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Primary Hyperparathyroidism in Adults – (Part II) Surgical Management and Postoperative Follow-Up: Position statement of the Endocrine Society of Australia, the Australian & New Zealand Endocrine Surgeons, and the Australian & New Zealand Bone and Mineral Society

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Relevant Disclosures: See Supplementary Table 1

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SUMMARY

Objective: To develop evidence-based recommendations to guide the surgical management and post-operative follow-up of adults with primary hyperparathyroidism.

Methods: Representatives from relevant Australian and New Zealand Societies used a systematic approach for adaptation of guidelines (ADAPTE) to derive an evidence-informed position statement addressing eight key questions.

Results: Diagnostic imaging does not determine suitability for surgery but can guide the planning of surgery in suitable candidates. First line imaging includes ultrasound and either parathyroid 4DCT or scintigraphy, depending on local availability and expertise. Minimally invasive parathyroidectomy is appropriate in most patients with concordant imaging. Bilateral neck exploration should be considered in those with discordant/negative imaging findings, multi-gland disease and genetic/familial risk factors. Parathyroid surgery, especially re-operative surgery, has better outcomes in the hands of higher volume surgeons. Neuromonitoring is generally not required for initial surgery but should be considered for re-operative surgery. Following parathyroidectomy, calcium and parathyroid hormone levels should be re-checked in the first 24 hours and repeated early if there are risk factors for hypocalcaemia. Eucalcaemia at six months is consistent with surgical cure; parathyroid hormone levels do not need to be re-checked in the absence of other clinical indications. Longer-term surveillance of skeletal health is recommended.

Conclusions: This position statement provides up-to-date guidance on evidence-based best practice surgical and post-operative management of adults with primary hyperparathyroidism.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common disorder with a significant health burden that arises from autonomous overproduction of parathyroid hormone (PTH) by abnormal parathyroid glands. It is typically characterised by the elevation of serum calcium levels with elevated or inappropriately normal PTH levels. There have been substantial changes in clinical presentation, understanding of the natural history and medical and surgical management over recent decades, with most recent international guidelines published between 2014-2016.¹⁻⁶ The aims of this position statement are to give updated guidance in contentious emerging areas of practice, and to adapt existing guidelines to better reflect the practice environment of Australia and New Zealand.

The position statement is divided into two parts: Part I Assessment and Medical Management and Part II Surgical Management and Postoperative Follow-Up. Representatives from the Australian & New Zealand Endocrine Surgeons (ANZES), the Endocrine Society of Australia (ESA) and the Australian & New Zealand Bone and Mineral Society (ANZBMS) were tasked to review and adapt guidelines using a systematic approach proposed by the ADAPTE working group⁷ to formulate clinical consensus recommendations on presentation, assessment, and both medical and surgical management of primary hyperparathyroidism in adults. It is expected that better health outcomes for individuals and the population will be achieved in a more standardised manner and at a decreased cost to the community.

PURPOSE AND SCOPE

This position statement is primarily intended for use by general practitioners, endocrinologists and endocrine surgeons. Medical practitioners in other specialties, such as general physicians, nephrologists, urologists, and geriatricians, will also come across patients with PHPT, and may find this position statement useful.

Part I of II of this position statement (published separately), focuses on the presentation, assessment, and clinical management of PHPT in adults, including specific considerations such as pregnancy and familial hyperparathyroidism.

Part II of this position statement focuses on the surgical, peri-operative and long-term management of PHPT in adults. Specifically, we address the following key questions:

1. *How Does Imaging Affect the Decision to Operate?*
2. *What Preoperative Localisation Studies Should Be Performed?*
3. *Who Should Perform Parathyroid Surgery and What Type of Surgery Should be Performed?*
4. *How Should Patients Be Managed Pre- and Post-Operatively?*
5. *What is the Definition of Surgical Success?*
6. *What Post-Operative Surveillance is Recommended?*
7. *How Should Recurrent or Persistent PHPT Be Managed?*

8. *What is the Appropriate Surgical Management of Parathyroid Carcinoma?*

METHODS

The Councils of the ANZES, ESA and ANZBMS invited expert representatives of the respective societies and additional authors with expertise in this field (radiology, nuclear medicine, pathology) to participate in a working group in 2020. An experienced academic endocrinologist (MG) was selected to chair the working group.

One face-to-face meeting, prior to COVID-19 restrictions, was held in March 2020. Subsequent communication within the working group was accomplished by email and virtual meetings, due to the COVID-19 pandemic. All potential conflicts of interests of participating authors were declared prior to commencing drafting of the manuscript (Supplementary Table 1).

Two authors (JG and SH) performed the initial search and review of previous guidelines with support from the Wellington Health and Medical Sciences Library (University of Otago). A systematic search of medical databases (Medline, Embase, Scopus and Cochrane Database of Systematic Reviews) was performed from 2010 to 2019, published in the English language and using an exhaustive list of search terms (see Appendix S1 for an example of unedited Medline search). When combining database results, 2155 references were initially identified which was reduced to 370 upon manual review of relevance and then 142 after removal of duplicates. Further manual review by two authors (JG and SH) limited to guidelines and/or consensus statements identified 21 publications deemed appropriate for inclusion.

The 21 identified guidelines were independently ranked in order of relevance by each member of the steering group (JM, MG, FM) and the 12 highest rank guidelines were reviewed by a further group of delegates (JG, SH, SF, CG, SDS, JS, FM, MG) and rated according to the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument and overall assessment (Supplementary Table 2). The scores for each domain were averaged based on the number of responses for each domain and guideline. Based on this assessment, the steering group devised a list of questions to be answered. All members responded and discussed these questions at a face-to-face session held in March 2020, and questions were allocated to subgroups of members. While ADAPTE methodology was used as the basis to inform our recommendations, given the large number of local experts involved generating our recommendations, and the independent feedback from the councils of the three stakeholder societies, the final recommendations are shaped by consensus opinions reflecting the collective expertise inputted into the final manuscript. We cannot report levels of evidence and Grading of Recommendations, Assessment, Development and Evaluation as we did not perform the original data extraction. Therefore, we do not provide evidence levels and refer readers to the original documents as needed.

All authors contributed to the writing of the manuscript and the final draft statement was agreed to by all authors. While the stakeholder was given the opportunity to review and comment on the manuscript, the stakeholder declined co-authorship to preserve their anonymity. External review was sought, and the draft statement was submitted to the councils of ANZES, ESA and ANZBMS who provided feedback. The working group responded to feedback and the final version was endorsed in

August 2021. This position statement will be reviewed and updated in 10 years or sooner if significant changes occur.

1. How Does Imaging Affect the Decision to Operate?

Imaging techniques deployed to identify parathyroid pathology are a tool for operative planning and in general have no role in the decision of whether to offer first-time surgery for PHPT. The success rates for image guided parathyroid surgery are comparable to those obtained when no pre-operative imaging is obtained.⁸

Recommendation 1.1: There is no role for imaging to make the diagnosis of PHPT.

The decision to perform localisation studies in PHPT should occur after the decision is made that surgery is indicated. In some cases, where concurrent neck (thyroid) pathology is suspected e.g. clinical goitre, or when previous neck surgery has been performed for non-parathyroid purposes, additional pre-operative imaging may be appropriate as guided by the clinical scenario.

Recommendation 1.2: The results of localisation studies should not influence the decision to offer surgery for primary hyperparathyroidism.

The decision to offer surgery for PHPT should be made in accordance with the recommendations in Part I - Chapter 4 of this position statement and in consultation with the patient. The results of localisation studies should not be used to select patients suitable for surgical referral nor should they adjust the threshold for offering surgical treatment.

These recommendations pertain to first-time surgery for PHPT. Parathyroid imaging in the re-operative setting is considered in Chapter 7 of this document.

2. What Preoperative Localisation Studies Should Be Performed?

80-90% of cases of PHPT are due to a single hyperfunctioning adenoma, and it is in this scenario when imaging is most successful.^{9,10} Imaging can facilitate surgical planning and reduce operative time and extent of dissection. It is particularly helpful for the localisation of ectopic parathyroid adenomas; up to 16% are ectopic in the neck or mediastinum.¹¹

Like parathyroid surgery, parathyroid imaging produces better results when protocolled and interpreted by experienced parathyroid imaging specialists. A good relationship with a parathyroid surgeon and regular feedback on operative findings will enhance the skills of the radiologist. Each imaging modality has advantages and disadvantages, and the choice of imaging is largely dependent on local resources and expertise. Different modalities often provide complementary information.

Ultrasound

Ultrasound is the least invasive and most affordable imaging technique and involves no radiation. It is dependent on local technical expertise, neck shape and girth, adenoma location, number, and size of adenomas, as well as coexistent thyroid

disease.¹² Concurrent assessment of thyroid size and documentation of incidental thyroid nodules is helpful and may identify thyroid disease that can be treated surgically at the same time. Targeted re-assessment with ultrasound is also of value in clarifying indeterminate findings of other imaging modalities. Ultrasound is a very user-dependent modality. A parathyroid surgeon who performs their own ultrasound benefits from invaluable feedback via operative findings. Ideally, the parathyroid surgeon should perform their own ultrasound to help plan surgery, often in the office and again on the operating table.

Parathyroid Scintigraphy

Parathyroid scintigraphy has evolved along with radiotracers and imaging capabilities. In dual isotope studies, the thyroid is imaged using Tc-99m-Pertechnetate uptake. These images are subtracted by computer from the images produced by Sestamibi uptake into both the thyroid gland and parathyroid adenomas.

Single isotope, dual phase studies using only Tc-99m-Sestamibi with early and late images take advantage of the longer retention of Sestamibi in pathological parathyroid tissue compared with thyroid tissue. Several protocols exist involving combinations of methods described in Appendix S2, to improve sensitivity and specificity. Superiority of one imaging method over the other has not been proved, however a small study demonstrated similar sensitivity between SPECT (Single-photon emission computed tomography using the gamma camera) and SPECT CT (which also employs a low-dose CT-scan), but better specificity (96% for SPECT CT vs 48% for SPECT).¹³ Although most adenomas are localised on the planar subtraction and/or early versus delayed SPECT, a smaller proportion of cases (approx. 15%) wash out early, possibly because of P glycoprotein expression, and are best seen on early images.¹⁴ Difficulties arise when there is parathyroid hyperplasia, multi-gland disease, small adenomas (< 500 mg), low oxyphil cell expression, P glycoprotein expression, confounding thyroid nodules, or Sestamibi uptake due to adjacent avid non parathyroid tissue such as salivary glands. If doubt exists, another mode of imaging such as 4DCT or ultrasound may provide added clarity.

Parathyroid 4DCT (Four dimensional computed tomography)

4DCT uses multiple phase non-contrast and contrast-enhanced scans through the same location, with the fourth dimension being time. Most centres use a 3-phase study with non-contrast, arterial and venous phases. Early dosimetry studies showed a higher radiation dose (approx. 11mSv) compared to Sestamibi /SPECT CT (approximately 7 mSv).^{12,15} More recent studies using newer generation CT scanners¹⁶ show radiation dose of 4DCT is less than Sestamibi. Interpretation of 4DCT, like Nuclear Medicine Sestamibi scans require close attention to technique and operative follow-up for quality assurance. Multiple papers have shown sensitivity and specificity of 4DCT to be equivalent and in some cases better than Sestamibi, especially when interpreted by experienced parathyroid radiologists.¹⁷⁻¹⁹

F-18 PET with Fluorocholine

This modality shows promise in parathyroid adenoma evaluation, with good sensitivity compared with Tc-99m Sestamibi.²⁰ Limitations include availability and

significant cost. Radiation dose is similar to dual phase and planar low dose Tc-99m-Pertechnetate plus Tc-99m-Sestamibi SPECT CT and 4D CT.

MRI

May become useful in the future as second- or third-line imaging but access, expense and interpretive skill are currently restrictive. There is limited current evidence to support use of MRI.

Recommendation 2.1: Parathyroid imaging should be limited to pre-operative assessment, after diagnosis.

Recommendation 2.2: Due to site variability in diagnostic accuracy, imaging is best performed at a central site with a high level of experience. In high volume centres, imaging is reported to have a sensitivity of up to 92%.¹⁸

While neck ultrasound and parathyroid scintigraphy are first-line imaging modalities in many cases, some centres prefer parathyroid multiphase CT as a first-line investigation. The choice of imaging modality is ideally left to endocrinologist and/or the surgeon, who are aware of local expertise.

Recommendation 2.3: Ultrasound assessment of the thyroid as well as for parathyroid adenomas is recommended to assist all imaging interpretation and adenoma localisation.

Ultrasound can be performed by a specialised parathyroid radiologist, but the surgeon may also perform their own ultrasound to further assess and verify findings.

Recommendation 2.4: Comparison of different nuclear medicine tracer findings as well as early and delayed imaging for both planar and SPECT-CT imaging increases diagnostic accuracy.

3. Who Should Perform Parathyroid Surgery and What Type of Surgery Should be Performed?

Recommendation 3.1: Most patients requiring parathyroid surgery can be appropriately managed by surgeons with adequate experience and a consistent annual volume of >15 cases.

Increased hospital volume is inversely related to complications and reoperations for persistent disease.²¹⁻²³ Outcomes in endocrine surgery however are dependent on surgeon, as opposed to institutional volume. Experienced surgeons achieve satisfactory outcomes regardless of setting (small community vs tertiary academic)²⁴.

Minimum surgical volumes are difficult to define. High volume surgeons achieve PHPT cure in >95% of index cases^{25,26}, but this drops to <70% where the annual surgeon volume is <10/year.²⁷ Lower volumes are associated with increased risk of recurrent nerve injury, neck haematoma and hypoparathyroidism.^{24,28}

Outcomes appear acceptable when completing at least 15 parathyroidectomies annually.²⁴

Recommendation 3.2: Surgery for persistent/recurrent disease should be managed by experienced parathyroid surgeons. Similarly, cases of non-localised disease, known multi-gland disease, hereditary syndrome related disease, paediatric cases, secondary or tertiary disease should be managed by experienced parathyroid surgeons.

Focussed surgery versus bilateral exploration; should one approach be employed for all patients?

Bilateral neck exploration (BNE) was the gold standard for surgical management of PHPT. However, most patients (>80%) have single gland disease and focused parathyroidectomy (or minimally invasive; targeted) has gained popularity.^{29,30} Multi-gland disease may be more prevalent in younger patients or those with a family history.³⁰⁻³² Recent reports suggest a trend back towards BNE,^{30,31} owing to an increasing incidence of recurrent disease with extended follow-up after focussed surgery.³² Regardless of the approach, biochemical cure outcomes are good and at least one large meta-analysis has shown minimally invasive surgery and BNE to be equivalent.²⁹ Higher annual volume and accrued experience of at least 150 – 200 parathyroid cases, in addition to experience in thyroid surgery, would be a reasonable expectation for surgeons performing more complex cases.

Recommendation 3.3: The majority of PHPT patients have single gland disease and a focussed approach is appropriate following discussion with the patient regarding the possibility of persistent disease.

Recommendation 3.4a: BNE should be preferentially considered in any patient with negative/discordant localisation imaging, known bilateral/multi-gland disease, known genetic/familial risk factors for multi-gland disease or those on provocative medications (eg. lithium).

Recommendation 3.4b: Lithium was previously considered to be routinely associated with multi-gland disease. However, recent data shows some contrary evidence³³ and where a single adenoma is localised on imaging, a focussed approach may be entertained.

Recommendation 3.5: Novel surgical techniques (eg. trans-oral; trans-axillary; endoscopic assisted; robotic) are not recommended except in the context of evaluation in specialist units. These techniques have been successfully employed in a small number of cases, but are yet to be broadly validated as safe and effective.^{34,35}

Are intra-operative adjuncts necessary?

Frozen section, intra-operative PTH (ioPTH), parathyroid aspiration (for measurement of PTH), radio-guidance, methylene blue, intra-operative ultrasound (ioUS), jugular venous sampling, neuromonitoring, and parathyroid fluorescence have all been used with the aim of improving parathyroidectomy outcomes.³⁶

Recommendation 3.6a: Frozen section may be employed to confirm resection of parathyroid tissue but is not mandatory.

Routine frozen section fails to influence surgical decision making in most cases but may be of utility when dealing with non-localised or normo-hormonal/-calcaemic disease, or to identify parathyroid tissue (if the macroscopic appearance of tissue is equivocal).³⁷

Recommendation 3.6b: ioPTH is not considered an essential adjunct to complete successful parathyroidectomy for PHPT within the Australian and New Zealand context.

IoPTH impacts on surgical decision making in a minority of cases, with some research suggesting that it is not cost effective³⁸ and does not translate into improved outcomes.^{32,39,40} Large volume local Australasian data have shown comparable long-term outcomes for focused parathyroidectomy without ioPTH.⁴¹

Methylene blue application in parathyroidectomy may be useful in quickly identifying large and abnormal parathyroid tissue, but does not improve outcomes. If the surgery is not simple and not concluded quickly, the tissues become blue, and subtle colour cues which may assist an experienced surgeon are lost. Intra-operative radio-guided surgery has not been shown improve outcomes⁴² and ioUS cannot be recommended as a routine adjunct. Intra-operative jugular venous sampling can assist in localising a difficult to find parathyroid lesion to one side or other, particularly where imaging is negative and other adjuncts have failed.⁴³

It is however reliant on ioPTH infrastructure which is often unavailable in Australia and New Zealand. Fluorescence based technologies are not yet considered helpful.³⁶

Recommendation 3.6c: Neuromonitoring of the laryngeal nerve is unnecessary at the index operation,⁴⁴ but surgeons should have a low threshold to use neuromonitoring in re-operative parathyroidectomy.⁴⁵

Re-operative parathyroid surgery is further discussed in section 7.

Recommendation 3.7: When a normal parathyroid gland is de-vascularised in parathyroidectomy for sporadic disease, it should be auto-transplanted..⁴⁶

In situ preservation of normal parathyroid glands to avoid hypoparathyroidism is fundamental. If surgical dissection results in possible devascularisation of one or more glands and especially if hypoparathyroidism is considered to be a risk, auto-transplantation and/or cryopreservation are options. It may be useful to send a fragment for histopathological confirmation, particularly if there is persistent hyperparathyroidism. Visual inspection of colour and capsular incision to assess perfusion are inaccurate techniques. Fluorescence as a marker of parathyroid perfusion is promising, but not yet of proven benefit.⁴⁷ Cryopreservation was previously employed where there was a significant risk of inadequate function eg. subtotal/total parathyroidectomy for multiple endocrine neoplasia (MEN)-1 related hyperparathyroidism. Cryopreservation is not common, however, given the required

resources and the infrequent recourse to transplantation of cryopreserved tissue. Graft tissue viability decreases dramatically after two years of storage.⁴⁸

4. How Should Patients Be Managed Pre- and Post-Operatively?

Pre-operative management of serum calcium

Recommendation 4.1: Most cases of PHPT do not require specific pre-operative calcium management.

Recommendation 4.2: Maintenance of daily calcium requirements and replacement of vitamin D deficiency should be encouraged.

Advice against daily calcium/vitamin D supplementation is inappropriate. Dietary or supplemental calcium intake has no significant impact on biochemical indices of disease^{49,50} and limiting daily requirements can worsen end organ manifestations. Maintaining a daily intake of calcium (1000mg/d), preferably via dietary intake, is recommended and vitamin D insufficiency should be replaced to a target of 50-75nmol/L.⁵¹ Vitamin D repletion and adequate dietary calcium intake minimise the risk of post parathyroidectomy hypocalcaemia.

Recommendation 4.3: Hypercalcaemic crisis is best managed in an inpatient setting by an endocrinologist, in conjunction with an endocrine surgeon for surgical planning as soon as is practical once the patient is medically stabilized.

Markedly and chronically elevated calcium, eg ≥ 3.0 mmol/L, may be tolerated well by some patients and not require urgent care. However, other patients with symptomatic hypercalcaemia with or without organ dysfunction may require urgent medical intervention. Hypercalcaemic crisis, acute hyperparathyroidism or parathyroid storm may be induced in a patient with PHPT and intercurrent illness or dehydration, and can result in multi-organ dysfunction.^{52,53}

Management goals include:

- 1) managing the precipitating illness;
- 2) restoring fluid/electrolyte balance (3-4L/24h normal saline in the absence of contraindications);
- 3) reducing active bone resorption with bisphosphonate therapy;
- 4) promoting renal calcium excretion and ensuring adequate urine output. Additional measures may include a loop diuretic (eg. frusemide; to assist with blocking calcium resorption and promote calciuresis);
- 5) parathyroidectomy once safe to proceed.^{52,53}

Glucocorticoids, calcitonin and cinacalcet can be employed but are rarely used. Prompt surgical management should follow medical optimisation.^{52,53}

Hypercalcaemia can complicate general anaesthesia with arrhythmias and antagonism of non-depolarising muscle relaxants.⁵⁴ If needed, parathyroidectomy can be successfully completed with good outcomes under local anaesthetic with sedation.⁵⁵⁻⁵⁸

Post-operative management of calcium

Recommendation 4.4: Post-parathyroidectomy hypocalcaemia is generally mild and can be managed in an outpatient setting.

Post-operative hypocalcaemia is seen in up to 50% of patients but is generally mild and self-limiting.⁵⁹⁻⁶¹ In one series, 42% of patients developed hypocalcaemia, most were symptomatic and only 2% required intravenous calcium.⁵⁹ Severe hypocalcaemia related to “hungry bones syndrome” can occur in up to 13% of cases in some series.⁶² Management is best led by an experienced endocrine surgeon or endocrinologist.

Recommendation 4.5: For patients at risk of post-parathyroidectomy hypocalcaemia, calcium supplementation per protocol (with periodic calcium testing) is safe and effective.

Symptomatic hypocalcaemia is rare after minimally invasive or focussed parathyroidectomy, and still uncommon after bilateral parathyroid exploration. Risk factors for the development of symptomatic hypocalcaemia include: pre-operative vitamin D deficiency, significantly elevated pre-operative PTH and/or calcium levels, elevated bone turnover markers (both resorption – C-terminal telopeptide of type 1 collagen (CTX) as well as formation -Procollagen type 1N propeptide (P1NP) or Alkaline Phosphatase (ALP), obesity, cardiovascular disease, osteoporosis, simultaneous thyroid surgery, and previous neck surgery.^{59-61,63-66}

Troughs in post-operative calcium typically occur around the 3rd to 4th post-operative day.⁶⁴ For high risk patients, oral calcium and calcitriol supplements may be commenced empirically after surgery, and early discharge with outpatient follow-up is generally safe and feasible. A complex interplay of severity of hyperparathyroidism, vitamin D deficiency and elevated bone turnover can contribute to varying degree and duration of post-operative hypocalcaemia. In select patients, specialist endocrine input is recommended for titration of calcium and calcitriol dosing, consideration of intravenous calcium and correction of hypomagnesaemia which may impair PTH secretion. The Therapeutic Guidelines offer guidance on the most appropriate replacement of calcium in patients with hypocalcaemia.⁶⁷

Permanent hypoparathyroidism is a rare (<1%) complication of parathyroidectomy and is typically encountered following subtotal parathyroidectomy or re-operation for persistent/recurrent disease.^{60,64,68} Endocrinology referral to establish long-term management is recommended.

Post-operative care

Recommendation 4.6: Parathyroidectomy can be completed as a short stay (day-case or one night stay) operation in the majority of cases.

Voice and swallow should be assessed to ensure laryngeal competence. In the absence of haematoma, hypocalcaemia or nerve injury, parathyroidectomy can be completed as a day-case operation within the appropriate clinical and logistical context.^{56-58,69} In the United States, high-volume endocrine surgery units that prefer day case surgery are able to achieve safe same day discharge in up to 90% of cases.⁷⁰ In Australia and New Zealand, most patients stay overnight.

The majority of acute compressive surgical site haematomas appear within the first 4-6hrs post-operatively.⁷¹ Thus, a period of observation of at least this long is required before safe discharge. Contra-indications to day-case parathyroidectomy include concern regarding 1) recurrent nerve injury; 2) post-operative haematoma; 3) parathyroid remnant viability; 4) hypocalcaemia; 5) complex comorbidity; 6) anticoagulation; 7) residence remote from the institution.

Patients should receive clear verbal and written instructions regarding symptoms of hypocalcaemia, delayed haematoma, or infection, and a plan if medical attention is required.

Recommendation 4.7: Initial post-operative biochemistry should include serum calcium and PTH.

Early post-operative review (1-4 weeks) should focus on voice, swallow and wound assessment. Biochemistry (to define biochemical cure) should include a serum calcium level. Serum PTH should be measured at least once between the end of surgery and 24 hours post-operatively to confirm the PTH is no longer elevated. After that, routine PTH monitoring in the setting of eucalcaemia is not required.

5. What is the Definition of Surgical Success?

Recommendation 5.1: Serum calcium should be measured six months after parathyroidectomy. Cure is defined as eucalcaemia six months after parathyroidectomy. (Elevated PTH with normal calcium after previous hypercalcaemia is common and is usually not associated with recurrent PHPT.)

For classic PHPT, normal PTH is not required to be sustained at six months after successful surgery. In fact, after an initial significant fall, often to sub-normal levels, it is common for PTH to rise again above normal sometimes even 2-3 times normal in around 45% of patients at one month, and 25% of patients at six months.⁷² The elevated PTH may persist for more than 1 year, and typically is not associated with recurrent hypercalcaemia.

This phenomenon represents a physiological response and is a form of secondary hyperparathyroidism. Prolonged hypercalcaemia may induce a downregulation of calcium-sensing receptors in the remaining parathyroid glands. A profound fall in calcium, pre-existing vitamin D deficiency, the use of anti-resorptive therapy, chronic renal dysfunction and/or “hungry bones” from severe hyperparathyroidism will amplify the rise in PTH.⁵⁷ Vitamin D supplementation with a target of >75nmol/L and adequate dietary calcium intake are beneficial in this situation to aid calcium absorption and restore calcium homeostasis.⁷³ Provided the calcium is not concurrently inappropriately in the high-normal range, re-elevation of PTH remains consistent with cure.

A broader definition of cure or success is return to normal calcium haemostasis for at least six months after surgery. More generally also, success leads to improvement in bodily aches and pains and general well-being, resolution of hypercalciuria, and gradual improvement in bone mineral density (BMD). Furthermore, success is achievement of the surgical goal, without complications.

Recommendation 5.2: Serum calcium and PTH should be measured six months after parathyroidectomy for normocalcaemic PHPT.

Success generally requires serum calcium and PTH to be normal for six months. Most commonly, the serum calcium will fall further into the normal range. A broader definition of cure or success is return to normal calcium haemostasis for at least six months after surgery.

6. What Long Term Post-Operative Surveillance is Recommended?

Recommendation 6.1: Following surgery, patients should be monitored for recurrence of disease with annual monitoring of serum calcium, and vitamin D. PTH should not be measured routinely; only if hypercalcaemia recurs or selectively if normocalcaemic hyperparathyroidism is suspected in the setting of ongoing bone loss or serum calcium at the top end of the normal range.

Recurrence of PHPT occurs in 5-14% of patients,^{74,75} and 1/3 of recurrences occur ten years or more after surgery.

Recommendation 6.2: Following surgery, patients should still be monitored for long-term sequelae of PHPT.

Skeletal health should continue to be optimised by ensuring adequate vitamin D levels (>50 nmol/L), regular weight-bearing exercise, and appropriate consumption of calcium-containing foods. Surveillance bone mineral density scans should be conducted, initially one to two years after surgery, and osteoporosis treated on its merits.

Although significant improvement is usually seen in BMD at 12 months following parathyroidectomy, patients with severe osteoporosis may remain at increased risk of fracture despite surgical cure of hyperparathyroidism. Thus, patients with osteoporosis at baseline should have appropriate monitoring of BMD and treatment may be indicated when fracture risk remains high.

There is insufficient evidence to recommend ongoing monitoring for renal tract calculi, cardiac, vascular or other sequelae. Discharge from follow-up and return of care to the primary care provider/GP can occur once eucalcaemia is confirmed and an investigation/management plan for end organ manifestations is in place. Some patients with established end organ manifestations may benefit from ongoing endocrine specialist input despite surgical cure.

7. How Should Recurrent or Persistent PHPT Be Managed?

***Persistent PHPT* is defined as elevated serum corrected calcium within six months of parathyroid surgery. *Recurrent PHPT* is defined as elevated serum**

corrected calcium that develops after more than six months of consistently normal serum corrected calcium post-parathyroidectomy. In the case of normocalcaemic PHPT prior to surgery, persistence or recurrence is not easily defined. Persistent PHPT occurs when abnormal parathyroid tissue remains after surgery. It may occur when a single adenoma is not found but is often due to failure to recognize and treat multi-gland disease.

Recommendation 7.1: Persistent or recurrent PHPT should be managed by specialist endocrinologists and parathyroid surgeons, with access to a multidisciplinary team including radiology, nuclear medicine, and pathology.

Most patients with PHPT are cured at their first operation. It is therefore unlikely that a low volume surgeon will develop expertise in this complex area of re-operative endocrine surgery. Where re-operative parathyroid surgery is carried out by experienced endocrine surgeons high cure rates (90-95%)⁷⁶⁻⁸⁴ are achievable. While complication rates of re-operation are higher than in primary surgery, with vocal cord palsy occurring in between 1% and 10% of cases and permanent hypoparathyroidism occurring between 14% and 20% of cases^{76-79,84,85} lower complication rates are achieved by more experienced surgeons.

Recommendation 7.2: A stepwise approach to the assessment and management of persistent or recurrent PHPT is needed.

The goal of a re-operative parathyroidectomy is biochemical cure while minimising risk. Pre-operative planning should aim to identify the missing or target parathyroid(s). Where localisation cannot be achieved, operative treatment may not be appropriate.

1. Re-confirm the biochemical diagnosis as per Chapter 2, Part I of the position statement
2. Re-evaluate the indication for surgical treatment
3. Review of all previous information
4. Further investigation if required
5. Plan the surgical strategy and conduct the operation

1: Re-confirm the biochemical diagnosis.

Refer to Part 1 of this position statement.

2: Re-evaluate the indication for surgical treatment

In most cases when there was an appropriate indication for parathyroid surgery, and there has been no biochemical or symptomatic improvement following the first operation, an indication for re-operation is likely to persist.

The benefit of curing the hyperparathyroidism must be weighed against the increased risk of re-operative surgery. Recurrent laryngeal nerve palsy from the first

operation is a major consideration, particularly if there is no localisation or the target parathyroid is on the contralateral side.

3: Review of all previous information

Careful review of the previous operation report, pathology report, and localisation studies is ideal. A diagram showing parathyroid glands identified, biopsied or removed (confirmed by pathology,) those areas of the neck which have been explored to date, and possible sites identified on imaging can assist in planning further investigation or operation.

A vocal cord check should be undertaken if one has not been completed following the initial operation.

4: Further investigation if required

Imaging prior to the primary operation may, upon review, be sufficient to identify the site of a gland that was missed.

When further imaging is required, Sestamibi/SPECT-CT⁸⁷ or parathyroid 4DCT⁸⁸ interpreted by an experienced parathyroid radiologist may be preferred according to local expertise. We recommend parathyroid surgeons routinely perform their own ultrasound in the office and on the operating table, if possible.⁸⁹

In select cases, parathyroid tissue can be confirmed by ultrasound guided fine needle aspiration and PTH needle wash. Selective venous sampling is a useful invasive investigation when other modalities have failed or produced equivocal results,^{76,90} but requires an experienced radiologist and meticulous protocol. Previous surgical ligation can alter the venous return from a parathyroid adenoma. Where lateralisation without localisation has been achieved, the field of re-operation may be narrowed. As with all re-operative parathyroid surgery, good judgement and careful counselling of the patient is required.

5: Plan the surgical strategy and conduct the operation.

Important considerations:

- Was the first operation a focused procedure or a BNE?
- Is a single abnormal parathyroid likely or multiple additional enlarged glands?
- Is imaging convincing?
- Was the previous surgeon experienced?
- Is there a recurrent nerve palsy?
- Is there a significant goitre?
- Is there a hostile neck?

The ideal condition for re-operative parathyroid surgery is to operate in a targeted fashion to remove the pre-operatively identified abnormal gland(s). In general, an image-guided focused re-operation is recommended.⁹¹ The patient should be counselled that there remains a risk of persistent or recurrent disease even after successful removal of an adenoma in this scenario, as well as a risk of hypoparathyroidism if normal glands were removed or devascularized at the initial operation.

If a focused approach was taken initially and an adenoma removed, one must choose between a second focused approach if there is good localisation, or exploring the remaining three glands regardless, as there is a higher risk of multi-gland disease.⁹²

Most missing glands will be in the neck and can be removed through a cervical incision. Accordingly, neck re-exploration is the usual re-operation. The lateral approach between the strap muscles and the sternomastoid is often undisturbed and takes the surgeon immediately to the posterior portion of the thyroid and tracheoesophageal groove. Lateral entry is especially useful for superior glands.

In the context of a prior truly minimally invasive parathyroidectomy and ongoing indication for surgery, an experienced parathyroid surgeon should perform a neck exploration even where imaging results are inconclusive.

The threshold for blindly exploring the mediastinum is high and would be a last resort in a patient with severe PHPT. Exploration of the anterior mediastinum and thymectomy can be performed thoracoscopically and may reveal the offending parathyroid adenoma.

Typical sites of pathologic parathyroid glands found at reoperation include 44% in a eutopic position, 19% in the thymus and antero-superior mediastinum, and 15% descended superior glands in a para-oesophageal, retro-oesophageal or postero-superior mediastinal location.⁹³

Recommendation 7.3: Re-operation for persistent PHPT should be delayed at least 3-6 months to allow acute inflammatory changes to settle, even though scarring tends to persist long term in the neck.

In some cases where it is relatively urgent to correct the hypercalcaemia, and a target is identified, it may be appropriate to re-operate as soon as practicable after all the steps above are completed.

Recommendation 7.4: Re-operative parathyroid surgery should be performed in a hospital with access to frozen section and intra operative neuromonitoring (ioNM).

Frozen section is sometimes helpful to confirm removal of parathyroid tissue when the gross appearance is atypical. IoNM should be considered for re-operative surgery,^{45,94} although the benefit remains unproven. ioNM should be utilised because of the increased risk of recurrent laryngeal nerve damage in re-operative surgery.⁸⁵

Recommendation 7.5: It is feasible to perform re-operative parathyroid surgery without ioPTH monitorin. Quick ioPTH is not widely available in Australia and New Zealand.

However, if available, ioPTH can be employed as a useful adjunct to re-operative parathyroid surgery.^{78,95}

8. What is the appropriate surgical management of parathyroid carcinoma?

Parathyroid carcinoma is uncommon (approximately 0.5% of all PHPT cases).^{96,97} Clinical and biochemical features of parathyroid carcinoma are detailed in Chapter 7, Part I of this position statement.

Recommendation 8.1: Where there is pre-operative or intra-operative suspicion of parathyroid carcinoma, consultation from an experienced endocrine surgery unit should be obtained. Needle biopsy should not be performed.

Where suspicion of parathyroid carcinoma exists pre-operatively, investigations should focus on defining local invasion. Airway, thyroid, oesophagus, carotid sheath, recurrent nerve and strap muscles should be assessed with US, and potentially CT or MRI.⁹⁸ Assessment of vocal cord function is important. Any suggestion of local invasion warrants tertiary referral and multidisciplinary consideration.

Needle biopsy is not recommended. The diagnosis of parathyroid carcinoma is based on demonstrating invasive growth therefore differentiating between benign/malignant parathyroid cells cytologically is impossible and risks needle tract dissemination.^{99,100}

Parathyroid malignancy can be encountered unexpectedly at operation, and difficult intra-operative decisions will be required without a definitive tissue diagnosis. The spectrum of disease is large and ranges from encapsulated to locally advanced disease with encasement/invasion of surrounding structures. Desmoplasia and fibrosis are typical macroscopic hallmarks.

Recommendation 8.2: Surgery is the only curative treatment modality and en-bloc resection of the disease with invaded structures is key. There is insufficient evidence to recommend for or against prophylactic lymphadenectomy.

Operative Principles:

Principles involve en-bloc resection of disease in continuity with involved tissues. Frozen section does not always assist diagnosis and the surgeon should have a low threshold for radical resection if the operative findings suggest parathyroid carcinoma. Resection without tumour capsular breach is important; outcomes are poor with tumour spillage or residual disease.⁹⁷ This may require en-bloc resection of adjacent thyroid tissue (lobectomy) and may also require partial resection of strap muscles, trachea, oesophagus and recurrent nerve.

Nodal metastases are variable and are seen in up to 19% of cases, more commonly in tumours >3cm.^{101,102} While resection of macroscopically involved nodes

is justifiable, there is insufficient evidence to support routine prophylactic lymphadenectomy.¹⁰²

Recommendation 8.3: Unequivocal histological evidence of invasive growth is required to make the pathological diagnosis but may not always be present. Opinion should be sought from an expert endocrine pathologist.

Pathologic Diagnosis:

The pathological diagnosis of parathyroid carcinoma requires the histological demonstration of invasive growth indicated by any of: invasion into adjacent structures, vascular/lymphatic invasion, perineural invasion, or metastasis.^{103,104} Histological confirmation of carcinoma can be difficult and sometimes may only be suspected or diagnosed after repeated local recurrence.¹⁰⁵⁻¹⁰⁷

Immunohistochemistry for parafibromin (*CDC73* gene product), PGP9.5, Ki-67, Rb, p27, Galectin-3 and E-cadherin may be used to support the diagnosis of parathyroid carcinoma in equivocal cases but no marker is definitive.^{104,105}

20-25% of patients with parathyroid carcinoma will have a germline *CDC73* mutation.¹⁰⁵⁻¹⁰⁷ Thus, hypoparathyroidism-jaw tumour syndrome should be considered in all patients with parathyroid carcinoma and genetic testing should be routinely offered. Parafibromin immunohistochemistry may help triage testing as normal (positive) expression particularly when accompanied by negative staining for PGP9.5 argues against *CDC73* mutation.¹⁰⁵⁻¹⁰⁹ Abnormal parafibromin expression can also be used to investigate the pathogenicity of variants of uncertain significance identified by molecular testing.^{108,109} However parafibromin immunohistochemistry is not widely available, can be a difficult stain to perform and interpret, and loss of parafibromin expression is not completely sensitive for *CDC73* mutation.¹⁰⁹ Therefore depending on local resources and pre-test probabilities, genetic testing should still be considered in patients with normal parafibromin expression or if parafibromin immunohistochemistry is not available.

‘Atypical parathyroid tumours’, (previously termed ‘atypical parathyroid adenomas’ or ‘parathyroid neoplasms of uncertain malignant potential’), describe parathyroid tumours with worrying histological features (eg. high mitotic rate, fibrosis, cytological atypia) but in which no unequivocal invasive growth can be demonstrated.^{110,111} Most atypical parathyroid adenomas do not recur^{110,111} and it has been suggested that they may be followed similarly to usual adenomas in the absence of concerning clinical features or immunohistochemical findings suggestive of *CDC73* mutation (parafibromin negative, PGP9.5 positive immunohistochemical profile).¹¹⁰⁻¹¹⁴

Staging:

The eighth edition of the American Joint Committee on Cancer (AJCC) staging manual includes a novel Tumour, Node, Metastases (TNM) staging system (Table 1).¹¹⁵ As yet, prognostic stage groups have not been defined.

Adjuvant therapy:

Adjuvant therapy is reserved for persistent disease and should be discussed in a multidisciplinary forum. Chemotherapeutics and immune modulators have been promoted but lack evidence.¹¹⁶⁻¹¹⁸ External beam radiotherapy may have some benefit as a palliative manoeuvre.^{119,120} Enrolment in clinical trials should be considered.

Recommendation 8.4: Residual disease may occur in up to 50% of patients with parathyroid carcinoma. Long term clinical, biochemical and imaging follow-up is required.

Prognosis and Follow-up:

5 and 10-year survival rates have been reported to be 85% and 49% respectively.¹²¹ 50% suffer recurrence¹²² at a median time of 33 months,¹²³ and recurrence correlated with serum calcium level and tumour rupture, and inversely with extent of operation. Age and vascular space invasion correlate with worse survival.^{97,122} Disease free and overall survival gains have not improved for forty years.¹²⁴

Follow-up involves clinical assessment and lifelong annual calcium and PTH, with radiologic assessment for suspected recurrence if there is a possibility of surgical redress or targeted therapy.

Palliative treatment

Principles involve managing local compressive symptoms, systemic/metastatic disease and associated hypercalcaemia.¹²² Local disease control may be possible with external beam radiotherapy.^{119,120} Palliative or compassionate use of chemotherapeutics/other novel agents may be employed depending on local resources^{117,118} and enrolment in clinical trials should be encouraged.

Intravenous hydration, diuresis and bisphosphonate therapy may assist with severe hypercalcaemia. If persistent, surgical debulking, calcimimetics such as cinacalcet and dialysis are options.¹²⁵

CONCLUSIONS

This collaboration between ANZES, ESA and ANZBMS provides evidence-based recommendations to guide pre-operative clinical evaluation, surgical management and post-operative and long-term follow-up of adults with PHPT in the Australian and New Zealand health care setting. While the ADAPTE is a validated and evidence-based approach to guideline evaluation, there was considerable authorship overlap among the 12 guidelines included, and many of these guidelines predominantly pertained to the management of asymptomatic PHPT. This position statement promotes safe, best practice management of adults with PHPT and can be considered a broad guide for approaching the surgical management of these patients.

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DISCLOSURE SUMMARY

See Supplementary Table 1

GLOSSARY

AGREE II Appraisal of Guidelines for Research and Evaluation II

AJCC American Joint Committee on Cancer

ALP Alkaline Phosphatase

ANZBMS Australian & New Zealand Bone and Mineral Society

ANZES Australian & New Zealand Endocrine Surgeons

BMD Bone mineral density

BNE Bilateral neck exploration

COVID-19 Coronavirus disease of 2019

CT Computed tomography

CTx C-terminal telopeptide of type 1 collagen

ESA Endocrine Society of Australia

FHH Familial hypocalciuric hypercalcaemia

ioNM Intra-operative neuro-monitoring

ioPTH	Intra-operative parathyroid hormone
ioUS	Intra-operative ultrasound
MEN	Multiple endocrine neoplasia
MRI	Magnetic Resonance Imaging
P1NP	Procollagen type 1N propeptide
PET	Photon emission tomography
PHPT	Primary hyperparathyroidism
PTH	Parathyroid hormone
SPECT	Single-photon emission computed tomography employing a gamma camera
SPECT CT	Single-photon emission computed tomography employing low dose computed tomography scan
TNM	Tumour, Node, Metastases
UMP	Uncertain malignant potential

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Table

Table 1: Pathological staging of solid tumours

Primary tumour	
TX	Primary tumour cannot be assessed
Tis	Atypical parathyroid neoplasm (neoplasm of UMP)
T1	Localised to the parathyroid gland with extension limited to soft tissue
T2	Direct invasion into the thyroid gland
T3	Direct invasion into recurrent laryngeal nerve, oesophagus, trachea, skeletal muscle, adjacent lymph nodes, or thymus
T4	Direct invasion into major blood vessel or spine
Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or superior mediastinal lymph nodes (level VII)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical (level I,II,III,IV, or V) or retropharyngeal nodes

Metastasis	
MX	No distant metastasis
M1	Distant metastasis

Adapted from AJCC TNM 8th edition¹¹⁵

UMP: Uncertain malignant potential