for the true number of pathological glands in the patient cohort. In studies where patients had persistently elevated PTH, these were a minority of the patient sample and hence less likely to significantly affect the sensitivity and specificity estimates. In theory an imperfect reference standard can be adjusted for by Latent Class Analysis (LCA), however the reviewers felt that this was not necessary for our review as the reference standard was adequate.

Quality of the included studies

The quality of the eligible studies was variable. Interpretation of the reference standard was not blinded as surgeons would have had access to the findings of the index test/s to help identify and remove the pathological parathyroid glands intraoperatively.

Completeness and relevance of the review

Several considerations were in place from the study design to ensure completeness and relevance of the review.

In addition to setting out appropriate inclusion and exclusion criteria, the keywords used for Medline and Embase database searches were kept relatively broad to ensure capturing of all relevant studies. Keywords that may restrict search results and affect the completeness of the review, such as *preoperative* or *localisation imaging*, were not used. Where subsets of studies were eligible for inclusion, they were included for analysis. For example, if a study reported PHPT and SHPT data separately, the SHPT data were extracted and evaluated.

It is not uncommon for studies of DTA to analyse the pooled sensitivity and specificity separately for a test, and to make comparison of pooled sensitivity and specificity separately. However, as indicated by the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy version 2.0, sensitivity and specificity are both important measures of DTA that should be analysed and interpreted together rather than separately.[43] The bivariate model jointly synthesises sensitivity and specificity to give summary estimates drawn on an SROC plot, along with a 95% confidence region, allowing appropriate analysis and visual representation of the DTA of different tests. It also takes into account heterogeneity across the studies. By employing the bivariate model, we were able to achieve meaningful comparison between sensitivity and specificity of US, MIBI, and SPECT/CT in the meta-analysis, ensuring the adequacy of the analysis and review.

Applicability of findings to the review question

Findings on the summary sensitivity and specificity of US, MIBI and SPECT/CT, along with the comparison of combination imaging modalities, appropriately addressed the review question of the DTA of preoperative localisation imaging modalities for SHPT. For THPT, only 1 study was eligible for the review and hence limits the application of the findings.

Qualities of preoperative localisation imaging

Most studies reported on its preoperative localisation imaging protocols, and these were comparable between the studies as shown in Tables 4 to 7.

Application to clinical decision-making in practice

SHPT and THPT are multi-gland disease. Successful parathyroidectomy is paramount as longstanding SHPT and THPT is associated with significant morbidity and mortality, and reoperative parathyroidectomy is associated a higher chance of perioperative complication including RLN injuries. Preoperative localisation imaging has the potential to help improving the success rate of parathyroidectomy for secondary and tertiary hyperparathyroidism. This is the first meta-analysis to compare preoperative imaging modalities for SHPT. We showed that between US, MIBI and SPECT/CT, SPECT/CT had the best DTA and therefore should be considered as the preferred imaging modality for localisation of pathological parathyroids prior to parathyroidectomy for SHPT. We also demonstrated, through systematic review, the potential for the combination of US and SPECT/CT to have more superior performance compared to single imaging modalities. However more studies on combination of imaging modalities are required to further evaluate their DTA and provide guidance to clinical utility. It should also be noted that preoperative US is still paramount as part of the preoperative workup for SHPT to exclude occult thyroid pathology, regardless of its DTA for localisation of parathyroid glands.

Conclusions

Implications for practice

SPECT/CT has demonstrated better DTA compared to US and MIBI in preoperative localisation of SHPT with a summary sensitivity of 80% (95% CI 72% to 86%) and specificity of 78% (95% CI 57% to 91%). Therefore, it should be considered as the preferred imaging modality for localisation of SHPT when single modality is utilised. Combination imaging with US and SPECT/CT may have more superior performance in localisation than single imaging modalities and should be considered in clinical practice. Preoperative US should be performed to exclude occult thyroid pathology regardless of its accuracy as a localisation imaging modality.

Implications for research

We identified that there was an insufficient number of studies evaluating combined imaging modalities for meta-analysis (at least 4 studies required). The 2 studies that evaluated combined imaging modalities of US and SPECT/CT demonstrated their potential superiority in DTA compared to single imaging modality of US, MIBI, or SPECT/CT. However more studies on combined imaging modalities are needed to allow meta-analyses of the results and provide more meaningful insights into clinical decision-making.

More studies on the DTA of preoperative localisation imaging for THPT are needed in order to guide clinical decision-making, as currently there is only 1 eligible study for meta-analysis or systematic review. There is currently a lack of studies on 4D CT for preoperative localisation in SHPT, which is likely due to the IV contrast load required and its negative impact on patients with renal failure.

Meta-analysis and systematic review of DTA of preoperative localisation imaging in SHPT and THPT are useful in the comparison of performance of different imaging modalities and guide clinical practice, however they do not provide direct evidence on the impact of various preoperative localisation imaging modalities on the success of parathyroidectomy or clinical outcomes. Future studies comparing clinical outcomes between patient groups receiving preoperative localisation imaging and groups without preoperative localisation imaging can be considered for more direct assessment of the clinical impact of different preoperative localisation imaging modalities.

Chapter 3: The WSLHD experience

Abstract

Background

Given the high incidence of CKD in WSLHD's socioeconomically diverse population, effective surgical management of SHPT and THPT is critical. An understanding of the WSLHD experience in the referral practice, choice and performance of preoperative localisation imaging, and other aspects of surgical management for patients with SHPT and THPT would provide insight into how we may be able to optimise their surgical care.

Methods

We performed a retrospective review of 61 consecutive patients that underwent parathyroidectomy for SHPT and THPT in WSLHD from 2009 to 2019. We evaluated the timing of referral for surgery and its correlation with preoperative disease severity; the DTA of preoperative localisation studies compared to international benchmarks; the distribution of residual parathyroid/s in postoperative persistent or recurrent hyperparathyroidism; and the impact of cinacalcet delisting from PBS Australia during the study period on surgical volumes and timings for SHPT and THPT.

Results

Mean time to surgery from onset of dialysis was 2886 (±1983) days with a wide range of distribution indicating highly variable timing of referral for surgery. Range of distribution was also wide for preoperative biochemical markers, such as PTH, ALP, corrected serum calcium and phosphate, and BMD scores, indicating highly variable disease severity at the time of referral for surgery. 9 patients (14.8%) had persistent disease and 7 patients (11.5%) had recurrent disease, 3 of whom required reoperation. 2 out of the 3 reoperative patients were found to have ectopic parathyroid glands. DTA analysis of preoperative localisation imaging showed significantly lower sensitivity and specificity of US and SPECT/CT compared to international benchmarks, with an improved sensitivity when US and SPECT/CT were combined. An increase in the average days to surgery from onset of dialysis after the delisting of cinacalcet was observed, potentially due to patients with prolonged duration of disease previously treated with cinacalcet needing surgery after its delisting.

Conclusion

Our study identified a need for the development of local guidelines to aid clinical decision-making in when to refer SHPT and THPT patients for parathyroidectomy, and a need for centralisation of preoperative localisation imaging to help improve imaging performance. Ectopic glands found during reoperations for persistent or recurrent disease further supports the role of preoperative localisation imaging. Delisting of cinacalcet from PBS may have

increased the need for surgery for a group of SHPT and THPT patients with more advanced disease and higher perioperative risks, offering insights into broader health policy implications.

Background

WSLHD is one of the largest health districts in Sydney, Australia (Population 1,144,280 in 2021) and services some of the most socio-economically disadvantaged populations in Sydney. WSLHD also has one of the largest cohorts of renal dialysis and renal transplant patients in Australia.[1 2]

SHPT and THPT are common sequelae of patients with advanced CKD, typically on renal dialysis or are post- renal transplant. SHPT and THPT patients refractory to medical treatment are referred for parathyroidectomy in the hope to halt and or reverse the metabolic and cardiovascular effects of the disease process. If all pathological parathyroids are not identified and resected intraoperatively, patients will likely have persistent hyperparathyroidism or develop recurrent hyperparathyroidism postoperatively, which are challenging to manage. Reoperative surgeries carry more significant morbidity than the index surgery, especially with increased risks to the RLNs.

The KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) recommends parathyroidectomy if SHPT or THPT is refractory to medical treatment.[4] The American Association of Endocrine Surgeons (AAES) Guidelines for Definitive Surgical Management of Secondary and Tertiary Renal Hyperparathyroidism recommends referral for parathyroidectomy in patients with SHPT if they fail medical therapy, have complications due to hyperparathyroidism, or prefer surgery. AAES recommends parathyroidectomy for patients with THPT within 12 months post- kidney transplant or if there is hypercalcemic THPT.[8]

There is, however, little literature on the optimal timing of referral and no local guideline with well-defined indications for surgery to guide clinical practice. There have also been no studies looking into the local practice of preoperative localisation imaging modalities, rate of persistent or recurrent disease postoperatively and other surgical outcomes. An understanding of the WSLHD experience in the referral practice, choice and performance of preoperative localisation imaging, and other aspects of surgical management for patients with SHPT and THPT would provide insight into how we may be able to optimise the surgical management of SHPT and THPT patients in WSLHD, develop local guidelines to address current challenges in local practice with reference to international guidelines, and improve quality of care. Our experience will also give insights into local health districts nationally and abroad, with similar patient demographics and clinical practice, regarding optimisation of surgical management of SHPT and THPT patients.

Examining the impact of cinacalcet delisting from PBS in Australia between 2015 and 2019 on the volume of parathyroidectomies and timing of surgery along the disease process will also provide insight into the effect of cinacalcet delisting on surgical management of SHPT and THPT patients and its broader health policy implications.

Objectives

To evaluate time to surgery from onset of dialysis, preoperative disease severity, and their correlations, for patients with SHPT and THPT in WSLHD, to help identify ways to optimise preoperative referral practice.

To evaluate the DTA of preoperative localisation studies in WSLHD and compare to international benchmarks.

To assess the distribution of parathyroid gland/s in persistent and recurrent hyperparathyroidism post-operation and provide insight into the potential role of localisation imaging in preventing persistent and recurrent disease.

To assess the rate of parathyroidectomy and time to surgery from onset of dialysis after delisting of cinacalcet from Australian PBS compared to before the delisting.

Methods

Ethics approval

This study was approved by the WSLHD Human Research Ethics Committee (HREC).

Patient selection

Data for a consecutive series of ESRD patients undergoing parathyroidectomy within WSLHD were retrospectively collected from prospectively kept databases and medical records. Information gathered included patient demographics, preoperative, intraoperative, and postoperative variables; histopathology results and surgical outcomes; postoperative complications; follow-up variables; and reoperative variables.

For this study, all patients that underwent parathyroidectomy for secondary and tertiary hyperparathyroidism from 1 January 2009 to 31 December 2019 at Westmead Hospital and Blacktown Hospital within WSLHD were included. Those that had reoperative parathyroidectomy during the study period with their index parathyroidectomy performed prior to 2009 were excluded. All parathyroidectomy for SHPT and THPT are referred to and performed by the Head and Neck Surgery team in Westmead Hospital and Blacktown Hospital, which are the two major centres that perform these surgeries within the WSLHD. The surgical approach within the team has been consistent between 2009 and 2019.

Databases searched to identify relevant patients included operating theatre databases, validated against surgeon case logs to ensure complete capturing of relevant cases. Databases searched to obtain relevant data included WSLHD renal dialysis and renal transplant databases and WSLHD electronic medical records. Preoperative localisation imaging results were extracted from formal imaging reports provided by the imaging providers.

Study design

Patients were separated into two groups according to their diagnosis of SHPT or THPT at the time of surgery. All THPT patients had persistent hyperparathyroidism despite renal transplant.

Primary and secondary outcome measures

The primary outcome measures were time to surgery from onset of dialysis, preoperative disease severity represented by biochemical markers, including PTH, corrected serum calcium, serum phosphate, and ALP; BMD scores; presence or absence of pathological fracture, brown tumour, or calciphylaxis; preoperative localisation imaging findings; intraoperative findings; and histological findings.

Secondary outcome measures were baseline patient characteristics, operation performed, surgical outcomes represented by biochemical markers, BMD scores, persistent or recurrent disease, surgical complications, readmission, reoperation, or death within 30 days of surgery, duration of follow-up, time of recurrence, intraoperative findings and histological findings from reoperation where applicable.

Statistical analyses

Data analysis was performed to evaluate the outcome measures, in particular:

Mean time to surgery from onset of dialysis.

Disease severity at time of surgery, represented by the mean value and distribution of biochemical markers and BMD scores, and incidence of pathological fractures.

Correlation between time to surgery from onset of dialysis and preoperative disease severity.

Accuracy of preoperative localisation imaging modalities. This was done by correlating operative and histological findings of pathological parathyroid glands with preoperative imaging findings. A true positive is when the imaging and the histologically confirmed pathological parathyroid gland are in the same quadrant of the neck. A false negative is when there is no positive signal on the preoperative imaging however there is a pathological gland identified intraoperatively and confirmed by histopathology in a respective quadrant of the neck. Sensitivity and specificity of preoperative localisation imaging modalities is then calculated and compared to the meta-analysis results from Chapter 2 of this thesis.

Incidence of persistent or recurrent disease

Incidence of parathyroidectomy and mean time to surgery from onset of dialysis pre- and post- cinacalcet PBS delisting.

For statistical analysis, Microsoft Excel was used. Several statistical steps were undertaken to ensure the validity and reliability of the findings.

Data cleaning: data was cleaned by removing or excluding data points with missing values to ensure that the dataset was complete and ready for analysis.

Data exploration: descriptive statistics were calculated to summarise the data. Measures such as mean, standard deviation, and 95% confidence intervals (CI) were calculated to provide insights into the central tendency, variability, and precision of the data.

Finding correlation and significance: correlation analysis was performed to determine the relationships between variables in the dataset. Depending on the nature of the variables involved, different statistical methods were employed:

> Pearson Correlation Coefficient was employed if both variables were continuous. It measures the strength and direction of the linear relationship between two continuous variables. The correlation coefficient ranges from -1 to +1, where values closer to -1 or +1 indicate a stronger correlation.
>
> Point-Biserial Correlation was used if one variable is continuous, and the other is binary. The correlation coefficient ranges from -1 to +1, where values closer to -1 or +1 indicate a stronger correlation.
>
> p-value: To determine if the observed correlations were statistically significant, hypothesis testing was conducted. The p-value was calculated, which represented the probability of observing the obtained correlation by chance alone. A p-value below a predetermined 0.05 indicates statistical significance.

Sensitivity and specificity of localisation imaging modalities were calculated in the same way as in the meta-analysis for consistency.

Results

Patient characteristics

In total, 61 parathyroidectomies were performed in WSLHD between 2009 and 2019 for patients with CKD, 46 for SHPT and 15 for THPT. The mean age of all patients was 55 (±14) years. Patient demographics are summarised in Table 10. Almost 30% of SHPT patients had kidney transplant as one of the indications for surgery, all these patients also had advanced renal osteodystrophy necessitating referral for surgery.

Table 10 Patient characteristics. SD Standard Deviation, PD Peritoneal Dialysis, HD Haemodialysis.

	Total N = 61	**SHPT N = 46**	**THPT N = 15**
Age Mean (SD)	55 (±14)	55 (±15)	55 (±9)
Days from Dialysis (SD)	2886 (±1983)	2571 (±1938)	3812 (±1820)
Mode of dialysis at time of surgery			
PD	11 (18.0%)	11 (23.9%)	0 (0.0%)
HD	34 (55.7%)	34 (73.9%)	0 (0.0%)
None	1 (1.6%)	1 (2.2%)	0 (0.0%)
Kidney transplant	15 (24.6%)	0 (0.0%)	15 (100.0%)
Transplant as indication for surgery			
Y		13 (28.3%)	
N		33 (71.7%)	

Time to surgery from onset of dialysis and surgical outcomes

Time to surgery

Mean time to surgery from onset of dialysis was 2886 (±1983) days. The distribution of days to surgery from onset of dialysis is shown in Figure 14. The number of days from onset of dialysis before a patient is referred for and undergoes parathyroidectomy ranges from 1 to 30 years. Majority of the patients had surgical exploration for their hyperparathyroidism between 1 to 14 years from the onset of the dialysis, which is a very wide range.

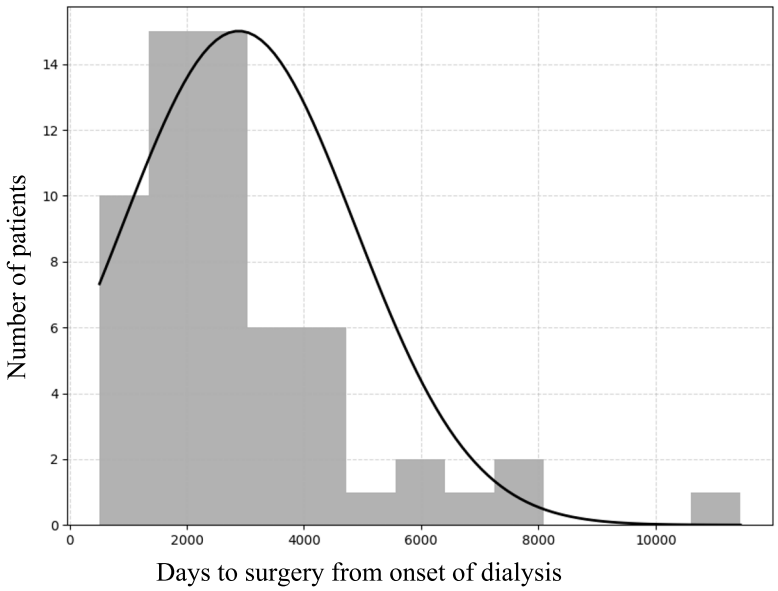

Figure 14 Distribution of days to surgery from onset of dialysis for SHPT and THPT patients

Preoperative disease severity

Biochemical markers

Mean preoperative PTH level was 142.8pmol/L (±103.3), corrected calcium was 2.5mmol/L (±0.3), phosphate was 1.6mmol/L (±0.7), ALP was 385.2U/L (±410.5). The distribution of biochemical marker results is shown in Figure 15. The range of values for preoperative biochemical markers is wide as shown in the histograms, indicating a wide range of preoperative disease severity.

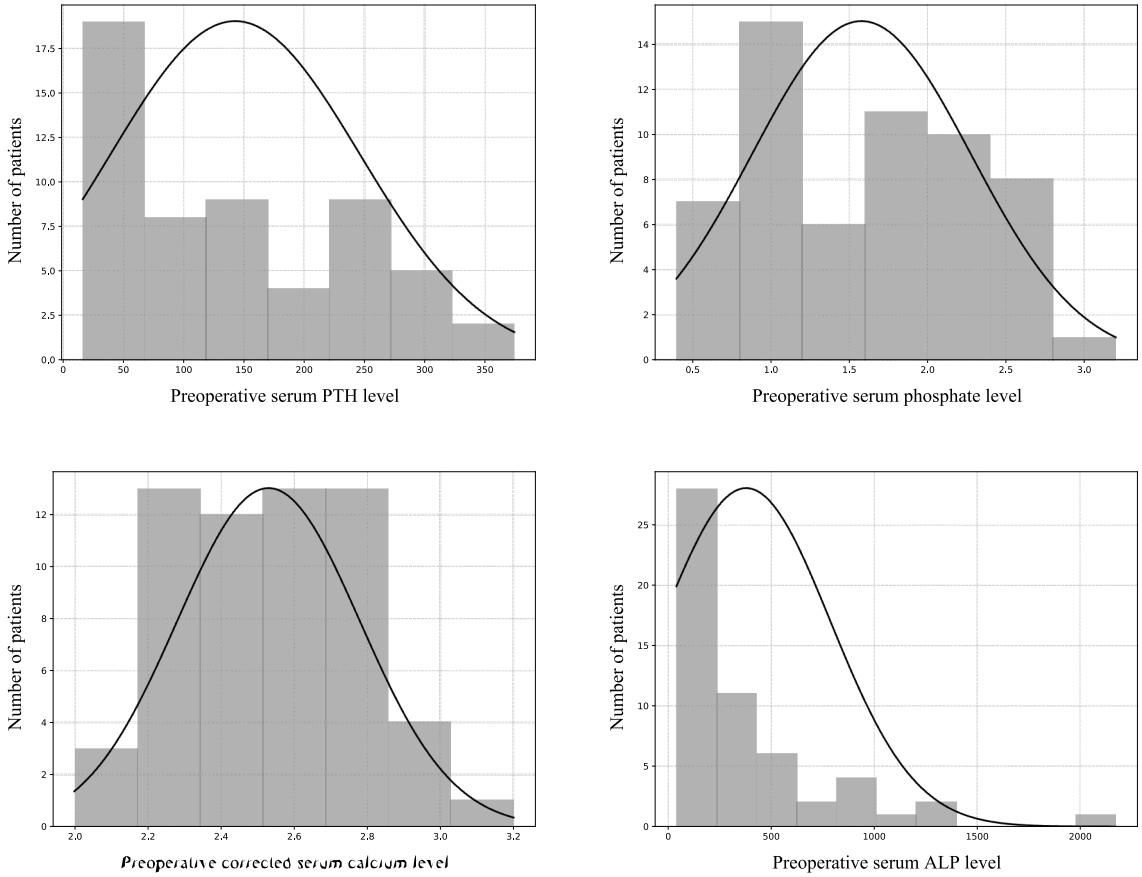

Figure 15 Distribution of preoperative biochemical marker levels for SHPT and THPT patients

BMD scores

Mean value for patient's lowest T-scores was -2.2 (±1.3), mean value for patient's lowest Z-score was -2.4 (±1.3). Distribution of lowest T-score and Z-score are shown in Figure 16. Again, the range of distribution is wide, similar to the preoperative biochemical markers.

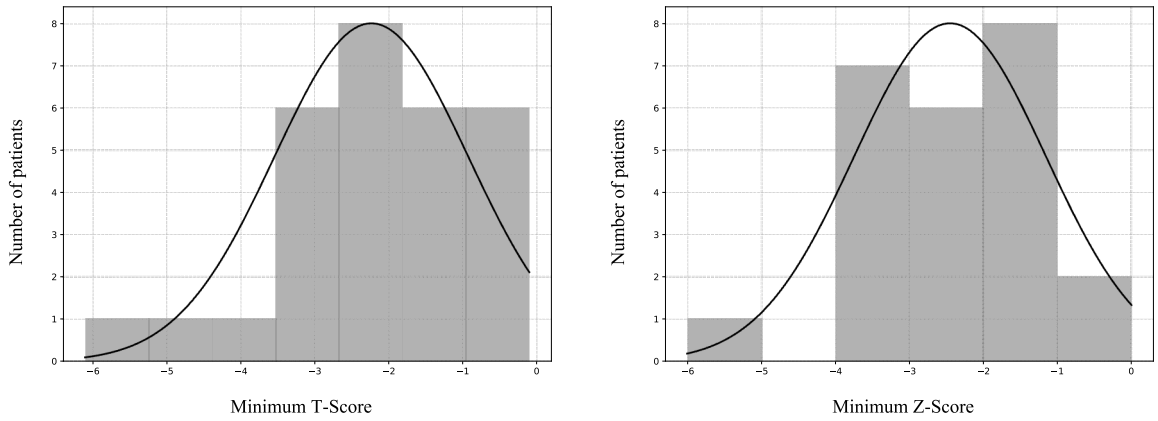

Figure 16 Minimum T-score and minimum Z-score on preoperative bone mineral density scans for SHPT and THPT patients

Pathological fractures

17 patients (27.9%) had documented pathological fractures. 9 patients (14.8%) had documented brown tumours. 3 patients (4.9%) had documented calciphylaxis, one being an ulcerating soft tissue mass in the buttock, one being a soft tissue lesion in the finger pulp, and one being a painful calcified mass in the soft tissue of the hip. All three suffered from symptoms of pain and associated functional impairment, however there was no associated mortality in these three patients.

Correlation between days to surgery from onset of dialysis and preoperative disease severity

No statistically significant strong correlation was observed between the preoperative biochemical markers and duration of disease based on days to surgery from onset of dialysis in our patient cohort as shown in Table 11. This is somewhat unexpected as one would assume that the longer the duration of disease the more deranged the biochemical markers become. However, the lack of positive correlation observed can be due to a few factors. The wide range of time to referral for surgery from onset of dialysis in our patient cohort may mean that biochemical derangements have plateaued much earlier in the disease process and therefore confounding the correlation based on preoperative biochemical markers. Results may also be confounded by the effects of medical treatment. Our sample size may also be a contributing factor.

Table 11 Correlation between days to surgery from onset of dialysis and preoperative biochemical markers for SHPT, THPT and, SHPT and THPT

SHPT	**Pearson's Correlation Coefficient**	**P-value**
Pre-op PTH	-0.07	0.65
Ca	-0.16	0.28
PO4	-0.25	0.09
ALP	0.01	0.97
Cr	-0.27	0.07
eGFR	0.01	0.92
THPT		
Pre-op PTH	0.29	0.34
Ca	0.10	0.74
PO4	0.04	0.90
ALP	0.22	0.49
Cr	0.50	0.08
eGFR	-0.36	0.25
SHPT and THPT		
Pre-op PTH	-0.21	0.13
Ca	0.00	1.00
PO4	-0.32	0.02
ALP	-0.07	0.61
Cr	-0.34	0.01
eGFR	0.16	0.24

Postoperative disease severity compared to preoperative disease severity

Biochemical markers

Mean value for postoperative biochemical markers were PTH 26.2pmol/L (±43.1), corrected calcium 2.3mmol/L (±0.3), phosphate 1.5mmol/L (±0.6), and ALP 132.4 mmol/L (±140.2), with marked improvement, especially for PTH and ALP, when compared to preoperative biochemical markers for disease severity. (Table 12)

Table 12 Biochemical markers, preoperative compared to 6-12 months post- operation

	Preop	**6-12 months postop**
PTH (SD)	142.8 (±103.3)	26.2 (±43.1)
Corrected Calcium (SD)	2.5 (±0.3)	2.3 (±0.3)
PO4 (SD)	1.6 (±0.7)	1.5 (±0.6)
ALP (SD)	385.2 (±410.5)	132.4 (±140.2)

BMD scores and pathological fractures

Mean value for patient's lowest T-score and Z-score 6-12 months post-operation were -0.9 (±1.1) and -1.6 (±1.2) respectively, which had marked improvement compared to preoperative BMD findings. (Table 13) 5 patients (8%) had new pathological fractures at 6-12 months post-operation.

Table 13 Minimum T-score and Z-score from BMD, preoperative compared to 6-12 months post-operation

	Preop	**6-12 months postop**
Minimum T-score	-2.2 (±1.3)	-0.9 (±1.1)
Minimum Z-score	-2.4 (±1.3)	-1.6 (±1.2)

Duration of follow-up

Mean duration of follow-up was 1611 days (±1050).

Surgical approaches

37 (61%) patients underwent TPTX + AT, where all parathyroid glands were identified and resected, and a portion of a parathyroid gland was transplanted into the SCM. 13 (21%) patients had incomplete parathyroidectomy where 1 or more parathyroid gland/s were not found. 9 patients (15%) underwent SPTX, where 3 and a half parathyroids were removed, leaving a portion of the most normal-appearing parathyroid gland behind with intact vascular supply. 2 patients (3%) had TPTX alone, where all parathyroid glands were removed without autotransplantation. 2 patients underwent concurrent ipsilateral cervical thymectomy in the setting of not finding an ipsilateral inferior parathyroid gland intraoperatively. Parathyroid glands were subsequently identified in both patients upon histopathology examination of the thymus specimens. 7 patients underwent concurrent hemithyroidectomy, 4 for concurrent thyroid pathologies (2 thyroid nodules, 2 multinodular goitres), 1 for a suspected intrathyroidal hyperplastic parathyroid gland identified on preoperative localisation imaging, which was subsequently confirmed on histopathology, and 2 for incomplete identification of ipsilateral parathyroid glands intraoperatively. 1 patient had total thyroidectomy in the same setting as the parathyroidectomy for concurrent papillary thyroid carcinoma. In the patients that underwent concurrent cervical thymectomy, hemithyroidectomy or total thyroidectomy, there were no postoperative complications, readmissions or reoperations directly related to these procedures. Frozen section was employed during surgery in some cases to help confirm removal of parathyroid gland/s, especially when appearance of suspected parathyroid tissue was equivocal intraoperatively.

Postoperative length of stay (LOS), calcium management and postoperative complications

Postoperative length of stay

The mean postoperative length of stay for the SHPT and THPT patients were 5.7 days (± 6.8) and 2.7 days (± 1.9) respectively.

Postoperative calcium management

All patients were prescribed regular oral calcium and calcitriol supplements postoperatively as per WSLHD post- parathyroidectomy calcium management protocol. 28 of the 46 SHPT patients and 1 of the 15 THPT patients had sufficiently low postoperative serum calcium levels mandating IV calcium infusion as per protocol. These comprised of 56.8% of the TPTX + AT group, 55.6% of the SPTX group, 50% of the TPTX alone group and 16.7% of the incomplete group. Understandably the incomplete parathyroidectomy group had the least prevalence of severe hypocalcaemia due to the effects of the remnant parathyroid gland/s. Correlation between lowest corrected serum calcium level and postoperative LOS was also evaluated, with the Point Biserial Correlation coefficient being $r_{pb} = 0.38$, indicating a weak positive correlation between the extent of hypocalcaemia and postoperative LOS ($p<0.01$).

Postoperative complications

1 patient required reoperation day 1 post-operation for a neck haematoma. 1 patient had transient RLN palsy in the setting of having had alcohol ablation to an ipsilateral parathyroid gland previously. No patient had permanent RLN palsy. 5 patients had readmission within 30 days, 2 for renal transplant, 2 for hypocalcaemia and 1 for an unrelated medical presentation. A total of 14 patients had documented post-operative complications. 8 of these patients had Clavien-dindo 1 complication, 3 Clavien-dindo 2, and 3 Clavien-dindo 3. The Clavien-dindo 3 complications were AV fistula thrombosis requiring angioplasty and stenting, haematemesis requiring gastroscopy, and postoperative haematoma requiring surgical evacuation. There were no reported events of cardiac complications postoperatively and no mortality within 30 days of surgery.

Incidence of persistent and recurrent disease

Persistent and recurrent disease was defined as having a PTH level ≥ 9 times of normal at 60pmol/L within 6 months of surgery and 6 months after the operation respectively. The threshold for PTH was determined based on consensus from local nephrology and surgical specialists involved in the care of CKD patients and the KDIGO recommendation of maintaining PTH levels in stage 5 patients with CKD in the range of 2 to 9 times the upper limit of normal to prevent hypocalcemia.[4] 9 patients (14.8%) had persistent disease, and 7 patients (11.5%) had recurrent disease. In total, 16 patients (26.2%) had residual (persistent or recurrent) disease. 7 of the 9 patients that had persistent disease had incomplete parathyroidectomy, as not all parathyroids could be identified intraoperatively. In contrast, only 1 of the 7 patients that developed recurrent disease had incomplete parathyroidectomy. 5 patients in total were referred for consideration of reoperation, 3 of the 5 patients went through with surgical re-exploration, 1 of the 5 patients improved with further adjustment in medical management and no longer required surgery, and 1 patient was not well enough to undergo surgery and required further medical optimisation.

Accuracy of preoperative localisation imaging in WSLHD and comparison to results from meta-analysis

In our patient cohort with SHPT, 35 of the 47 patients had accessible formal reports of preoperative localisation imaging. Sensitivity for US was low at 33% (95%CI 23% - 43%), specificity for US was 64% (95%CI 36% - 92%). Sensitivity for SPECT/CT was low at 41% (95%CI 28% - 54%) and specificity was 60% (95%CI 17% - 100%). The combination of US and SPECT/CT improved sensitivity to 50% (95%CI 37% - 63%) with a decrease of specificity to 40% (95%CI 0% - 83%). Performance was better in the THPT group. (Table 14)

Table 14 Sensitivity and Specificity of preoperative localisation imaging done in the WSLHD patient group, compared to sensitivity and specificity of preoperative localisation imaging from meta-analysis in Chapter 2 of thesis

	Sensitivity, WSLHD	**95% CI**	**Specificity, WSLHD**	**95% CI**	**Sensitivity, Benchmark**	**95% CI**	**Specificity, Benchmark**	**95% CI**
SHPT								
U/S	0.33	0.23-0.43	0.64	0.36-0.92	0.67	0.54-0.79	0.65	0.44-0.81
SPECT/CT	0.41	0.28-0.54	0.60	0.17-1.00	0.80	0.72-0.86	0.78	0.57-0.91
U/S + SPECT/CT	0.50	0.37-0.63	0.40	0.00-0.83				
THPT								
U/S	0.54	0.37-0.71	0.77	0.54-1.00				
SPECT/CT	0.57	0.39-0.75	0.90	0.71-1.00				
U/S + SPECT/CT	0.61	0.43-0.79	0.88	0.65-1.00				
SHPT and THPT								
U/S	0.39	0.31-0.47	0.73	0.64-1.00				
SPECT/CT	0.46	0.36-0.56	0.80	0.60-1.00				
U/S + SPECT/CT	0.52	0.42-0.62	0.69	0.44-0.94				

In 4 of the 8 patients that had incomplete parathyroidectomy and postoperative persistent or recurrent hyperparathyroidism, the intraoperatively missed parathyroid gland could not be identified on the preoperative localisation imaging. These 4 patients underwent preoperative SPECT/CT or CT with or without an ultrasound through 4 different imaging providers. The 61 SHPT and THPT patients had preoperative imaging through at least 7 different imaging providers within WSLHD, which can significantly contribute to the variability in performance and accuracy of preoperative localisation imaging in our patient cohort.

Distribution of parathyroid gland in persistent and recurrent disease, and correlation with localisation imaging findings

3 patients with persistent or recurrent hyperparathyroidism post- operation underwent reoperative surgery with localisation imaging done prior to the reoperation to help identify the pathological parathyroid gland. Of the 3 patients, a 38-year-old male patient with SHPT, on dialysis for 7 years, had a preoperative localisation neck ultrasound prior to the index surgery that did not identify any abnormal parathyroid gland and a SPECT/CT that identified an enlarged left inferior parathyroid gland only. Intraoperatively, an enlarged right superior, left superior and left inferior parathyroid glands were identified and removed with the right inferior parathyroid gland not found. A right hemithyroidectomy and cervical thymectomy was performed concurrently. Patient had a persistently elevated PTH postoperatively of 153.1mmmol/L indicating persistent SHPT. Histopathology confirmed that the 3 resected glands were hyperplastic parathyroid glands, however no parathyroid tissue was found in the right hemithyroidectomy or thymectomy sample. Repeat localisation ultrasound post-operation showed mainly focal postoperative haematoma posterior to the thyroid, however SPECT/CT done at a different imaging provider to the initial SPECT/CT demonstrated findings suggestive of an ectopic 1.5cm hyperplastic or adenomatous parathyroid gland posterior to the manubrium, which was not shown in the initial SPECT/CT prior to the index operation. Two months after the index surgery, patient underwent a video-assisted thoracoscopy by a cardiothoracic surgeon and an enlarged retrosternal parathyroid gland consistent with the second SPECT/CT findings was identified and resected. Postoperative PTH improved to 11.7mmol/L from 207.4mmol/L indicating that there was no residual hyperfunctioning parathyroid gland/tissue. Histopathology confirmed a 38mm x 24mm x 18mm hyperplastic parathyroid gland.

The second patient that underwent reoperative surgery was a 45-year-old male with SHPT, on dialysis for 6 years, who had a successful subtotal parathyroidectomy where three and a half parathyroid glands were removed, with postoperative PTH level improving to 55.1mmol/L from 242mmol/L and histopathology confirming all three and a half glands resected being hyperplastic parathyroid glands. There was no documented information or accessible reports for preoperative localisation imaging findings before the index operation. PTH level remained under 60mmol/L for the first six months, however over time increased to 266.5mmol/L. SPECT/CT suggested a 26mm x 16mm enlarged parathyroid gland posterior to the right lobe of the thyroid gland. Patient underwent a reoperative neck exploration 8 years after their index operation, where an enlarged right superior and inferior parathyroid glands were identified and removed, a right hemithyroidectomy and excision of a piece of right neck subcutaneous nodular tissue was also performed. Histopathology confirmed the right superior and inferior parathyroid glands and right neck subcutaneous tissue to be hyperplastic parathyroid tissues, and presence of parathyroid tissue within the right hemithyroidectomy specimen. Of note were the right superior and inferior hyperplastic glands despite previous successful resection and the presence of subcutaneous nodular parathyroid tissue, which suggest potential parathyroid gland rupture at the index operation. Postoperative PTH remained significantly high at 188.8mmol/L. There was no documentation of further surgery at the time of the study.

The third patient was a 58-year-old female with SHPT, on dialysis for 9 years, who had a preoperative localisation SPECT/CT showing a hyperplastic/adenomatous ectopic left

superior parathyroid gland in the left upper neck medial to the left carotid artery. Patient underwent a total parathyroidectomy, where 4 bilateral enlarged superior and inferior parathyroid glands were identified and removed, with autotransplantation of a portion of a parathyroid gland into the SCM. Postoperative PTH remained significantly high at 219.0mmol/L compared to 374.0mmol/L preoperatively, indicating persistent SHPT. Histopathology showed three hyperplastic parathyroid glands however the left inferior parathyroid gland sample was confirmed to be thyroid tissue only. Patient was referred for reoperation 3 years after the index operation. Further localisation US suggested a 15mm x 33mm x 15mm hyperplastic/adenomatous parathyroid gland located lateral to the superior pole of the left thyroid lobe, and a localisation SPECT/CT suggested a 30mm parathyroid gland in the left upper neck medial to the left carotid artery. Patient underwent a reoperative neck exploration, with identification and resection of a large ectopic parathyroid gland medial to the left carotid and immediately inferior to the left submandibular gland. Postoperative PTH level improved to 19.1mmol/L from >318.0mmol/L. Histopathology confirmed a 35mm x 15mm x 15mm hyperplastic parathyroid gland. This is an example of an ectopic undescended parathymus high up in the neck between the superior pole of the left thyroid lobe and carotid artery, in the posterior submandibular region, which was demonstrated both in the localisation imaging done prior to the index operation and the reoperation. It highlights the role of localisation imaging in identifying ectopic parathyroid glands.

Cinacalcet

Rate of parathyroidectomy and average time to surgery from onset of dialysis pre- and post-cinacalcet delisting

Cinacalcet was delisted from PBS in 2015. Though there seemed to be an increasing number of parathyroidectomies done for SHPT and THPT in WSLHD between 2015 and 2019, average numbers were similar compared to before 2015. (Figure 17)

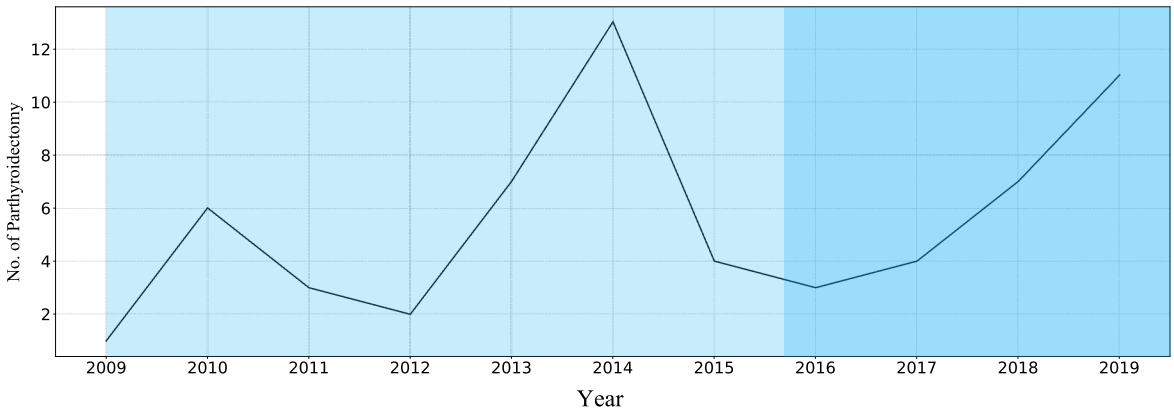

Figure 17 Number of parathyroidectomies for SHPT and THPT in WSLHD from 2000 to 2019.

**Cinacalcet delisting in August 2015*

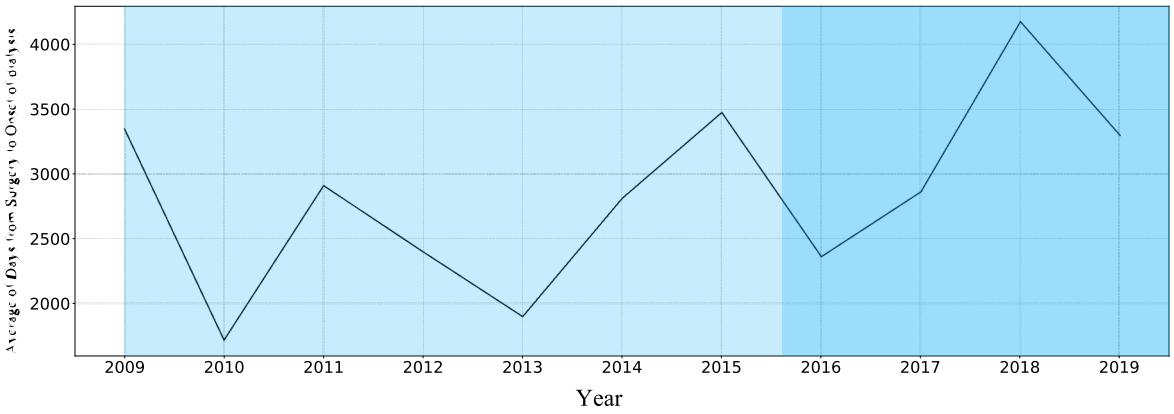

*Figure 18 Average days to surgery from onset of dialysis in WSLHD SHPT and THPT patients from 2009 to 2019. *Cinacalcet delisting in August 2015*

There was an overall increase in the average days from surgery to onset of dialysis for patients undergoing parathyroidectomy for SHPT and THPT between 2015 and 2019, after cinacalcet was delisted, compared to before 2015. In 2018, the average days from surgery to onset of dialysis was over 4000 days or 11 years, which was the longest since 2009. (Figure 18) This could be due to the addition of patients who were managed medically with cinacalcet with a prolonged duration of disease requiring surgery after the delisting of cinacalcet.

Discussion

In our patient cohort with SHPT and THPT, time to surgery from onset of dialysis as a surrogate for time to referral from onset of disease showed a wide range of distribution, indicating that patients were referred for surgery along various stages of their disease process. Preoperative disease severity as represented by preoperative biochemical markers and BMD imaging findings also showed a wide range of disease severity in patients referred for surgery. We observed that a significant proportion of patients were referred many years after onset of disease and with advanced disease, including pathological fractures indicating severe renal osteodystrophy and calciphylaxis. Though there was no strong positive correlation between time to surgery from onset of dialysis and preoperative disease severity shown, the variability in when patients were referred for surgery and the severity of disease for which patients were referred indicates a potential need for local guidelines to aid clinical decision-making in when to refer SHPT and THPT patients for parathyroidectomy. Surveying physicians managing CKD patients regarding the timing of referral would also be useful as part of the quality improvement initiative.

Majority of the patients that had preoperative localisation imaging had US and or SPECT/CT. We observed that the DTA of US or SPECT/CT in our patients was markedly lower than that found in the meta-analysis, which can be considered as the benchmark of performance for the purpose of the review. Sensitivity of US in our patient cohort was 33% (95%CI 23% - 43%) compared to the meta-analysed sensitivity of 67% (95%CI 54% - 79%). Sensitivity of SPECT/CT was 41% (95%CI 28% - 54%) in our study, compared to 80% (95%CI 72% - 86%) in the meta-analysis. We also observed that the combination of US and SPECT/CT

improved sensitivity in our patient cohort, which was consistent with the systematic review results.

More careful examination of the imaging reports showed that the localisation imaging in our patients were done through various imaging providers in WSLHD, whereas in most of the studies included in the meta-analysis these were done through a single institution and interpreted by specialists experienced in interpreting localisation imaging for SHPT and THPT. This raises the potential need to centralise preoperative localisation imaging in WSLHD, given parathyroidectomy for SHPT and THPT is a relatively rare occurrence and the technical challenges associated with identifying multiple pathological parathyroid glands on preoperative localisation imaging. Centralisation of service may help improve experience and performance of the imaging providers, hence improve quality of service. Improved performance of preoperative imaging may help improve surgical success and prevent morbidity associated with persistent or recurrent disease, particularly in cases where ectopic parathyroid glands are present. This is in the context of studies showing that the incidence of ectopic and supernumerary parathyroid glands in patients with SHPT and THPT can be up to 45% and 37% respectively.[30 31 32 33 34] Consideration for preoperative localisation imaging with a combination of US and SPECT/CT may also improve the yield and clinical utility of the tests. SPECT/CT is easily accessible, not too costly, and well tolerated by SHPT and THPT patients given no IV iodine contrast is required.

Above considerations may be applicable to other health districts with similar size and patient demographics to WSLHD, where centralisation and optimisation of service is even more paramount for a relatively small but comorbid patient group such as those with SHPT and THPT requiring parathyroidectomy. Consideration should also be given for future studies on the direct impact of preoperative localisation imaging on surgical outcome in SHPT and THPT, potentially by comparing surgical success rate and outcomes in patient groups with specific preoperative localisation imaging and those without preoperative localisation imaging.

The distribution of pathological glands in the 3 patients that had persistent disease or developed recurrent disease, and subsequently underwent reoperative parathyroidectomy, gave insights into why surgery may be unsuccessful in SHPT or THPT, and how outcomes may be improved. For the patient that had the mediastinal gland that was not identified on the initial localisation imaging prior to the first surgery, the gland was shown on the SPECT/CT done through a different imaging provider prior to the reoperative surgery. This can potentially be due to the gland uptaking more radioactive tracer after other pathological parathyroid glands were removed, however given its final size of >3cm in maximal diameter, it may have been identified in the initial SPECT/CT if done at a centralised imaging provider with more experience in the acquisition and interpretation of SPECT/CT for SHPT and THPT.

The third reoperative patient had a persistent left upper neck ectopic parathyroid gland medial to the carotid and abutting the submandibular gland, consistent with an undescended parathymus, which was identified on both the initial localisation imaging and subsequent imaging prior to reoperative surgery after confirming postoperative persistent disease. A normal piece of thyroid tissue was mistaken as the pathological parathyroid gland and removed at the index surgery, leaving the ectopic gland behind. This highlights the role of

preoperative localisation imaging in help identifying ectopic parathyroid glands, as well as the challenges of intraoperative identification and confirmation of all pathological parathyroid glands in SHPT and THPT where a multi-gland disease process occurs. Intraoperative frozen sections of resected sample usually are time consuming and are limited by hospital laboratory operating hours. Other intraoperative adjuncts such as probe radioguidance, intraoperative ICG fluorescence imaging or an intraoperative auto-fluorescence detection system, or ioPTH may help to improve the identification, confirmation, and removal of all hyperplastic or adenomatous parathyroid glands, thus improving surgical success and outcomes. Probe radioguidance has been shown to have a high sensitivity of identifying hyperfunctioning parathyroid glands and decrease overall operative time. Fluorescence imaging has also been shown to have a high sensitivity of 83% - 92% in identifying parathyroid tissue. ioPTH monitoring, with appropriately set criteria, can help predict complete removal of hyperfunctioning parathyroid glands and surgical success.[69] Challenges with setting the appropriate threshold for ioPTH to predict surgical success lies with the impaired metabolic clearance of PTH in patients with CKD. Current limitations of the use of these intraoperative adjuncts relate to the lack of consistent evidence on their impact on surgical success in SHPT and THPT.[8 38 70]

The second reoperative patient developed recurrent disease at the same location as where hyperplastic parathyroid glands were successfully identified and removed in the index surgery and was also found to have ectopic intrathyroidal parathyroid tissue, which was not evident in the index operation, in addition to subcutaneous nodular parathyroid tissue. Recurrence in the same anatomical location where pathological glands were resected may mean development of disease in remnant gland intentionally left behind in subtotal parathyroidectomy, from remnant of pathological glands unintentionally left behind, or supernumerary glands that have become pathological over time. The use of intraoperative adjuncts may also be useful in these circumstances to help improve detection and removal of remnant disease that are not intended to be left behind and improve the success of the index operation. Recurrent disease that develops from intentionally left behind gland or autotransplanted gland however cannot necessarily be prevented and contributes to the incidence of recurrent disease for SHPT and THPT even in the most experienced surgical hands. Recurrence in the same anatomical location as a resected gland in addition to the development of nodular subcutaneous parathyroid tissue may also be due to gland rupture at the index operation and subsequent parathyromatosis, which would highlight the need for careful handling of parathyroid glands intraoperatively to avoid gland rupturing.

We observed that most SHPT patients that had persistent disease had incomplete parathyroidectomy. This again highlights the potential role for adjuncts to aid the intraoperative detection, confirmation and removal of all pathological parathyroid glands and improve surgical outcome.

The average time to surgery from onset of dialysis increased from 2015 to 2019 after the delisting of cinacalcet from PBS. This could be related to patients needing parathyroidectomy as a result of cessation of cinacalcet. These patients usually have been on prolonged dialysis therapy with cinacalcet previously keeping symptoms and complications of hyperparathyroidism at bay and now require surgery post- cessation of cinacalcet. In addition to placing more strain on the limited resources available for surgery in the public health system, these patients also tend to be more comorbid with more advanced CKD and therefore

potentially have higher perioperative risks. Fortunately, cinacalcet has been relisted on PBS since 2022 to optimise the management and minimise risks for this unique patient group.

Some of the strengths of our study was that parathyroidectomies for SHPT and THPT in WSLHD were centralised to a surgical team, therefore there was consistency in the surgical approaches to these patients. There was no postoperative mortality, the incidence of severe postoperative morbidity was low, and there was overall good length of follow-up.

The limitations of our study included the overall sample size and retrospective data collection. On average, WSLHD performed 6 parathyroidectomy per annum for SHPT and THPT. In comparison, a recent study by the Northern Sydney Local Health District (NSLHD) reported an average volume of 10 parathyroidectomy per annum for SHPT. The difference in surgical volume despite having similar patient population sizes can be due to a few different factors, including perioperative resource availability, local referral pattern, and volume of referral from centres external to the local health district.[71] The retrospective design of this study may have led to various biases. For example, the reason for choosing certain preoperative localisation imaging modality or modalities for each patient could not be ascertained in retrospect, which could have led to selection bias. A retrospective study design meant that there was no control over the choice of imaging providers for the preoperative localisation imaging, which was reflected by the number of imaging providers used and the heterogeneity of imaging performance. Additionally, findings from the single-centre set-up of this study may not be generalizable to all other institutions, depending on differences in patient demographics, clinical practice and healthcare resources.

Conclusion

Our study identified a need for the development of local guidelines to aid clinical decision-making in when to refer SHPT and THPT patients for parathyroidectomy. We also identified a need for centralisation of preoperative localisation imaging for SHPT and THPT to help improve imaging performance and clinical utility. Combination imaging modalities with US and SPECT/CT should be considered for preoperative localisation, especially within WSLHD, where single modality test accuracy seems to be low. Future studies should be considered to assess the direct impact of preoperative localisation imaging on surgical success and outcomes, potentially by comparing patient groups with and without preoperative localisation imaging. The use of intraoperative adjuncts can be considered to help with the identification and confirmation of removal of all pathological parathyroid glands. Delisting of cinacalcet from PBS may have increased the need for surgery for a group of SHPT and THPT patients with more advanced disease and higher perioperative risks. This should be taken into consideration for any future decisions regarding the public funding of cinacalcet in Australia.

Chapter 4: Summary

Through meta-analyses, SPECT/CT has demonstrated superior DTA compared to US and MIBI in preoperative localisation of SHPT with a summary sensitivity of 80% (95% CI 72% to 86%) and specificity of 78% (95% CI 57% to 91%). Therefore, it should be considered as the preferred imaging modality for localisation of SHPT when a single modality is used. Combination imaging with US and SPECT/CT may have better performance in localisation than single imaging modalities and should be considered in clinical practice. Preoperative US of the neck remains crucial to exclude occult thyroid pathology regardless of its utilisation as a localisation study.

There is a need for standardisation of indications and timing for referral of SHPT and THPT patients for parathyroidectomy and development of local guidelines in WSLHD and similar health districts so that surgery can be considered before severe hyperparathyroidism and complications such as pathological fractures or calciphylaxis develop.

There is also a need for the centralisation of preoperative localisation imaging in WSLHD and similar health districts, prior to parathyroidectomy for SHPT and THPT, to help improve the performance of localisation imaging. The combined use of US and SPECT/CT should be considered as the preferred imaging modality with more superior performance both locally and as suggested in the systematic review.

Based on evaluation of persistent and recurrent cases that underwent reoperative surgeries in WSLHD, the adoption of intraoperative adjuncts, such as probe radioguidance, fluorescence imaging, or ioPTH, should be considered in WSLHD and similar health districts to potentially help improve surgical success in identifying and removing all pathological glands in SHPT and THPT in the index surgery.

An increase in the average time to surgery from onset of dialysis in SHPT and THPT patients requiring parathyroidectomy after cinacalcet was delisted from PBS in 2015 may reflect an increased need for parathyroidectomy in patients that were previously on cinacalcet. These patients are often more comorbid with more advanced CKD and higher perioperative risks, especially in local health districts with similar patient demographics to WSLHD. These are important factors to be taken into consideration for the public funding of cinacalcet in Australia.

Directions for future research

More DTA studies on combined imaging modalities for preoperative localisation of SHPT and THPT, in particular US and SPECT/CT, are needed to allow meta-analysis of results and more accurate interpretation of the performance of combined imaging modalities compared to single imaging modality. More comparative studies directly comparing preoperative localisation imaging modalities for SHPT and THPT are needed to allow potential meta-analysis of these comparative studies and stronger evidence for clinical decision in the choice of imaging.

Future studies comparing the clinical outcomes of patients undergoing preoperative localisation imaging and those without imaging would provide more direct insight into the clinical impact of various preoperative localisation imaging modalities.

Prospective study evaluating changes in DTA of preoperative localisation imaging for SHPT and THPT in WSLHD after centralisation of service compared to prior to centralisation would give insight into the potential effectiveness of such a quality improvement project. Prospective studies assessing the impact on surgical success and incidence of persistent and recurrent disease post- surgical exploration in WSLHD after introduction of intraoperative adjuncts would provide valuable information for their effectiveness and potential role in surgical quality improvement.

Appendix

Appendix A – Basic and Derived Formulas for Contingency Table, Sensitivity, Specificity, Accuracy, Prevalence, Positive and Negative Predictive Values

Basic Formulas	
Sens	TP / (TP + FN)
Spec	TN / (TN + FP)
PPV	TP / (TP + FP)
NPV	TN / (TN + FN)
Acc	(TP + TN) / (TP + TN + FP + FN)
Pre	(TP + FN) / (TP + TN + FP + FN)

Derived Formulas	
TP	N * Pre * Sens
TN	N * (1 - Pre) * Spec
FP	N * Pre * (1 - Sens)
FN	N * Pre * (1 - Sens)
Sens	PPV * (TP + FP) / Pre
Spec	NPV * (TN + FN) / (1 - Pre)
Acc	(Sens * Pre) + (Spec * (1 - Pre))
	((N * Pre * Sens) + (N * (1 - Pre) * Spec)) / N
Pre	PPV * (Spec - 1) / (Sens * (PPV - 1) + PPV * (Spec - 1))
	(Acc - Spec) / (Sens - Spec)

Abbreviations	
TP	True Positive
TN	True Negative
FP	False Positive
FN	False Negative
Sens	Sensitivity
Spec	Specificity
PPV	Positive Predictive Value
NPV	Negative Predictive Value
Acc	Accuracy
Pre	Prevalence
N	Sample Size

Appendix B – Noteworthy Discrepancy from the Studies Included in Meta-Analysis

Study	Discrepancy
Yuan 2016	The Accuracy of US listed in the study should be 0.75 instead of 0.82, based on the contingency table provided: TP = 155 FP = 19 FN = 37 TN = 17

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