Pre-operative localisation and surgical outcomes for Primary Hyperparathyroidism (PHPT): an 11-year review at a South African hospital.

by

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VWYTIR001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree

MMed (Surgery)

/Publication-ready format/

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of submission: 15 August 2018

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ABSTRACT

HREC REF 338/2016

**Title:** Pre-operative localisation and surgical outcomes for Primary Hyperparathyroidism: an 11-year review at a South African hospital.

**Introduction:**

*Primary Hyperparathyroidism* (PHPT) is characterized by hypersecretion of PTH leading to hypercalcaemia with successful surgery being the only definitive cure. Broadly, three techniques of parathyroidectomy exist: open bilateral neck exploration and minimally invasive parathyroidectomy, which is subdivided into open focused approaches and endoscopic focused approaches. A focused parathyroid gland exploration guided by pre-operative imaging is associated with less morbidity compared to a bilateral approach. Focused explorations may target either the side or the specific parathyroid gland identified.

**Aim:**

The primary aim of this study was to evaluate the accuracy of pre-operative localisation for PHPT in a single centre. The secondary aim was to review the type of parathyroid surgery performed and the final Parathyroid Hormone (PTH) levels in patients who have undergone parathyroidectomy for PHPT.

**Methods:**

This is a retrospective review of all patients who underwent primary surgery for PHPT between 2005 and 2015. Patients were identified from a general operative database. Data was collected from pathology records, operative notes, nuclear medicine and radiology reports and captured on a confidential data sheet.

**Results:**

Records of 98 patients were found and included. Sestamibi had a sensitivity of 88%, a positive predictive value of 83% and an accuracy of 75%. Ultrasound had a sensitivity of
52%, a positive predictive value of 78% and an accuracy of 44%. The total number of cases in which both ultrasound and sestamibi were done was 73. Sestamibi and ultrasound showed concordant results in 25 cases. The overall surgical success rate was 94% (92/98). The cure rate for patients in whom sestamibi and ultrasound were concordant, was 96% (24/25). The minimum and maximum calcium levels in the cohort were 2.2 and 4.41 respectively, with a mean of 2.86. PTH levels ranged between 4.2 and 186 with a mean of 33.8. One double adenoma was proven on histology. The rest were all single adenomas. The total number of malignancies were 3 of which 1 was part of a MEN syndrome.

**Conclusion:**

Our surgical success rate was 94%. When imaging modalities were concordant, surgical success was achieved in 24 cases, thus in 96% of the subgroup. Our figures compare favourably with international standards. There is scope for improvement in the accuracy of both ultrasound (46%) and sestamibi (75%) localization. Currently a combination of both imaging modalities is still recommended.
ACKNOWLEDGEMENT AND CONTRIBUTIONS:

I sincerely thank Dr Lydia Cairncross, my supervisor, for her tireless guidance, help and advice with the completion of this dissertation.

A warm thank you also goes to Dr Juan Klopper who assisted with the statistical evaluation of the data herein.
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ABBREVIATIONS:

PHPT: Primary Hyperparathyroidism
PTH: Parathyroid hormone
MEN: Multiple endocrine neoplasia
TC-99-sestamibi: Tecnetium-99-sestamibi
SPECT: Single Photon Emission Computed Tomography
OFS: Osteitis Fibrosa Cystica
ioPTH: Intra-operative PTH
MIP: Minimally Invasive Parathyroidectomy
BNE: Bilateral neck exploration
UNE: Unilateral neck exploration
OMIP: Open minimally invasive parathyroidectomy
VAP: Video-assisted parathyroidectomy
VAP-LA: Video-assisted parathyroidectomy through a lateral approach
MIVAP: Minimally-invasive video-assisted parathyroidectomy
EP: Purely Endoscopic Parathyroidectomy
Chapter 1: LITERATURE REVIEW

1. Introduction:

Primary Hyperparathyroidism (PHPT) is a condition characterized by the autonomous hypersecretion of parathyroid hormone (PTH) with resultant hypercalcaemia, or high-normal serum calcium with elevated, or inappropriately “normal” serum PTH. ¹ PHPT is the third most common endocrine disorder, after diabetes and thyroid disease. Primary Hyperparathyroidism is the most common cause of hypercalcaemia in the community affecting 1 in 500 women and 1 in 2000 men.

It was Sir Richard Owen, professor and conservator of the Museum at the Royal College of Surgeons in the UK, who, in 1852, published the earliest reference to the existence of the parathyroid glands. He described a “small, yellow, compact glandular body attached to the thyroid gland” on necropsy of a Great Indian Rhinoceros (Rhinoceros unicornis). The discovery and naming of the glands, however, is attributed to Sandstrom, a Swede. In 1880 he found structures “on both sides of the inferior border of the thyroid, the size of a small pea” in a dog. He proceeded to find the same structures in other animals including rabbit, cat, horse and ox and finally, he confirmed his findings in human tissue. He named these structures “glandulae parathyroidae”. ²

A French physiologist, Gley, observed in 1891 that tetany and death could follow experimental thyroidectomy in dogs only if the excised tissue included the glands described by Sandström. He thus concluded that these glands were essential to life. ²

By 1909 MacCallum and Voeghin had realised that parathyroid hormone’s main function was control of the calcium level in the plasma. Resection of these glands resulted in calcium loss in the stools and a drop of blood calcium levels with resultant tetany. The first doctor to correlate parathyroid activity with diseases of the bone (1915) was Shlagenhauser, a Viennese physician. He ascerted that in patients with osteitis fibrosa cystica, the bone disease was the result rather than the cause of parathyroid hyperplasia. He found a single enlarged parathyroid gland to be the aetiological agent in these cases. Collip said in 1925 that “The extraction of the parathyroid hormone prevents or controls parathyroid tetany and regulates the level of blood calcium”. This was confirmed when Felix Mandl performed
the first successful parathyroidectomy in Vienna in 1925 on a patient with osteitis fibrosa cystica with a significant relief of the bone disease. ²

Initially, all surgery for parathyroid disease required four gland exploration but, over the years, as imaging studies have become more accurate in their ability to localize an adenoma, the operation has evolved from an invasive bilateral neck exploration to a unilateral, more focused exploration. A unilateral exploration is associated with less morbidity than the traditional four-gland exploration. Certain international centres have taken the minimally invasive technique to the next level by targeting a single quadrant and thus a single gland when performing a focused exploration.

2. Parathyroid glands - anatomy and variation:

Parathyroids may be found anywhere along the tract of embryological development. Variation in position is especially seen in the inferior parathyroids, which develop from the third branchial pouch and migrate with the thymus. The upper parathyroids develop from the fourth branchial pouch and migrate inferiorly with the thyroid.

Cadaveric studies describe four parathyroid glands in 84% of human specimens. In 13% of cadavers five or more glands may be found. Each normal gland measures about 5mm in diameter and is often encased in an area of fatty tissue.

The expected location of the two superior glands is midway along the posterior aspect of the superior portion of the thyroid gland, adherent to the thyroid capsule. They lie above the level at which the inferior thyroid artery crosses the recurrent laryngeal nerve, at a depth superficial to the nerve. The two inferior glands are found in the same position relative to the inferior thyroid lobes. They generally lie caudal to the inferior thyroid artery and at a level deep to the recurrent laryngeal nerve but may extend to positions lateral or inferior to the base of the thyroid along the branches of the inferior thyroid veins. Both sets of glands are supplied by the inferior thyroid arteries, which originate from the subclavian artery via the thyrocervical trunk. They are supplied in a single end artery structure. Arterial supply to the inferior thyroid lobe branches off prior to the vessel entering the parathyroid gland. ³
Glands located above or below the level of the thyroid gland or distant from its posterior aspect are considered ectopic. Ectopic gland locations may include: in the thymus, on the carotid sheath, within the thyroid, in the superior mediastinum, in the thyrothymic ligament and in the retropharyngeal area. Adenomas more often originate from inferior glands. 

3. Incidence:

0.7% of the general population in the Western world is affected by PHPT which translates to 28 per 100 000 in the US per year. A 2-3 times predominance is seen in women.

4. Pathophysiology:

PHPT is a biochemical diagnosis based on an elevated or inappropriately normal PTH with high calcium levels and the exclusion of secondary causes for elevated PTH such as decreased calcium intake, vitamin D deficiency, renal insufficiency and hypercalciuria of renal origin. Other expected laboratory abnormalities are: low serum phosphate, calciuria
 (>100mg/24hrs excludes Familial Hypocalciuric Hypercalcaemia), low 25-hydroxyvitamin D (associated with severe disease) and hyperchloraemic metabolic acidosis (secondary to an inhibition of bicarbonate reabsorption by PTH).  

The increased production of PTH in PHPT occurs as a result of autonomously functioning parathyroid adenomas. These are most often found as single glands (80%-85%) but double adenomas are found in 3-5% of cases. Parathyroid carcinoma is a rare cause of PHPT (1%) and may occur in familial forms usually as part of multiple endocrine neoplasia (MEN).

5. Symptomatology / clinical manifestations:

PHPT is often discovered incidentally on routine blood work-up. Symptoms are often non-specific and include subtle complaints of aches and pains.

5.1 Abdominal Manifestations:

29% of patients with PHPT experience vague abdominal pain. The precise pathophysiological mechanism of abdominal manifestations is poorly understood. One theory states that changes in gene expression occur secondary to the sustained stimulation of PTH receptors. Another theory suggests that serum calcium has a direct effect on the smooth muscle of the digestive tract. Both result in smooth muscle atony of the upper and lower GI tracts. Abdominal manifestations of this include constipation, loss of appetite, reflux and nausea, which occur in 33%, 30%, 24% and 15% of cases respectively.

The causative relationship between hypercalcaemia and acute pancreatitis is well established. The sustained exposure of pancreatic acinar cells to high calcium levels can lead to premature pancreatic protease activation and pancreatitis. Once the diagnosis of PHPT-induced pancreatitis is made, parathyroidectomy is imperative as it prevents recurrence.

5.2 Musculoskeletal:

Patients may complain of back pain, joint pain and proximal muscle weakness. Continuous exposure to high levels of PTH is associated with catabolic effects on bone, thus resorption.
Intermittent exposure to low levels of PTH has an anabolic effect. In severe PHPT, an increase in bone turnover, driven by excess osteoclast activity, leads to the efflux of calcium from bone. This results in Osteitis Fibrosa Cystica (OFC) also known as Brown tumours. These are fibrotic, lytic bone changes, which appear radiolucent on x-ray and may present with skeletal deformities, bone pain and pathological fractures of the long bones.

Low bone mineral density is reversible with successful parathyroidectomy. In a study conducted by the Columbia University Medical Centre, patients gained bone mineral density after successful parathyroidectomy as measured by DXA (dual energy X-ray absorptiometry) at 5, 10, and 15 years respectively of 9, 6, and 12% in the lumbar spine and 4, 8, and 7% in the distal radius.

5.3 Renal involvement:

Patients may complain of polydipsia and polyuria. Many patients are diagnosed after being treated for multiple episodes of nephrolithiasis. In severe cases, mineralisation of renal tissue - nephrocalcinosis - may occur. Calcium oxalate or calcium phosphate stones are expected. These are radiolucent.

5.4 Cognitive function and neuropsychiatric symptoms:

The literature presents mixed evidence linking PTH, cognition and dementia. Non-specific symptoms may dominate: tiredness, depression and memory loss. These are difficult to define and diagnose as manifestations of a symptom complex. Neuronal calcium dysregulation, hypoperfusion and disrupted neuronal signalling are linked to the symptomatology. According to a systematic review conducted by Laurida et al, no large, well-designed studies have shown whether cognition improves after normalizing PTH levels.

6. Asymptomatic PHPT:

There is a definite move in the developed world towards the incidental diagnosis of patients on routine blood tests prior to them experiencing any symptoms. As a result of this, the entity of asymptomatic PHPT has been recognised and described along with its
own guidelines for management. Parathyroidectomy is indicated if one of the criteria below is present or if the patient is unable to follow up regularly. 8

Table 1: Indications for surgery as per 2013 International Workshop on the Management of Asymptomatic PHPT Guidelines for Parathyroid Surgery in patients with Asymptomatic Primary Hyperparathyroidism 8

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Indication for surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>• &lt;50</td>
</tr>
<tr>
<td>Serum Calcium</td>
<td>• &gt;0.25 mmol/L above upper limit of normal</td>
</tr>
</tbody>
</table>
| Bone mineral density         | • T-score <2.5 i.e. osteoporosis  
• Vertebral fracture on imaging |
| Creatinine clearance         | • <60 ml/min  
• 24hr urine calcium > 400mg/day  
• Nephrolithiasis or nephrocalcinosis on imaging |

7. Diagnosis:

Biochemical confirmation as described above is needed to make the diagnosis of PHPT. Imaging studies play no role in the diagnosis as imaging is only used to localise pathologic glands in order to guide resection. Imaging thus aids in planning surgery by determining whether the surgeon should expect single- or multigland disease.

8. Imaging:

A successful imaging study implies that the study did not miss an adenoma on the contralateral side. Localising diseased parathyroid glands becomes important when one considers the anatomic and embryologic variations of gland location. The international benchmark is set at a sensitivity of 88% and specificity of 94% for ultrasound. When combining TC-99-sestamibi scintigraphy with SPECT-CT the sensitivity improves to 97% and the specificity to 100%. 12,16

8.1 Sestamibi:
99mTc-sestamibi is a monovalent cationic lipophilic molecule that accumulates in mitochondria. Parathyroid glands contain mitochondria-rich oxyphil cells. 99mTc-sestamibi is also taken up by the thyroid but washes out more rapidly than from the parathyroids. The parathyroid adenomas are visible 1.5 – 3 hrs after administration. 99mTc-Sestamibi also collects in the myocardium, salivary glands and brown fat.

Two techniques of sestamibi imaging are used: the first uses a subtraction technique with either I-123 or Tc-99m pertechnetate. The second technique uses dual imaging with sestamibi as a single tracer in early and delayed imaging. Regardless of the technique used, sestamibi has a reported sensitivity in most series of 80 – 90%. Sestamibi is more predictive for the location of the hyperactive gland compared to ultrasound with a positive predictive value of 93%. It, however, loses its sensitivity in multi-gland disease (88% for single adenomas, 44% for hyperplasia and 30% for dual adenomas).

Causes of false positive results in sestamibi scans include: solitary thyroid nodules or the presence of a multinodular goiter, thymoma or breast, lung, head and neck malignancies. False negatives are more likely with smaller adenomas (<500mg are less likely to be visualized), and with multi-gland disease. Differences in perfusion and metabolic activity, the amount of oxyphilic cells and the expression of P-glycoprotein affect sestamibi uptake. It has been suggested that MIBI uptake is increased the higher the serum calcium and PTH levels. Interestingly, it has also been reported that ultrasound pick-up could be more successful in cases of higher PTH levels although calcium levels do not seem to influence ultrasound success.

8.2 Ultrasound:

Ultrasound is performed with a 7.5 – 19 MHz transducer from the mandible to the sternal notch. Retromanubrial and mediastinal visualization is not possible. Normal parathyroids cannot be visualized sonographically. Parathyroid adenomas are usually well-circumscribed, ovoid and solid and are also relatively hypoechoic to thyroid tissue due to their compact cellularity, as are parathyroid carcinomas and hyperplasia. Visualization is easier the larger the gland is. False positives are caused by thyroid nodules and cervical lymph nodes. The
reason for a missed adenoma may be due to poor sonographic penetration in the setting of a multinodular thyroid. In the presence of thyroid abnormalities, the sensitivity of ultrasound decreases by 20-25%.

Ultrasound is highly user dependant. Surgeon performed ultrasound is reported as being as sensitive as radiologist performed ultrasound but with the added benefits of intra-operative use and same user imaging and resection. A group from Charlottesville, Virginia recorded data on 200 patients with PHPT who underwent neck ultrasound in the surgeon’s office. In 144 (72%) patients, an adenoma was identified with a high level of confidence. All 200 patients underwent successful surgery. They concluded that surgeon-performed ultrasound is expedient, convenient, inexpensive, and accurate. In their setting, they were able to proceed to a focused exploration and avoid additional imaging 93% of the time.

8.3 Ultrasound-Sestamibi combination:

A study conducted in Padua, Italy and published in 2000 looked at 91 patients with PHPT. In the group of patients with solitary tumours (n=86), the sensitivity of sestamibi was 88% and ultrasound 82%. Ultrasound correctly localized the adenoma in 7 out of 10 patients with negative sestamibis. The combined sensitivity of ultrasound and sestamibi was 97%. (In the setting of multiglandular disease, both imaging studies were considered positive only when at least two adenomas were identified).

8.4 SPECT/CT:

Most nuclear medicine departments perform only planar images (sestamibi), which show two dimensions. This remains the most appropriate imaging study for pre-operative localization when combined with ultrasound. The gold standard for localization in cases of reoperation and ectopic adenomas is SPECT (Single Photon Emission Computed Tomography) or SPECT/CT in association with sestamibi scintigraphy. 3-D anatomical localization is possible when glandular function is combined with anatomical location in combination sestamibi-SPECT images.

SPECT/CT is useful for ectopic parathyroid lesions and to help differentiate thyroid from parathyroid foci.
9. Surgery:

Surgical resection of the causative parathyroid adenomas offers the only potential for cure. Different definitions of cure exist i.e. normal PTH levels or normocalcaemia post-operatively. Some centres accept the Irvin Criteria as measure of cure: 50% drop in PTH levels from highest pre-excision level, at 20 min post-excision. Callender and Udelsman defines surgical cure after parathyroidectomy as normocalcaemia at 6 months after surgery.

Accurate localization is defined as the localization by an imaging study of a pathological parathyroid gland to either the left or right side of the neck. That gland should then be confirmed as an adenoma on histology and resection thereof should result in a biochemical cure. The inference is then that the imaging study did not miss an adenoma on the contralateral side. This allows the surgeon to perform a focused or unilateral neck exploration, which is associated with less morbidity than the traditional four-gland exploration. Localization to the same side of the neck is thus considered sufficiently specific as the surgical approach remains the same whether the gland is in the superior or inferior quadrant, or in both, as long as only one side of the neck is involved. However, some centres do target a single gland when performing a focused exploration.

2014 guidelines from the Fourth International Workshop on PHPT recommend that all symptomatic patients with biochemically confirmed PHPT should undergo surgical resection. The current surgical trend is to perform a focused exploration of a single pathological parathyroid gland instead of the conventional bilateral neck dissection. This approach is guided by radiologic studies and intra-operative PTH assays. Localising diseased parathyroid glands becomes important when one considers the anatomic and embryologic variations of gland location.

If performed in high volume centres by experienced surgeons, cure rates in excess of 99% may be expected. For example, 1650 parathyroidectomies were performed in a series described by Udelsman in 2011. 1037 Minimally Invasive Parathyroidectomies (MIP) were performed with a cure rate of 99%. 613 patients underwent bilateral neck explorations with cure rate of 97%.
Udelsman described a 3% complication rate for bilateral neck exploration and a 1% complication rate for MIP in an earlier retrospective review of 656 parathyroidectomies. 

Table 2: Comparison between focused techniques and MIP: 

<table>
<thead>
<tr>
<th>Open Techniques:</th>
<th>Minimally invasive parathyroidectomy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bilateral neck exploration (BNE)</td>
<td>Open focused approaches:</td>
</tr>
<tr>
<td></td>
<td>• Open minimally invasive parathyroidectomy (OMIP)</td>
</tr>
<tr>
<td></td>
<td>Endoscopic unilateral:</td>
</tr>
<tr>
<td></td>
<td>• Minimally-invasive radio-guided parathyroidectomy (MI-RP)</td>
</tr>
<tr>
<td></td>
<td>Endoscopic Focused:</td>
</tr>
<tr>
<td></td>
<td>• Video-assisted parathyroidectomy (VAP)</td>
</tr>
<tr>
<td></td>
<td>• Video-assisted parathyroidectomy through a lateral approach (VAP-LA)</td>
</tr>
<tr>
<td></td>
<td>• Minimally-invasive video-assisted parathyroidectomy (MIVAP)</td>
</tr>
<tr>
<td></td>
<td>• Purely Endoscopic Parathyroidectomy (EP)</td>
</tr>
</tbody>
</table>

9.1 Open bilateral neck exploration:

In this technique, exploration with 4-gland visualization is performed and the pathological gland(s) is resected when seen. This approach traditionally has a success rate of more than 95% when performed by experienced endocrine surgeons. BNE still has a role in modern surgical practice and is recommended when no enlarged parathyroid glands are visualized; localizing procedures show equivocal results; there is discordance between imaging studies or two or more enlarged parathyroid glands are detected by imaging studies.

9.2 Minimally invasive parathyroidectomy:

The definition of MIP according to the 2002 summary statement on asymptomatic PHPT is a set of techniques employing pre-operative imaging with or without intra-operative parathyroid hormone assays (ioPTH), to limit surgical visualization to only the suspected
Several variations exist. A unilateral exploration visualizes both upper and lower quadrants on the side of the neck where the adenoma is suspected to be. The adenoma is then found and resected in a focused manner guided by pre-operative imaging. Exploration may be conducted by endoscopic or open techniques. The rationale behind unilateral exploration is that a single adenoma is implicated in >85% of cases of PHPT. When localization studies cannot detect an adenoma or results are discordant, the likelihood of multi-glandular disease is >30% and a bilateral exploration is indicated.

9.2.1 Open focused approaches - Open minimally invasive parathyroidectomy (OMIP):

This is the most commonly used minimally invasive focused parathyroidectomy technique. A small (2.5 – 5cm) central or lateral incision is made. Lateral incisions are aimed over the site of the adenoma in the region of the anterior border of the Sternocleidomastoid muscle. OMIP is associated with shorter operative times than the video-assisted technique, with no significant difference in post-operative outcomes. Advantages over BNE are: better cosmesis, shorter operative time, lower risk of post-op hypocalcaemia. Complication rates are similar between BNE, OMIP and MIVAP.

9.2.2 Endoscopic Focused - Minimally-invasive video-assisted parathyroidectomy (MIVAP):

MIVAP facilitates recognition of the recurrent laryngeal nerve, allows a shorter scar length and is associated with significantly less pain 24hrs post-operatively.

Table 3: Comparison between MIVAP and OMIP:

<table>
<thead>
<tr>
<th></th>
<th>MIVAP (Minimally-invasive video-assisted parathyroidectomy)</th>
<th>OMIP (Open minimally invasive parathyroidectomy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visualization of neck structures</td>
<td>Better</td>
<td></td>
</tr>
<tr>
<td>Cosmesis</td>
<td>Better</td>
<td></td>
</tr>
<tr>
<td>Post-operative analgesic requirements</td>
<td>Less</td>
<td></td>
</tr>
<tr>
<td>Cure rates</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Operative times</td>
<td>Depends on surgeon’s</td>
<td>(Shorter than BNE)</td>
</tr>
</tbody>
</table>
### Experience

<table>
<thead>
<tr>
<th>Complication rates</th>
<th>Similar</th>
<th>Similar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative hospital stay</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Costs</td>
<td>Significantly more expensive</td>
<td></td>
</tr>
</tbody>
</table>

### 10. Intra-operative confirmatory techniques:

Measuring intra-operative PTH (ioPTH) is guided by the Miami Criteria developed by Irvin and colleagues. \(^8\) PTH has a half-life of 5min and thus allows a blood assay to be performed intra-operatively. PTH is measured 20 min after adenoma excision. A greater than 50% decrease in PTH levels compared to highest pre-excision values may act as a checkpoint i.e. to confirm successful resection/cure or guide to further exploration. It has the greatest value where there has been discordance in the traditional two pre-operative imaging studies. An insufficient drop in PTH levels indicates persistent PHPT.

According to a study published in the Journal of Otolaryngology in 2013, ioPTH does not add any value, in the presence of frozen section, when two concordant imaging studies are available. However, ioPTH added an estimated average time of 30.9 minutes to the surgical time. \(^18\)

The sensitivity of frozen section for predicting an adenoma is 97% and the specificity 81%. If frozen section confirms an adenoma or hypercellular gland, it is unnecessary to confirm further with ioPTH measurement. \(^18\) Frozen section is a faster and more readily available modality in many clinical settings.

Radio-guided sestamibi: In this technique, sestamibi is injected immediately prior to surgery. An intra-operative gamma probe reading is taken and radioactive counts in the resected gland are expected at >20% of background. In our centre this method is employed in the setting of a re-operation for previous unsuccessful resection.

### 11. Post-operative complications:

Persistent (dependent on the definition used) or recurrent (after 6 months) hyperparathyroidism resulting from failed surgery, may be considered a complication. \(^24\)
Injury to the recurrent laryngeal nerve injury with vocal cord paralysis has a 0.5 – 1% incidence. Long-term hypoparathyroidism (with resultant hypocalcaemia) after bilateral neck exploration occurs in 0.1% of cases.

Hungry Bone Syndrome is a condition of rapid, severe (serum calcium <2.1mmol/l) and prolonged (> 4 days post-operatively) hypocalcaemia that may follow parathyroidectomy. It may be accompanied by hypophosphataemia and hypomagnesaemia. It is more common in patients who had severe PHPT with a high pre-operative bone turnover. An increased influx of calcium into bone occurs secondary to the sudden reversal of the previously high PTH’s effect on bone osteoclasts. The incidence of Hungry Bone Syndrome in patients with radiological evidence of hyperparathyroid bone disease can be as high as 25 – 90%. In patients without skeletal involvement it is 0 – 6% however. 20

Other rare complications may include neck haematomas with a 0.2% incidence, infection, pneumothoraces and cerebrovascular incidents.

12. Success after parathyroidectomy:

Surgical success equates a biochemical cure which is the normalization of PTH values post-operatively.

Operative failure may be explained by ectopic, multigland disease and the presence of supranumery glands. 5 – 20% of patients with PHPT have multiglandular disease. This scenario lends itself to ambiguity on imaging studies, missed resections and persistent disease. 28

13. Evidence from the developing world:

There is a clear preponderance to overtly symptomatic disease in the developing world with the classic “bones, stones, abdominal groans and psychic moans” presentation still prevalent. This is in contrast with more asymptomatic disease in the developed world.

While there is limited data from the developing world, the few studies published demonstrated high percentages of symptomatic disease and difficulty with pre-operative localisation. This trend is well demonstrated by an Indian systematic review conducted by
the Narayana Medical College and Superspeciality Hospitals in Andhra Pradesh. 61 Indian publications related to PHPT with 858 PHPT patients covering retrospective reviews and case reports from 1980 – 2010 were analysed. The majority of patients with PHPT were overtly symptomatic at the time of diagnosis, which was made late in the course of the disease. (Mean duration of symptoms at time of diagnosis 84 +/- 57 months). Authors attributed this to the limited access to medical treatment available and the fact that there is no screening of the healthy population for hypercalcaemia.

In South Africa, a study at Groote Schuur Hospital published in 1970, documented that presenting symptoms spanned bone disease in 5 cases (4 bone pain, 1 pathological fracture), renal stones in 23 cases, hypercalcaemic symptoms (GI disturbance, polyuria, polydipsia, weakness, drowsiness) in 7 cases, incidental presentations in 3 cases, and 1 case of pancreatitis. Pre-operative localisation in this study predated sestamibi scans. Rather, selenium-labelled methionine isotope scanning was used as an imaging modality but was successful only in the case of large tumours. Thyrocervical arteriography was also used and could illustrate a “blush” if the tumour was large enough. In some cases, intravenous toluidine blue dye was also used intra-operatively. Pre-operative localization was identified as an area where improvements were needed.

Table 4: Comparing outcomes of five studies performed in the developing world between 1970 and 2013

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study period</th>
<th>Type of study</th>
<th>No. of patients included</th>
<th>Most common reason for presentation</th>
<th>Mean sPTH at presentation</th>
<th>Sestamibi accuracy</th>
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<th>Persistent disease</th>
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<tbody>
<tr>
<td>Nelson Mandela School of Medicine KZN</td>
<td>South Africa</td>
<td>5.5 years</td>
<td>Retro-spective review</td>
<td>28</td>
<td>Hyper-calcaemia</td>
<td>34.7 +/- 41.5</td>
<td>97% (18 / 19)</td>
<td></td>
<td>1/19</td>
</tr>
<tr>
<td>Narayana Medical College</td>
<td>India</td>
<td>30 years</td>
<td>Systematic review of retro</td>
<td>858</td>
<td></td>
<td>5% (1/19)</td>
<td></td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>
14. Conclusion:

In the 1980s sensitivities for parathyroid localization ranged between 35% and 74% for sestamibi and between 34% and 82% for ultrasound. In the 1990s pre-operative imaging was considered not to be cost effective and did not contribute to shortening the operative time. Currently these two imaging studies are considered complimentary. The individual and overall sensitivity of these imaging modalities have improved to such an extent that surgery can now be focused on the specific pathological gland, which shortens operative times and decreases the morbidity and invasiveness of the explorative procedure.
REFERENCES:


29. Kreidieh OI, Almdieh G, Akl EA, Fuleihan GE. Minimally invasive parathyroidectomy guided by intraoperative parathyroid hormone monitoring (ioPTH) and preoperative


Chapter 2: Publication-ready manuscript

ABSTRACT

HREC REF 338/2016

Title: Pre-operative localisation and surgical outcomes for Primary Hyperparathyroidism: an 11-year review at a South African hospital.

Introduction:

Primary Hyperparathyroidism (PHPT) is characterized by hypersecretion of PTH leading to hypercalcaemia with successful surgery being the only definitive cure. Broadly, three techniques of parathyroidectomy exist: open bilateral neck exploration and minimally invasive parathyroidectomy, which is subdivided into open focused approaches and endoscopic focused approaches. A focused parathyroid gland exploration guided by pre-operative imaging is associated with less morbidity compared to a bilateral approach. Focused explorations may target either the side or the specific parathyroid gland identified.

Aim:

The primary aim of this study was to evaluate the accuracy of pre-operative localisation for PHPT in a single centre. The secondary aim was to review the type of parathyroid surgery performed and the final Parathyroid Hormone (PTH) levels in patients who have undergone parathyroidectomy for PHPT.

Methods:

This is a retrospective review of all patients who underwent primary surgery for PHPT between 2005 and 2015. Patients were identified from a general operative database. Data was collected from pathology records, operative notes, nuclear medicine and radiology reports and captured on a confidential data sheet.
Results:

Records of 98 patients were found and included. Sestamibi had a sensitivity of 88%, a positive predictive value of 83% and an accuracy of 75%. Ultrasound had a sensitivity of 52%, a positive predictive value of 78% and an accuracy of 44%. The total number of cases in which both ultrasound and sestamibi were done was 73. Sestamibi and ultrasound showed concordant results in 25 cases. The overall surgical success rate was 94% (92/98). The cure rate for patients in whom sestamibi and ultrasound were concordant, was 96% (24/25). The minimum and maximum calcium levels in the cohort were 2.2 and 4.41 respectively, with a mean of 2.86. PTH levels ranged between 4.2 and 186 with a mean of 33.8. One double adenoma was proven on histology. The rest were all single adenomas. The total number of malignancies were 3 of which 1 was part of a MEN syndrome.

Conclusion:

Our surgical success rate was 94%. When imaging modalities were concordant, surgical success was achieved in 24 cases, thus in 96% of the subgroup. Our figures compare favourably with international standards. There is scope for improvement in the accuracy of both ultrasound (46%) and sestamibi (75%) localization. Currently a combination of both imaging modalities is still recommended.

Introduction:

Primary Hyperparathyroidism (PHPT) is a condition characterized by the autonomous hypersecretion of parathyroid hormone (PTH) by parathyroid adenomas with resultant hypercalcaemia. PHPT is the third most common endocrine disorder, after diabetes and thyroid disease. The biochemical picture of a high PTH and high serum calcium is required to make the diagnosis. The majority of PHTP is caused by a single adenoma (80 – 85%) but some patients may have a double adenoma, four-gland hyperplasia or very rarely a parathyroid carcinoma.

Surgical resection of the causative parathyroid adenoma offers the only potential for cure, however, there is more than one definition of cure for PHPT. Cure may be defined as a drop in PTH of >50% of baseline 10 to 15 minutes after target gland resection (Miami Criteria).
a post resection PTH drop into the normal range;\(^2\) or that the patient is eucalcaemic after 6 months (American Association of Endocrine Surgeons).\(^3\) Ectopic glands, multi-gland disease and the presence of supranumery glands may explain operative failure.\(^4\)

Pre-operative imaging localisation with sestamibi and ultrasound assists in identifying the causative gland/s. It may also assist in determining whether the surgeon should expect single or multiple gland disease intra-operatively.\(^5\) Sestamibi scanning and ultrasound have been in use for several decades but it is only in the last 10 – 15 years that the accuracy of the studies has been considered high enough to have a positive impact on surgical interventions and cure rate. Even in more recent studies, there is a wide variation in reported sensitivity for both these investigations ranging from 77 - 100\% for sestamibi and 77 - 91\% for ultrasound with an average of 87\% and 77\% respectively.\(^6\)

The value of localization studies that suggest single-gland disease is that they allow patients to undergo a focused/minimally invasive parathyroidectomy (MIP). Several variations of focused parathyroidectomy/MIP exist but it essentially refers to a procedure that minimises the trauma of surgical exposure and dissection.\(^7\) Broadly, three techniques of parathyroidectomy exist: open bilateral neck exploration and minimally invasive approaches i.e. open focused parathyroidectomy and endoscopic focused parathyroidectomy. Focused approaches may target either the side (as in our unit) or the specific parathyroid gland identified. The benefit of MIP is that it obviates bilateral neck exploration, which carries an inherent higher risk profile.\(^2\) However, when localization studies cannot detect an adenoma or results are discordant, the likelihood of multi-glandular disease is >30\% and a bilateral exploration is still indicated.\(^6\)

Open minimally invasive parathyroidectomy (OMIP) is the most commonly used minimally invasive focused parathyroidectomy technique. A small (2.5 – 5cm) central or lateral incision is made. Lateral incisions are aimed over the site of the adenoma and overlying the anterior border of the sternocleidomastoid muscle. Advantages of MIP over bilateral neck exploration (BNE) are better cosmesis, shorter operative time, less risk to recurrent laryngeal nerve and lower risk of post-operative hypocalcaemia. Complication rates are similar between BNE, OMIP and MIVAP (Minimally invasive video-assisted parathyroidectomy).\(^7\)
There is very limited published data from South Africa or other middle-income countries on either pre-operative localisation or surgical success rates for PHPT. This study was therefore conducted to audit the surgical management and present clinical data from within this context.

Aims:

The primary aim of this study was to evaluate the accuracy of pre-operative localisation for PHPT in a single tertiary centre. The secondary aim was to review the type of parathyroid surgery performed and the final Parathyroid Hormone (PTH) levels in patients who have undergone parathyroidectomy for PHPT.

Patients and Methods:

This retrospective series included all patients who had undergone primary surgery for PHPT between 2005 and 2015 at a single tertiary unit. Patients who underwent repeat surgery for any reason were excluded. Patients were identified from a general operative database and nuclear medicine reports, ultrasound reports, operative notes and pathology records were used to gather data. Data was captured on a confidential data sheet which included: patient demographics, presenting biochemistry, the results of the sestamibi and ultrasound scans, details of the operative technique used, the final histology result and the last recorded PTH.

Pre-operative Localisation Definitions:
Focused parathyroidectomy in this study referred to an open minimally invasive parathyroidectomy through a midline incision. True positive (TP): the abnormal parathyroid gland(s) was correctly lateralized by the imaging techniques as measured against operative findings in patients who had successful surgery. False positive (FP) meant that the imaging study showed an adenoma but on the wrong side. False negative (FN): the imaging study did not detect an adenoma but one was found at surgical exploration i.e. the imaging study incorrectly indicates that an adenoma is absent thus it missed an adenoma. 6 Accuracy was defined as successful lateralization divided by total number of investigations performed.

Statistical analysis:
Data analysis was performed using Python version 3.6 in a Jupyter notebook environment. Statistical inference calculations were made using the Scientific Library for Python. Numerical variables were summarised and expressed as mean values. Proportions were expressed as percentages, with the sum total used in the calculation of sensitivity, positive predictive values, and accuracy. The nature of the research precluded the identification of true negative findings and this was omitted in the calculations for accuracy. The non-parametric Kruskal-Wallis test was used to compare numerical variables between groups.

Results:

Records of 98 patients who had parathyroidectomy were found and included. There were 81% (79/98) females and 19% (19/98) males. The age range of the patients was 13-81 years with a mean age of 56. Table 1 details the presenting complaints for this series of patients. The majority of patients in our series were symptomatic 69% (66/98) Of these, the commonest clinical presentation was recurrent renal stones, followed by 21 who had non-specific musculoskeletal symptoms. 10 patients presented with neuropsychiatric symptoms including confusion and 5 with fractures. Brown’s tumours were present in 4 cases. Asymptomatic patients, 31% (30/98) were diagnosed on calcium tests performed for an unrelated medical conditions.

Table 1
Clinical Presentation:

<table>
<thead>
<tr>
<th>Presenting complaints</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental</td>
<td>30</td>
</tr>
<tr>
<td>Renal stones</td>
<td>29</td>
</tr>
<tr>
<td>Non-specific musculoskeletal symptoms</td>
<td>21</td>
</tr>
<tr>
<td>Osteopaenia</td>
<td>17</td>
</tr>
<tr>
<td>Hypercalcaemic crisis</td>
<td>6</td>
</tr>
<tr>
<td>Confusion</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Fractures</td>
<td>5</td>
</tr>
<tr>
<td>Brown’s Tumours</td>
<td>4</td>
</tr>
<tr>
<td>Non-specific abdominal symptoms</td>
<td>0</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---</td>
</tr>
<tr>
<td>Non-specific cognitive decline</td>
<td>0</td>
</tr>
</tbody>
</table>

**Graph 1: Number of presenting problems per patient**

70 patients presented with a single symptom. 15 presented with two symptoms and 5 with 3 symptoms.

The minimum and maximum calcium levels in the cohort were 2.2 and 4.41 respectively, with a mean of 2.86. There was no statistically significant correlation between calcium levels and symptoms. PTH levels ranged between 4.2 and 186 with a mean of 33.8.

**Accuracy of Pre-Operative Ultrasound:**

70/98 (71%) patients underwent a pre-operative ultrasound. Three 3/70 (4%) of these ultrasounds were done for patients whose surgery was unsuccessful and thus the accuracy of these three scans could not be assessed. Of the remaining 67, 38/67 (57%) scans identified an adenoma and 29/67 (43%) scans reported no adenoma identified. In 16/67 (24%) scans, the ultrasound correctly identified the adenoma by quadrant and in a further 15/67 (22%), it correctly identified the side, making the total that accurately lateralised the adenoma, 31/67 (46%). Thus ultrasound had a sensitivity of 52%, a positive predictive value of 78%, and an accuracy of 46%.
Graph 2: Ultrasound results:

Accuracy of Pre-Operative Sestamibi Scans:

A total of 93/98 (95%) sestamibi scans were performed but in 6/93 (6%) of these patients, surgery was unsuccessful and therefore the accuracy of these scans could not be assessed. A total of 87 sestamibi scans were therefore analysed. Nine (9/87 10%) of these were negative studies, with no imaging features to suggest the presence or the location of a parathyroid adenoma. Of the 78/87 (90%) positive sestamibi scans, 65/87 (75%) accurately predicted the side of the adenoma, 21/ 87 (24%) to right or left only and 44/87 (51%) to the correct quadrant. Sestamibi therefore had a sensitivity of 88%, a positive predictive value of 83% and an accuracy of 75% in predicting the laterality of the adenoma (left vs right), but was less accurate in predicting the exact site (superior vs inferior).
Graph 3: Sestamibi results:

Most adenomas were located to the right inferior position by sestamibi 40/93 (43%).

Graph 4: Adenoma position as detected by sestamibi

Sestamibi/Ultrasound Concordance:

The total number of cases in which both ultrasound and sestamibi were performed was 73 (74%). Sestamibi and ultrasound showed concordance in only 25 cases (34%). Of those, surgical success was achieved in 24 cases, thus in 96% of the subgroup.
Surgical Results:

A total of 98 parathyroidectomies were included in the study. Of these, 92 patients had a recorded normal PTH in the early or late post-operative period. Some patients only had an early PTH result due to inadequate and inconsistent follow up of patients. This is an operative success rate of 94%. In 74 patients (76%) of surgeries, focused explorations were performed and in 24 (24%) four-gland explorations were performed either as a planned procedure or as a conversion from focused to four-gland exploration intra-operatively.

![Graph 5: Subdivision of operations](image)

Single adenomas were resected in 80% of cases. In 13 cases (13%), two glands were resected however only one patient had a double adenoma on histology. Two patients had 3 glands resected (2%) and no glands were removed in 4 operations (4%). The number of operations in which multiple glands were resected was thus 15.
6 adenomas were found in ectopic locations: intra-thoracic, left mediastinum, right intra-thyroid, retro-oesophageal, right infra-thyroid and centrally in isthmus. The total number of malignancies were 3 of which 1 was part of a MEN syndrome.

16 frozen sections were done. 15 of those corresponded with the final histology report but in one case, frozen section reported a parathyroid gland but final histology proved it to be a thyroid nodule.

Table 2
Summary of the results:

<table>
<thead>
<tr>
<th></th>
<th>Number US</th>
<th>Number MIBI</th>
<th>Combination US/MIBI with concordant results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total analysed</td>
<td>67</td>
<td>87</td>
<td>25</td>
</tr>
<tr>
<td>Number correctly lateralized</td>
<td>31</td>
<td>65</td>
<td>24</td>
</tr>
<tr>
<td>Accuracy (%) (of correctly lateralizing adenoma)</td>
<td>46%</td>
<td>75%</td>
<td>96%</td>
</tr>
<tr>
<td>Sensitivity (%) (of correctly lateralizing an adenoma)</td>
<td>52%</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>78%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>International standard for</td>
<td>76–87%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>sensitivity</td>
<td>97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>International standard for positive</td>
<td>93 – 97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>predictive value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International standard for accuracy</td>
<td>88%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>97%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion:

Clinical presentation and biochemistry:
The majority of patients in this study were symptomatic. Only 31% of patients were diagnosed incidentally. In parts of the developed world, as evidenced by data from the USA, up to 80% of PHPT diagnoses are based on incidentally discovered hypercalcaemia.² Our high incidence of symptomatic disease is mirrored in published data from other parts of the developing world where the overt symptoms of the classic “bones, stones, abdominal groans and psychic moans” remains prevalent. Most referrals in our centre came from the urology service and comprised patients presenting with recurrent renal stones. Also, the majority of our patients presented with a single symptom rather than a complex of symptoms.

Evidence from the developing world:
While there is limited data from the developing world, the few studies published demonstrated high percentages of symptomatic disease and difficulty with pre-operative localisation. This trend is well demonstrated by an Indian systematic review conducted by the Narayana Medical College and Superspeciality Hospitals. In this study, 61 Indian publications related to PHPT including 858 PHPT patients were reviewed and case reports from 1980 – 2010 were included in the analysis. The majority of patients with PHPT were overtly symptomatic at the time of diagnosis with a mean duration of symptoms at time of diagnosis of 84 months. They explained this by the limited access to medical treatment available and the fact that there is no screening of the healthy population for hypercalcaemia.⁸

In South Africa, a study at Groote Schuur Hospital published in 1970, documented that presenting symptoms included bone disease in 5 cases, renal stones in 23 cases, hypercalcaemic symptoms (GI disturbance, polyuria, polydipsia, weakness, drowsiness) in 7 cases, incidental presentations in 3 cases, and 1 case of pancreatitis.⁹ Pre-operative
localisation in this study predated sestamibi scans. Rather, selenium-labelled methionine isotope scanning was used as an imaging modality but was successful only in the case of large tumours. Thyrocervical arteriography was also used and could illustrate a “blush” if the tumour was large enough. In some cases, intravenous toluidine blue dye was also used intraoperatively. Pre-operative localization was identified as an area where improvements were needed.⁹

Table 3
Comparing outcomes of five studies performed in the developing world between 1970 and 2013:

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study period</th>
<th>Type of study</th>
<th>No. of patients included</th>
<th>Most common reason for presentation</th>
<th>Mean sPTH at presentation</th>
<th>Sestamibi accuracy</th>
<th>Ultrasound accuracy</th>
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</tr>
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<tbody>
<tr>
<td>Nelson Mandela School of Medicine KZN ¹⁰</td>
<td>South Africa</td>
<td>5.5 years</td>
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<td>Narayana Medical College and Super speciality Hospitals ⁸</td>
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<td>30 years</td>
<td>Systematic review of retrospective reviews and case reports</td>
<td>858</td>
<td>Renal stones</td>
<td>5%</td>
<td>2%</td>
<td>(1/19)</td>
<td></td>
</tr>
<tr>
<td>University of Pretoria Radiology Dept ⁴</td>
<td>South Africa</td>
<td>18 months</td>
<td>series</td>
<td>12</td>
<td>Renal stones</td>
<td>100%</td>
<td>(12/12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groote Schuur Hosp ¹⁷</td>
<td>South Africa</td>
<td>16 years</td>
<td></td>
<td>36</td>
<td>Renal stones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Accuracy of ultrasound:
Ultrasound was not performed on all patients in our study. The reasons for this included a long waiting time for ultrasound bookings and an anecdotal recognition of the lower utility of ultrasound as demonstrated by the high number of negative scans. Thus, ultrasound was performed in only 71% of cases. The sensitivity and positive predictive value for ultrasound in our study were 52% and 78% respectively. The accuracy was 46%. This does not compare favourably with the reported international sensitivity of ultrasonography being 76–87% with a positive predictive value of 93–97% and diagnostic accuracy of 88%. The relatively wide range of sensitivities quoted for ultrasound in other series is indicative of the user-dependent nature of the imaging modality. In our study, ultrasound had a high positive predictive value when an adenoma was detected. However, in 29 of the 70 ultrasounds done, no adenoma was detected at all. This significantly detracts from the usefulness of the modality. These findings may be the result of the high turnover of radiology staff, ultrasounds frequently being performed by radiology trainees and also the low volume of disease seen in our centre.

Accuracy of sestamibi:
Sestamibi was utilised in almost all of our patients (95%). In our study, sestamibi had an overall accuracy of 75% compared with an international accuracy of 97%. We demonstrated a sensitivity of 88% compared with a published international sensitivity of 93%. The combination of the two imaging modalities improves the success of localization dramatically with a positive predictive value of 97% as quoted in published studies. In our centre, a surgical success rate of 96% was achieved when combining studies but only 75% of patients had both imaging studies performed.
Surgical results:
Our overall operative success rate was 94%. The international standard for high-volume centres with high-quality parathyroid imaging reaches 99% for MIP and 97% for bilateral neck exploration. It is well-established that rates of unsuccessful surgery and complications are higher in low volume centres though the definition of a high volume unit is variable. Charles Meltzer from The Permanente Medical Group in California defines high volume as more than 40 cases per year. Our centre averages 9 operations for PHPT per year, which is well below this number..

Of the 98 patients included, 76% underwent focused explorations (OMIP). The remaining 24% were four-gland explorations. We use a short central neck incision, which permits conversion to four-gland exploration if necessary and allows the surgeon to explore both the superior and inferior glands on the localised side decreasing the chances of missed four-gland hyperplasia. While it is reported that 5 – 20% of patients with PHPT have multi-glandular disease in our study, only one patient had a double adenoma and no patients with four-gland hyperplasia were identified.

Initial surgery was unsuccessful in six patients. In two of these, the parathyroid localised by sestamibi was removed but the PTH remained high and on subsequent imaging another location was identified by sestamibi. The adenoma in these two patients was then was successfully removed on repeat surgery. In four patients, the pre-operatively localised parathyroid adenoma was not successfully identified at surgery and the PTH remained high post-operatively. Three of these patients were lost to follow up before repeat exploration could be attempted and one patient died of unrelated causes.

Conclusion:
Primary hyperparathyroidism is a common diagnosis which, in our setting is usually diagnosed in symptomatic patients. Accurate pre-operative localisation of the causative adenoma with sestamibi and ultrasound permits focused parathyroidectomy in the majority of patients though strategies to improve the accuracy of ultrasound are necessary. When ultrasound and sestamibi results are concordant, surgical success rates improve from 94% to 96%. A standardised definition of success after parathyroid surgery and better follow up of patients who undergo both successful and unsuccessful primary surgery is necessary to
inform improvements in the surgical management of PHPT patients in the developing world setting.
References:


17. Morks AN et al. Intra-operative parathyroid hormone measurements – experience of a non-academic hospital. SAJS August 2011; 49(3).


List of tables:

Table 1: Presenting complaints and number of each
Table 2: Summary of the results
Table 3: Comparing outcomes of five studies performed in the developing world between 1970 and 2013

List of graphs:

1. Number of presenting problems per patient
2. Ultrasound results
3. Sestamibi results
4. Adenoma position as detected by sestamibi
5. Subdivision of operations
6. Glands resected per number of patients
Data Capture sheet

Primary Hyperparathyroidism: Pre-operative localisation and final surgical outcomes at a single surgical centre.

* Required

1. 1. Patient name *

2. 2. Patient surname *

3. 3. Folder number *

4. 4. Presenting complaint *
   
   Check all that apply.
   
   □ Incidental
   □ Renal stones
   □ Confusion
   □ Musculoskeletal symptoms
   □ Psychiatric symptoms
   □ Other

5. 5. Pre-operative PTH *

6. 6. Pre-operative calcium *

7. 7. Ultrasound done? *
   
   Mark only one oval.
   
   □ Yes
   □ No
8. 8. Gland identified?
   Mark only one oval.
   ☐ Yes
   ☐ No

9. 9. Position on ultrasound?
   Check all that apply.
   ☐ Right superior
   ☐ Right inferior
   ☐ Left superior
   ☐ Left inferior

10. 10. Sestamibi scan done? *
      Mark only one oval.
      ☐ Yes
      ☐ No

11. 11. Gland identified?
      Mark only one oval.
      ☐ Yes
      ☐ No

12. 12. Position on Sestamibi scan?
      Check all that apply.
      ☐ Right superior
      ☐ Right inferior
      ☐ Left superior
      ☐ Left inferior

13. 13. Operative plan:
      Mark only one oval.
      ☐ Four gland exploration
      ☐ Focussed exploration
14. **Final intra-operative technique - Glands looked for**  
*Check all that apply.*
- Right superior
- Right inferior
- Left superior
- Left inferior

15. **Final intra-operative technique - Glands identified**  
*Check all that apply.*
- Right superior
- Right inferior
- Left superior
- Left inferior

16. **Final intra-operative technique - Adenoma identified**  
*Mark only one oval.*
- Yes
- No

17. **Final intra-operative technique - Parathyroid/s removed**  
*Check all that apply.*
- Right superior
- Right inferior
- Left superior
- Left inferior

18. **Number of glands removed**  
*Mark only one oval.*
- 1
- 2
- 3
- 4

19. **Frozen section**  
*Mark only one oval.*
- Yes
- No
20. **If yes, result:**

..................................................................................................................................................................................
..................................................................................................................................................................................
..................................................................................................................................................................................
..................................................................................................................................................................................
..................................................................................................................................................................................

21. **Histology: Parathyroid**

*Mark only one oval.*

☐ Yes  
☐ No  
☐ Other: ..................................................................................................................................................................

22. **Site of adenoma**

*Check all that apply.*

☐ Right superior
☐ Right inferior
☐ Left superior
☐ Left inferior

23. **Other tissue excised**

*Check all that apply.*

☐ Lymph node
☐ Thyroid nodule

24. **Post-operative PTH**

..................................................................................................................................................................................

25. **Post-operative calcium**

..................................................................................................................................................................................

26. **Post-operative complications**

*Check all that apply.*

☐ Insufficient drop in PTH
☐ Damage to recurrent laryngeal nerve
☐ Hypocalcaemia
☐ Local wound complications - Infection
☐ Local wound complications - Haematoma
30 May 2016

HREC REF: 338/2016

Dr L Cairncross
Department of Endocrine Surgery
J45.49
OMB

Dear Dr Cairncross

PROJECT TITLE: PRE-OPERATIVE LOCALIZATION AND SURGICAL OUTCOMES FOR PRIMARY HYPERPARATHYROIDISM: A TEN YEAR REVIEW AT A SINGLE TERTIARY CENTRE (MMeD-candidate T van Wyngaard)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30 June 2017.

Please obtain permission from the UCT student and staff administration to conduct research at UCT.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student, Tersa van Wyngaard will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC 338/2016
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies
to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical
Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on
Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH
2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and
The Human Research Ethics Committee granting this approval is in compliance with the ICH
Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
and FDA Code Federal Regulation Part 50, 56 and 312.
HREC office use only (FWA00001637; IRB00001938)
This serves as notification of annual approval, including any documentation described below.

☐ Approved  Annual progress report  Approved until/next renewal date  30.7.2018

☐ Not approved  See attached comments

Signature Chairperson of the HREC

Date Signed  30/6/2018

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)  24/7/18

HREC REF Number  338/2014  Current Ethics Approval was granted until  30/6/17

Protocol title  Pre-operative localization and surgical outcomes for primary hyperparathyroidism (PHPT): An eleven year review at a South African hospital.

Protocol number (if applicable)

Are there any sub-studies linked to this study?  ☐ Yes  ☐ No

If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.

Principal Investigator  Lydia Cairncross

Department / Office Internal Mail Address  lydia.cairncross@uct.ac.za

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(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)
1.1 Does this protocol receive US Federal funding?

☐ Yes ☐ No

1.2 If the study receives US Federal Funding, does the annual report require full committee approval?

☐ Yes ☐ No

Note: Any annual approvals for Full Committee review MUST be submitted on the monthly HREC submission dates.

(Please send electronic copy for full committee review to hrec-enquiries@uct.ac.za)

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Annual Approval for full committee review - R 3420 (inclusive of vat)

For invoicing purposes, please provide:

- Sponsor's name
- Contact person
- Address
- Telephone number
- Email Address

2. List of documentation for approval

3. Protocol status (tick ✓)

☐ Open to enrolment

☐ Closed to enrolment (tick ✓)

- Research-related activities are ongoing
- Research-related activities are complete, long-term follow-up only
- Research-related activities are complete, data analysis only
- Main study is complete but sub-study research-related activities are ongoing
- Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date

Number of participants enrolled, since last HREC Progress report (continuing review)

12 March 2018

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)
5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part) 0

6. Cumulative summary of participants

<table>
<thead>
<tr>
<th>Total number of participants who provided consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants determined to be ineligible (i.e. after screening)</td>
</tr>
<tr>
<td>Number of participants currently active on the study</td>
</tr>
<tr>
<td>Number of participants completed study (without events leading to withdrawal)</td>
</tr>
<tr>
<td>Number of participants withdrawn at participants’ request (i.e. changed their mind)</td>
</tr>
<tr>
<td>Number of participants withdrawn by PI due to toxicity or adverse events</td>
</tr>
<tr>
<td>Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)</td>
</tr>
<tr>
<td>Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.</td>
</tr>
</tbody>
</table>

Number of participants no longer taking part for reasons not listed above. Please provide reasons below:

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report, as well as any relevant comments/issues you would like to report to the HREC:

Data collection complete. Finalizing data analysis and write-up. Revised submission planned for 15 August 2018.

8. Protocol violations and exceptions (tick ✓ all that apply)

- [X] No prior violations or exceptions have occurred since the original approval
- [ ] Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved

12 March 2018

(Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)
9. Amendments (tick ✓ all that apply)
- □ No prior amendments have been made since the original approval
- □ Prior amendments have been reported since the last review and have already been approved
- □ New protocol changes/amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).

Specific changes in the amended protocol and consent/assent forms must be bolded, italicised or tracked and all changes must include a rationale.

10. Adverse events
10.1 Please provide below or attach a narrative summary of serious adverse events and/or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.

N/A

10.2 Have participants received appropriate treatment/follow-up/referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?

- □ Yes
- □ No
- □ Not applicable

If yes, please describe:

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?

- □ Yes
- □ No
- □ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?

- □ Yes
- □ No
- □ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.

<table>
<thead>
<tr>
<th>Agency Name</th>
<th>Report attached</th>
<th>DSMB report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ Yes</td>
<td>□ Yes</td>
</tr>
<tr>
<td></td>
<td>□ No</td>
<td>□ No</td>
</tr>
<tr>
<td></td>
<td>□ Not applicable</td>
<td>□ Not applicable</td>
</tr>
</tbody>
</table>

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(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)
11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?

☐ Yes  ☒ No
If yes, please explain:

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:

☐ Increased
☐ Decreased
☒ Shown no change
If there has been a change, please explain:

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)

☐ Yes  ☐ No
If yes, please explain and if necessary attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):

14. Signature

My signature certifies that the above is complete and correct.

Signature of PI

Date 26/07/18
Form FHS011: Study deviation

HREC office use only (FWA00001837; IRB00001938)

This serves as acknowledgement of a protocol deviation as described below.

Chairperson of the HREC signature [Signature] Date 30/7/2018

Principal Investigator to complete the following:

1. Protocol information

<table>
<thead>
<tr>
<th>Date (when submitting this form)</th>
<th>24/7/18</th>
</tr>
</thead>
<tbody>
<tr>
<td>HREC REF Number</td>
<td>388</td>
</tr>
<tr>
<td>Project Title</td>
<td>Pre-operative localization and surgical outcomes for primary hyperparathyroidism (PHPT) at a South African Hospital</td>
</tr>
<tr>
<td>Protocol number (if applicable)</td>
<td>Am eleven year review at a South African Hospital</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Hydria Conviction</td>
</tr>
<tr>
<td>Department / Office Internal Mail Address</td>
<td>-</td>
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</tbody>
</table>

2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.

Failed to submit annual HREC renewal.

A retrospective chart review. Data was already completed.

3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.

HREC application for renewal submitted

3.2 Please describe what action(s) have or will be taken to prevent similar deviations in future.

Correct assumption that renewal needed even if data capture complete, still meet all aims.

4. Principal Investigator's acknowledgement of responsibility

This signature indicates the PI has reviewed the deviation, taken appropriate follow-up action and implemented or plans to implement preventative steps where possible.

Signature of PI [Signature] Date 25/7/2018

20 June 2018 Page 1 of 1 FHS011
Plagiarism Declaration

“This thesis/dissertation has been submitted to the Turnitin module (or equivalent similarity and originality checking software) and I confirm that my supervisor has seen my report and any concerns revealed by such have been resolved with my supervisor.”

Name: Tirsa van Wyngaard
Student number: VWYT1R001
Signature: [Signature]
Date: 12/08/2018
UNIVERSITY OF CAPE TOWN
FACULTY OF HEALTH SCIENCES
FORM D18 - DECLARATION/WORD COUNT FORM -- MASTER'S DEGREE CANDIDATES

Title:                      Student No:   VNY11001
Name, Surname:             Tel No’s:       082 402 5619
Email add:                 Dissert Title:   Pre-operative localization and surgical outcomes for Primary
                             Hyperparathyroidism (PHPT): an eleven-year review at a
                             South African Hospital

Supervisor:                Word count:     9038 No. of pages 62

1. IMPORTANT NOTES:

1.1 Candidates for graduation in June and December may expect to receive notification of the outcome of the examination of the dissertation not later than 1st week in June and last week in November, respectively, provided the dissertation was submitted by the due date. Where a dissertation has been submitted well in advance of the due date, earlier notification will be given, if possible. However, the University does not undertake to reach a decision by any specific date.

1.2 Candidates who are required to revise and re-submit for re-examination are required to register during the revision phase. Fees will be calculated according to the date of the notification of the “revise and re-submit” result and the date of re-submission. [Faculty will advise Fees by sending copy of R&R result to Fees.]

1.3 Candidates are asked to note that the University will not permit degree/diploma qualifiers to graduate if they have any outstanding fees, fines, interest or dues. The final date for payment of outstanding amounts is 30 April in the case of qualifiers for June graduation and 31 October in the case of qualifiers for December graduation.

1.4 Please note that should your examination process run into the following year, you will have to re-register in order to be considered for graduation.

2 DECLARATIONS:

2.1 I am presenting this dissertation in FULL/PARTIAL fulfillment of the requirements for my degree.

2.2 I know the meaning of plagiarism and declare that all of the work in the dissertation, save for that which is properly acknowledged, is my own.

2.3 I hereby grant the University of Cape Town free licence to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever of the above dissertation.

Signature Signed by candidate Date: 12/08/2018
FUNDING AND FEES:

Candidates submitting have a choice in regard to fees and funding options:

3.1 To claim a fee rebate* and discontinue funding through the PGFO, if applicable (the student remains registered until graduation or the start of the next academic year (see University Rule G5.2).
*(Only applicable in second or subsequent year in which the dissertation is being completed - Fee Rule 8)

3.2 To remain registered and engaged in the department while writing up a paper for publication, with full student rights and full access to facilities, full liability for fees for the year and continued eligibility for funding already awarded for that academic year. Access will extend only until such time as you graduate. Should you need access beyond this, you will need to arrange for 3rd party access within your department.

Please indicate your preference

| I wish to claim the rebate and discontinue funding (if applicable) and physical and library access** | X |
| I wish to continue fee liability, funding eligibility (if applicable) and access to all facilities |

**Students asking for a fee rebate acknowledge

a) the implications of the fee rebate on their access to facilities and eligibility for funding, and

b) that if they were to stay on in the department and receive payment through the payroll, such payment is taxable.

Signature [Signed by candidate] Date: 12/08/2018

FOR COMPLETION BY FACULTY OFFICE

I acknowledge receipt of the uploaded copy (on PeopleSoft) of the Master’s dissertation of the above candidate submitted for examination:

<table>
<thead>
<tr>
<th>Abstract submitted</th>
<th>Date:</th>
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<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

cc  Fees
IAPO
PGFO
Student Housing
**AUTHORSHIP**

All named authors must give consent to publication. Authorship should be based only on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting the article or revising it critically for important intellectual content; (iii) final approval of the version to be published. All three of these conditions must be met (Uniform requirements for manuscripts submitted to biomedical journals: www.icmje.org/index.html).

**CONFLICT OF INTEREST**

Authors must declare all sources of support for the research and any association with the product or subject that may constitute conflict of interest.

**PROTECTION OF PATIENT'S RIGHTS TO PRIVACY**

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. Informed consent for this purpose requires that the patient be shown the manuscript to be published. (www.icmje.org)

**ETHNIC CLASSIFICATION**

Work that is based on or contains reference to ethnic classification must indicate the rationale for this.

**MANUSCRIPTS**

Short items are more likely to appeal to our readers and therefore to be accepted for publication. Please provide a word count for all submissions.

Original articles of 3 000 words or less, with up to 6 tables or illustrations, should normally report observations or research of relevance to clinical medicine. References should preferably be limited to no more than 15.

Short reports or scientific letters, which include case reports, side effects of drugs and brief or negative research findings should be 1000 words or less, with 1 table or illustration and no more than 6 references.

Editorials, Opinions, Issues in Medicine, etc. should be about 800 words and are welcome, but unless invited, will be subjected to the SAMJ peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, if intended for the correspondence column, should be marked for publication’, signed by all authors and presented in triple spacing. Letters should be no longer than 400 words with only one illustration or table.

Obituaries should not exceed 400 words and may be accompanied by a photograph.

**MANUSCRIPT PREPARATION**

1. Please send your manuscript on disc accompanied by three printouts, in triple spacing, with wide margins and paginated.
2. Research articles should have a structured abstract not exceeding 250 words comprising: Objectives, Design, Setting, Subjects, Outcome measures, Results and Conclusions.
3. Refer to articles in recent issues for guidance on the presentation of headings and subheadings.
4. Abbreviations should be spelt out when first used in the text and thereafter used consistently.
5. Scientific measurements should be expressed in SI units except: blood pressure should be given in mmHg and haemoglobin values in g/dl.
6. In doubt, refer to ‘uniform requirements’ above.

**ILLUSTRATIONS**

1. Figures consist of all material that cannot be set in type, such as photographs and line drawings.
2. Tables and legends for illustrations should appear on separate sheets and should be clearly identified.
3. Line drawings should be arranged to conserve vertical space. Note that reduction to 80 mm for a single column or 170 mm for double columns should not render lettering illegible. Explanations should be included in the legend and not on the figure itself.
4. Figure numbers should be clearly marked on the back of prints and the top of illustrations should be indicated.
5. If any tables or illustrations submitted have been published elsewhere, written consent to republication should be obtained by the author from the copyright holder and the author(s).
6. A limited number of illustrations are free at the discretion of the editor. Colour illustrations are encouraged but are charged to the author.
quote will be provided on request. Consider sponsorship.

REFERENCES

References should be inserted in the text as superior numbers and should be listed at the end of the article in numerical and not in alphabetical order.

Authors are responsible for verification of references from the original sources.

References should be set out in the Vancouver style and approved abbreviations of journal titles used; consult the List of Journals in Index Medicus for these details.

Names and initials of all authors should be given unless there are more than six, in which case the first three names should be given followed by et al. First and last page numbers should be given.

Journal references should appear thus:


Book references should be set out as follows:


Manuscripts accepted but not yet published can be included as references followed by (in press).

Unpublished observations and personal communications may be cited in the text, but not in the reference list.

GALLEY PROOFS

Galley proofs will be forwarded to the author before publication and if not returned within 2 weeks will be regarded as approved. Please note that alterations to typeset articles are costly and will be charged to the authors.

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Please notify the Editorial Department of any address changes so that proofs and invoices may be mailed without delay.

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ISSN: 2078-5151