Systematic Review of Minimally Invasive Parathyroidectomy

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June 1999

Australian Safety & Efficacy Register of New Interventional Procedures – Surgical

The Royal Australasian College of Surgeons
Systematic review of minimally invasive parathyroidectomy

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Safety and Efficacy Classification for Minimally Invasive Parathyroidectomy

The ASERNIP-S Procedure Classifications were revised in August 1999 by the ASERNIP-S Management Committee. As such, each of the four procedures already assessed by ASERNIP-S was allocated a new classification from the following list:

1. Safety and efficacy is established. Procedure is equal to, or better than the nominated gold standard. Procedure may be introduced into practice.

2. The safety and efficacy of the procedure cannot be determined due to an incomplete and/or poor quality evidence-base. One of the following recommendations is made:
   2.1 An audit is required.
   2.2 A Controlled Clinical Trial, preferably prospective with concurrent controls, is required.
   2.3 A Randomised Controlled Clinical Trial is required.

3. Safety and efficacy of procedure is shown to be unsatisfactory. Procedure should not be used.

The new classification for Minimally Invasive Parathyroidectomy is 2.2. A Controlled Clinical Trial is required to assess both safety and efficacy.

References to previous classifications remain unchanged in the document.

Important Note: The information contained in this report is a distillation of the best available evidence located at the time the searches were completed as stated in the protocol. Please consult with your medical practitioner if you have further questions relating to the information provided, as the clinical context may vary from patient to patient.
The Systematic Review of Minimally Invasive Parathyroidectomy, Recommendations were ratified by the ASERNIP-S Management Committee while the Safety and Efficacy Classification was revised to a level 2.

The procedure is sufficiently close to a procedure of established safety and efficacy to give no reasonable grounds for questioning safety and efficacy. Procedure may be used subject to continuing audit.

ASERNIP-S Management Committee Meeting
May 8th 1999
Auckland, New Zealand.

The Council of the Royal Australasian College of Surgeons in June 1999
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Review Protocol

Minimally Invasive Parathyroidectomy

October 1998

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1. Objective

To assess the literature regarding the procedures of minimally invasive parathyroidectomy, in comparison to bilateral open neck exploration in patients with primary hyperparathyroidism (PHPT) and make recommendations on the safety and efficacy of the minimally invasive technique.

2. Background

The parathyroid glands are endocrine organs secreting parathyroid hormone (PTH) for maintenance of calcium homeostasis. Although there are usually four glands there may be both supernumerary glands and ectopic glands situated outside of their normal cervical location. Primary hyperparathyroidism usually results from an adenoma involving a single gland but may also be due to multiglandular adenomatous change as well as diffuse hyperplasia

Primary hyperparathyroidism is a surgically correctable disease with a success rate of up to 98% at initial surgery by an experienced surgeon. The standard technique involves bilateral neck exploration for identification and removal of abnormal parathyroid tissue. Reasons for surgical failure include ectopic glands, multiglandular disease, supernumerary glands or surgical inexperience with failure to identify the primary lesion. Very rarely ectopic mediastinal glands require a median sternotomy.

Preoperative imaging techniques for localisation of abnormal glands have not been widely used for initial surgery due to limited success, significant costs and the very high success rate of surgery by an experienced operator.

Minimally invasive approaches for a parathyroidectomy have been advocated recently as being superior to the standard technique, both from a cosmetic viewpoint, reduced patient discomfort and potentially easier access to the upper mediastinum. The disadvantages associated with these techniques include an absolute requirement for preoperative imaging with its associated significant costs, the potential of increased morbidity from gas embolism and local bleeding, and possibility of a reduced success rate due to undetected multiglandular disease.

Minimally invasive parathyroidectomy needs to be further assessed for its safety and efficacy compared with the current standard technique of bilateral open neck exploration in PHPT.
Reference List


3. **Inclusion Criteria**

Papers were selected for inclusion in this literature review on minimally invasive parathyroid surgery based on the following criteria.

- **Participants:**
  
  Human and animal studies were included in this review. Specifically, for human studies, patients with PHPT.

- **New Intervention:**
  
  If the paper to be included concerned the new intervention, it dealt with:
  
  Minimally invasive parathyroid surgery with preoperative imaging
  
  - Endoscopic technique
  
  - Unilateral approach

- **Comparative Intervention:**
  
  Papers included for the comparative intervention were reviews of the technique of bilateral open neck exploration for hyperparathyroidism, which represented the current safety and efficacy of this technique.

- **Outcomes:**
  
  The papers included contained information on at least one of the following outcomes of the intervention:

  1. Pre and postoperative serum calcium and PTH levels
  2. Postoperative morbidity including: recurrent nerve palsy, postoperative haemorrhage
  3. Postoperative mortality
  4. Conversion rate to standard operation
  5. Failed exploration
  6. Parathyroid capsule breach
  7. Recurrent hyperparathyroidism
  8. Incision length/scar
  9. Use of analgesics
  10. Length of hospital stay
  11. Costs
Types of studies:

Papers included in the review of the new intervention were in one of the following forms:
- Randomised controlled trials, controlled clinical trials (historical, non-randomised), case-series and case-reports.
- Additional published material in the form of letters, commentary and discussions should be included in the submissions to the review surgeon as background information.
- Study types other than those mentioned above may be included if they are felt to be relevant and if valid reasons are given in the protocol.

Papers to be included in the assessment of the comparative intervention were review articles.

4. Exclusions

- The ASERNIP-S data manager and the protocol surgeon excluded references that clearly did not meet the inclusion criteria.
- Reasons were documented for excluding particular references that did meet the inclusion criteria.

5. Additional Information

- Guidelines on assessing the published material in terms of methodological design and validity (i.e. hierarchy of study designs, bias, confounding, sample size, and statistical power) were sent to the Review Surgeon. Supplementary material on the review process was attached, including excerpts from The Cochrane Collaboration Handbook, and the NH&MRC 1999 guidelines for assessing research evidence.
- As this review was an exclusively narrative systematic review, data is summarised in table format, rather than through meta-analysis.
6. Literature Search Strategies

Databases searched:
- SilverPlatter Medline (WinSpirs)
- Ovid Current Contents
- Lexis-Nexis Embase

Search Terms: Search strategies were devised by the Data Manager and Protocol Surgeon for the Medline, Current Contents and Embase databases.

1. New Intervention Search

The search was performed to enable the retrieval of papers dealing with minimally invasive parathyroid surgery techniques, including endoscopic and unilateral approaches with preoperative imaging for patients with PHPT. The search terms entered were:

(endoscop* or (minimal* and invasive) or unilateral) and parathyroid*

NB:
* is a truncation symbol, which retrieves variations of the indicated text, e.g. endoscop* retrieves endoscope, endoscopy, endoscopic. In Medline the truncations symbol is *; in Current Contents it is $; in Embase it is !.

The same search terms were utilised for all databases except for The Cochrane Collection database because the restricted searches turned up very few references.

The simple search terms entered were:

Parathyroidectomy or Parathyroid resection*

2. Comparative Intervention Search

This search was performed to enable retrieval of review articles published in the last five years on parathyroidectomy by bilateral open neck exploration. The search terms used were:

(parathyroid* and ((surg* or management) in CITN) and (review in PT) and English in LA) [since 1993]
Search Time Frame:

1. SilverPlatter Medline (WinSpirs)
   New Intervention - Year range = 1984 - August 1998
   Comparative Intervention - Year range = 1993 - August 1998

2. Ovid Current Contents
   New Intervention - Year range = 1993 - Week 38 1998
   Comparative intervention - Year range = 1993 - Week 38 1998

3. Lexis-Nexis Embase
   New Intervention - Year range = 1974 - August 1998
   Comparative Intervention - Year range = January 1993 - August 1998

   - Year range searched = 1966 -1998

Literature Databases:

Minimally Invasive Parathyroidectomy: 41 references formed the Reference Manager database after exclusions of duplicates and articles that clearly did not meet the inclusion criteria.

Parathyroid review: 13 references formed the Reference Manager Database after exclusions by Data Manager.
An Assessment of Minimally Invasive Surgery for Primary Hyperparathyroidism, as Compared to Standard Bilateral Neck Exploration

Emeritus Professor Tom Reeve AC CBE

February 1999
Executive Summary

This report has been made to ASERNIP-S. It is comprised of an assessment of procedures, which in toto are referred to as minimally invasive parathyroidectomy, in comparison to the established bilateral open neck exploration in patients with primary hyperparathyroidism (PHPT). Observations and recommendations are made on the safety and effectiveness of the minimally invasive procedure.

The review provides a basis for the Review Group to make recommendations to the Management Committee of ASERNIP-S. Once approved the review is submitted for ratification by the Council of the Royal Australasian College of Surgeons.

The literature relating to the management of PHPT has been addressed in three sequential areas: -

i conventional bilateral neck exploration
ii unilateral neck exploration
iii minimally invasive exploration

Further segments have overviewed the safety of minimally invasive parathyroid surgery and its introduction into Australian practice.

A short narrative has been provided to introduce the subject.
INTRODUCTORY NOTES
Introduction

Surgery of the parathyroid gland is a comparative newcomer to the armamentarium of surgeons, commencing when Felix Mandl operated on Albert, a streetcar conductor, in Vienna in 1925\(^1\). The procedures for investigation and management of parathyroid disease have been carefully developed, and have become incorporated as an integral part of current surgical practice\(^2,3\).

This is not to say, however, that PHPT is a cut and dried disease or that surgery for the disease has remained static since 1925. Far from this being so, a surgical procedure has developed over time, which produces a satisfactory outcome in 95-98% of patients operated upon\(^3,4,5\). There are, however, some caveats required to achieve such results. Firstly, before surgery the diagnosis needs to be clearly established and criteria for patients should in general meet those required by the NIH Consensus Development Conference, 1990\(^6\). These outline that all patients with PHPT should be considered for surgery. Those with a high serum calcium level who are symptomatic present as clearly appropriate for operation. While asymptomatic patients should be considered as candidates for surgery, some on the other hand, may be considered suitable for conscientious long term medical surveillance after rigorous evaluation to determine whether they can be followed safely without surgical therapy\(^6,7\).

The clinical pattern of PHPT is demonstrating elements of change, particularly the increase in the number of patients presenting with diminution in bone density and patients with the enervating effects of hypercalcaemia\(^4,8\), both of which are capable of significant improvement when patients with these problems are submitted for parathyroidectomy\(^4\). There is also literature on population-based studies revealing that untreated patients with PHPT have a greater risk, when compared with age and sex-matched controls in the normal population, of dying from cardiovascular disease and malignancy. Furthermore, their risk of death can be reduced and perhaps eliminated if treated by parathyroid surgery. Surgery at an early stage of the disease confers considerable therapeutic benefit on patients with PHPT\(^5,6\).

The Standard Surgical Approach

The current approach to surgery for PHPT has been to proceed through a collar incision to bilaterally explore the neck, locate abnormal parathyroid tissue and remove it. It is customary to sight four parathyroid glands where possible. The literature on this approach is made up of reviews from case series, some of which report a success rate of 95-98%\(^3\) (Table I, Papers Reviewed – Bilateral Neck Exploration). The most recent Australian series has a yield of 98% success\(^5\).

Virtually all reviews aver to the need for experience if surgeons are to achieve this level of success (Table I, Papers Reviewed – Bilateral Neck Exploration).
What comprises an experienced parathyroid surgeon?

The surgeon; to become experienced, needs to have developed a sound knowledge of parathyroid disease and its physiology, be clearly acquainted with the anatomy and surgical pathology of the glands and their vagaries, have been trained by an experienced surgeon, and have had significant operative experience under supervision in the appropriate surgical skills.

In approximately 80% of operations there is one enlarged gland that requires excision. Its recognition and removal are the prime function of the surgery, and it results in essentially 100% cure, if there is only one pathological gland. Surgical failure is due to one or more of a number of causes, including gland(s) in ectopic positions, multiglandular disease, and supernumerary glands, or lack of surgical experience. On rare occasions ectopic glands may be in the mediastinum and mediastinotomy may be required. The parathyroid surgeon must be able to address all these surgical situations.

Does Surgical Experience Count?

Experience has demonstrated to endocrinologists and surgeons that the statement by John Doppman, (Chief, Department of Diagnostic Radiotherapy, NIH) a radiologist of the highest reputation, at the NIH Consensus Development Conference (1991) on PHPT that “the only localisation study needed by a patient undergoing initial parathyroid surgery is to locate an experienced parathyroid surgeon” is correct. Preoperative localisation studies have not yielded a level of accuracy to surpass that as achieved by experienced surgeons (Table 1, Papers Reviewed – Bilateral Neck Exploration).

As already noted, this surgical approach gives satisfactory results, but when the surgeon approaches an operation for PHPT there is an element of doubt about outcome until the pathology is located. Is a 2-5% failure rate at primary surgery, accompanied by low morbidity, acceptable? Is the concentrated training required to become an expert at parathyroid surgery too big an ask? Can experienced surgeons maintain a sufficient caseload to maintain skills at high levels? Should all cases be referred to special clinics?

A New Approach?

The aim to improve and simplify current surgical practice is a given and the newer methods of less invasive surgery are being explored in many anatomical locations of the body, now it is the parathyroid’s turn. It is time for a more deliberative approach to assess the new, using the very satisfactory old as a yardstick by which to gauge the results. The outcome for patients is the test.

Even the best reports on parathyroid surgery have a small element of failure. It is the uncertainty that accompanies each initial exploration for parathyroidectomy that has encouraged the development of more direct approaches to surgery of the parathyroid.

1. Conventional Bilateral Neck Exploration

Literature supplied by the Protocol surgeon and ASERNIP-S Researcher and other material has been reviewed. This comprises a comprehensive body of data that relates to the standard approach for management of PHPT.
It is of note that PHPT occurs in about one in every 1,000 individuals and in as frequently as one in every 500 women aged 60 years and over\(^\text{13}\).

Seventeen papers have been reviewed; there are no randomised controlled trials. Publications are in the review format, case series and case reports. The papers reviewed and their type are listed in Table I, Papers Reviewed – Bilateral Neck Exploration.

The findings emerging from the review of the published material are of importance to the overall approach to PHPT.

1. Primary Hyperparathyroidism is the leading cause of hypercalcaemia in non-hospitalised patients in the USA\(^3,10\). This is probably the case in Australia also.

2. Demonstration of hypercalcaemia and subsequent diagnosis of PHPT frequently follows performance of a routine serum biochemistry profile\(^2,4\).

3. A body of patients appear to be asymptomatic, but previously unrecognised symptoms resolve after surgery has corrected PHPT\(^2,3,4,9,11\).

4. Expectant management may be used for PHPT but demands rigorous monitoring to ensure that no deterioration of the patients’ clinical state occurs\(^2,6,11,14\).

5. Surgical management comprising bilateral neck exploration and excision of pathological tissue is curative in 95-98\%\(^2,3,6,7\).

6. i. Preoperative localisation of abnormal parathyroid tissue has not been seen as indicated if the conventional surgical approach is followed\(^3,7\).

6. ii. “The only localisation study required by a patient undergoing critical parathyroid surgery, is to locate an experienced parathyroid surgeon”\(^6,7\) (Doppman).

7. A sound knowledge of the regional anatomy is essential to safe parathyroid surgery\(^17\), the presence of undiscovered supernumerary and ectopic parathyroid glands are the commonest cause of failure\(^3\).

8. A significant concern amongst endocrinologists and surgeons relates to the underlying pathology in each patient who has parathyroid disease. Whilst in the majority, single adenomatous disease is the cause, more than one adenoma may be found in 2-10\% of patients. Furthermore, in 5-13\% of patients hyperplasia of multiple glands may require the removal of more than one gland to achieve cure\(^3,5\).

9. Bilateral neck exploration, the evaluation of all four parathyroid glands and excision of parathyroid pathology by an experienced parathyroid surgeon, provides the best available outcomes for PHPT\(^2,4,6,9,12,14-18\). Cure of the disease lies between 95 and 98\% in the hands of experienced surgeons\(^3,5,7,16,17\).
Reference List


<table>
<thead>
<tr>
<th>Author</th>
<th>Time</th>
<th>Setting</th>
<th>Study Type</th>
<th>No. of Patients</th>
<th>Who Should Operate?</th>
<th>Imaging</th>
<th>Asymptomatic</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Allerheiligen et al</td>
<td>1998</td>
<td>GP Dept, Uni Wyoming</td>
<td>GP review</td>
<td>N/A</td>
<td>Experienced surgeon = best approach.</td>
<td>Possible, may be necessary.</td>
<td>favour surgery</td>
<td>-</td>
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<td>Clark OH</td>
<td>1996</td>
<td>Mt Zion UCSF</td>
<td>General review</td>
<td>&gt;1000</td>
<td>Experienced endocrine surgeon.</td>
<td>Ultrasound 70% accuracy.</td>
<td>favour surgery</td>
<td>&gt;95% cure &lt; 1% HPT ? &lt; 1% RLN injury.</td>
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<td>Clark OH</td>
<td>1996</td>
<td>Mt Zion UCSF</td>
<td>General review</td>
<td>-</td>
<td>Experienced endocrine surgeon. Success &lt; 70% with inexperience.</td>
<td>Outlines availability.</td>
<td>favour surgery</td>
<td>95% cure.</td>
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<td>Deftos LJ et al</td>
<td>1993</td>
<td>UC San Diego</td>
<td>General review</td>
<td>-</td>
<td>Experienced surgeon.</td>
<td>Seldom indicated. NB History PE and Serum PTH.</td>
<td>favour surgical consideration</td>
<td>Mentions rapid intraoperative PTH study.</td>
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<td>Delbridge et al</td>
<td>1998</td>
<td>RNSH, Uni Sydney</td>
<td>Case series</td>
<td>733</td>
<td>Trained and experienced surgeon.</td>
<td>? cost effective.</td>
<td>favour surgery</td>
<td>99% cure vocal palsy 1%.</td>
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<td>Willeke et al</td>
<td>1998</td>
<td>Uni Heidelberg, Germany</td>
<td>Review of surgeons and their operative results</td>
<td>230 consecutive</td>
<td>Trained and experienced surgeons and trainees under supervision.</td>
<td>N/A</td>
<td>N/A</td>
<td>Results of experienced surgeons and trainees under supervision.</td>
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<td>Kahky M</td>
<td>1993</td>
<td>MD Anderson, Uni of Texas, Houston</td>
<td>Review – personal and literature</td>
<td>N/A</td>
<td>Experienced, trained and knowledgeable surgeon.</td>
<td>N/A</td>
<td>N/A</td>
<td>Commonest cause of failure = surgical inexperience.</td>
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<td>Rice DH</td>
<td>1996</td>
<td>Otolaryngeal Head and Neck, UCLA</td>
<td>Overview</td>
<td>N/A</td>
<td>No comment.</td>
<td>Depending on extent of surgery.</td>
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<td>Endocrinology, UCLA</td>
<td>Overview – medical</td>
<td>N/A</td>
<td>No comment.</td>
<td>N/A</td>
<td>Follow up. If parameters worsen; surgery.</td>
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<tr>
<td>Author</td>
<td>Time</td>
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<td>Study Type</td>
<td>No. of Patients</td>
<td>Who Should Operate?</td>
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<td>Sivula A and Pelkonen R (41 refs)</td>
<td>1996</td>
<td>Med and Surg. Uni of Helsinki</td>
<td>Overview</td>
<td>N/A</td>
<td>Experienced surgeon.</td>
<td>Surgeon = best.</td>
<td>highly favour surgery</td>
<td>Surgery reduced death due mainly to cardiovascular disease. 1° PHPT → visible factor causing morbidity and mortality at all serum levels of Ca^{++}.</td>
</tr>
<tr>
<td>Van Heerden J (8 refs)</td>
<td>1998</td>
<td>Mayo Clinic</td>
<td>Collective overview</td>
<td>-</td>
<td>Experienced surgeon = of great importance.</td>
<td>Points to change in spite of good results with imaging.</td>
<td>favour surgery</td>
<td>97% cure in busiest state centre.</td>
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<tr>
<td>Consensus Development Statement NIH</td>
<td>1990</td>
<td>NIH Diabetics, Digestive and Kidney Diseases</td>
<td>Statement of view at meeting</td>
<td>N/A</td>
<td>Experienced surgeon.</td>
<td>Not usually necessary.</td>
<td>Should be considered for surgery</td>
<td>Promote research to seek outcomes in truly asymptomatic patients.</td>
</tr>
</tbody>
</table>
2. The Unilateral Cervical Approach to the Management of Primary Hyperparathyroidism

In this segment, 13 references have been reviewed (Table II, Unilateral Neck Exploration), one has been rejected on the basis that the reporting is open to bias.

There is no randomised trial. The requirements to mount a successful randomised trial rule out its performance.

There are a series of case studies in which the majority of decision-making takes place after the first side of the neck has been explored in patients with an accurate diagnosis of PHPT.

The retrospective studies are of value in that they clearly outline the variation in incidence of pluriglandular disease between centres. However, they probably reflect an intrinsic bias by adherence to a promotion of the conventional approach for PHPT.

Conventional bilateral neck exploration provides a satisfactory approach to PHPT however, results of 95-98% successful outcomes, leave a small group of patients requiring secondary surgery. Secondary surgery for PHPT can be very difficult and leads to greater morbidity that relates to the recurrent laryngeal nerve and permanent hypoparathyroidism. The operative conditions matching those observed in secondary thyroidectomy.

In 1982, Tibblin proffered the view that if on neck exploration, the pathological parathyroid tissue and one normal gland were located on the first side explored, the contra-lateral side could be left alone. Should surgery fail, exploration of the neck at a later time would take place in a virgin anatomical field. The risk was clearly that in the process, when the affected parathyroid gland and the normal parathyroid were removed, that there still may be disease in the remaining side of the neck. Tibblin and his group studied the excised tissue microscopically during surgery with Oil Red O and made a decision to explore further or to close the neck on the observed reduction of intracytoplasmic fat droplets in excised parathyroid tissue. Four groups were studied, each of 25 patients. The group having unilateral surgery on the serendipitous basis of being the first side chosen and containing the pathology, demonstrated a number of benefits. Length of operating time was reduced, there was no recurrent laryngeal nerve injury, there was a statistically reduced incidence of postoperative hypocalcaemia and need for calcium and vitamin D support. Tibblin and co-workers make a significant statement that the unilateral approach provided “more favourable technical conditions for reoperation”. After two to four years of follow up, the unilaterally treated cases did not reveal evidence of recurrence of PHPT.

The problem that remained with this approach was knowing how to select the “correct” side to explore in the first instance. On the face of it, there is an even chance of choosing correctly or incorrectly.

In 1994, a further paper appeared from Tibblin supporting the same approach, but looking for more accuracy in choosing the laterality of an adenoma. Ultrasound and technetium-thallium scanning had not been as effective as expected, it being difficult to differentiate small colloid nodules of the thyroid from a parathyroid adenoma. The isotope concentration revealed too much variance in activity to make the diagnostic value of the method reliable.
Tibblin and Bergenfelz\textsuperscript{5} suggest that a newly described rapid parathyroid assay may be of assistance but at that time sampling errors were substantial. They continued to endorse the approach to unilateral surgery.

Ultrasound had been used more successfully by others\textsuperscript{6} in a study where 16 patients were examined by ultrasound before exploration for PHPT with sensitivity of correct localisation being 80\%, a specificity of 95\% and diagnostic accuracy of 91\%. The lateral anatomical approach was used in this study and provided excellent exposure with minimal disturbance of structures of the neck. A discussant of the paper warned of possible disappointment with ultrasound, being caused by other pathology in the neck and by unusual locations of the parathyroid pathology\textsuperscript{7}.

Continued support for bilateral neck exploration as the more appropriate surgery for PHPT, was the result of studies, which contested that the operation was quicker or more efficient. The other major factor was that unilateral exploration continued to miss an appreciable number of hyperfunctioning parathyroids in patients with multiglandular disease\textsuperscript{8}. Zmora \textit{et al}\textsuperscript{8}, who studied 79 patients preoperatively with ultrasound and nuclear scanning, reported that unilateral neck exploration was feasible in 73.4\% and that they found additional large parathyroids on the contra-lateral side in 8.6\% of those patients. The level of failure of the unilateral approach was regarded as unacceptable.

Others\textsuperscript{9} have also reported no reduction in operative time with an approach that embraces preoperative localisation of parathyroid tumours.

There are units, however, that have used the unilateral approach over a period of time with sporadic hyperparathyroidism\textsuperscript{10}, 371 patients were reviewed retrospectively. If no nodularity was encountered on opening the median raphe in the neck, the right side was arbitrarily explored. When an adenoma and normal gland were confirmed on histology, the contra-lateral side was not explored. In 125 (34\%) patients a unilateral operation was proposed, 122 were successful, but three were not appropriate. One patient with unrecognised hyperplasia required re-exploration and two others had parathyroid carcinoma leaving 97.6\% success, no major complications and shorter operating time than the bilateral procedure. In the 246 patients undergoing bilateral exploration, there were 18 with hyperplasia, four double adenomas and four parathyroid cancers. Eighteen patients (7.3\%) failed on bilateral exploration, 14 persistent, four recurrent PHPT. When the conditions were right, unilateral exploration proved to be the best procedure. Unilateral neck exploration was further reviewed by Duh \textit{et al}\textsuperscript{2}, who developed a sophisticated mathematical model to analyse the strategy and to determine the variables that influence the probability of missing a tumour on the unexplored side of the neck. They found that only 41\% of patients prepared for unilateral approach would undergo a unilateral approach. This is increased to 62\% if a localisation study with a sensitivity of 80\% is used preoperatively. The probability of missing a tumour on the unexplored side of the neck parallels the prevalence of multiple adenomas.

No randomised (RCT) study has been done to compare the unilateral and bilateral approach. If a prospective RCT was proposed, it would however, require 684 patients to conduct a trial with sufficient statistical power to resolve the issue. This would seem to be a prohibitive number and would be difficult to achieve\textsuperscript{2}.

The probability of missing parathyroid pathology on the unexplored side of the neck is determined by the prevalence of multiple adenomas, approximately half to two thirds of
patients who have multiple adenomas will have a missed tumour on the unexplored side of the neck. Thyroid pathology acts as a further distracter. It is suggested by the model and verified clinically by other authors that the addition of sensitive preoperative imaging studies decreases the risk of missed tumours\textsuperscript{10,11,12}. Some authors still prefer clinical selection of laterality, reporting that it provides safe and effective surgery with a satisfactory level of patient outcome\textsuperscript{13} and yet others\textsuperscript{14} find no material or statistical difference in success rates between patients undergoing bilateral parathyroid surgery without imaging (95.5\%) and with imaging (96.4\%).

A body of papers address the issue of multiglandular disease in a more deliberative manner. In assessing the frequency of multiglandular disease; before 1989 findings were recorded in 624 cases, between 1989 and 1991 Proye and co-workers\textsuperscript{15} introduced Oil Red O staining to assess hyperfunction, the cases were studied retrospectively. Multiple gland disease was 17.7\% before 1989 and was 11\% after 1989 with a 3\% incidence of multiple adenomas. Unilateral exploration in this study had missed 78\% of second enlarged glands. Proye and co-workers continued with bilateral neck exploration as their prime approach to manage PHPT.

In the approach to unilateral neck exploration, a retrospective study was made of 40 patients with PHPT, all of whom had sestamibi scanning prior to first time surgery\textsuperscript{16}. Twenty-eight had single adenomas, nine had multiple adenomas and three had hyperplasia. The sestamibi scans were correct in 20 (71\%) of 28 patients with single adenoma, four (44\%) in nine patients with multiple adenomas and none (0\%) of three patients with hyperplasia. Had the explorations been done unilaterally on the basis of the sestamibi localisation, four (10\%) of patients would have had a failed parathyroidectomy. In Shen’s view, unilateral exploration on the basis of sestamibi scanning would have a higher failure rate than would surgeons performing bilateral neck exploration.

Where imaging has been used to direct the surgeon towards the appropriate side for exploration, quality issues have been raised\textsuperscript{1}. The retrospective study by Vogel and co-workers reports best results in a group of patients in whom ultrasound studies were done by a dedicated radiologist and compared those with random radiological reporting. The results of reporting are tedious and open to bias – the paper was rejected for review.
Points Arising from Review of Unilateral Neck Exploration of Primary Hyperparathyroidism

i. Unilateral exploration of the neck for parathyroid pathology has a distinct appeal to some, but not to all surgeons.

ii. a. Being able to explore only one side of the neck and preserving a virginal anatomical site on the second side is seen as a plus, should there need to be a secondary approach.

b. Other surgeons would rather be surer of cure and explore both sides at the same operation.

iii. There is some dispute as to the unilateral approach being quicker. There is mixed evidence, some for it being so and some for it being the same. The operative time would appear to relate to the experience of the operator.

iv. In retrospective studies outcome results do not routinely equal results from conventional bilateral neck exploration, although in Tibblin’s study, which was highly selective, the results were excellent at 100% cure.

v. There is no gain in the first part of the operation, as the approach is the same as if there were going to be a bilateral procedure.

vi. The fact that both sides of the neck are explored if the first side does not contain an adenoma and a normal parathyroid gland, leaves about a 10% risk for missing pluriglandular disease unless such measures as Oil Red O are used.

vii. The unilateral approach has demonstrated that with more specific localisation, a more defined approach could be made in many patients. The specificity of localisation and the ruling out of pluriglandular disease being the challenges.
Reference List

<table>
<thead>
<tr>
<th>Author</th>
<th>Time</th>
<th>Setting</th>
<th>Study Type</th>
<th>No. of Patients</th>
<th>Successful Localisation</th>
<th>U/Sound</th>
<th>Thallium</th>
<th>Sestamibi</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibblin S, Bergenfelz A (15 refs)</td>
<td>1994</td>
<td>Uni Lund, Sweden</td>
<td>Case studies</td>
<td>102</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>U/s and thallium Tc-99m – unsatisfactory 15 minutes (quick) PTH – use suggested.</td>
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<tr>
<td>Pyrtek LJ, McClelland A (10 refs)</td>
<td>1994</td>
<td>Hartford Hospital, Connecticut</td>
<td>2 case studies</td>
<td>14 patients – u/s 80% sensitivity 91% specificity 95% diagnostic accuracy</td>
<td>-</td>
<td>80% sensitivity</td>
<td>-</td>
<td>-</td>
<td>Less optimal, satisfactory with LA in high-risk patients. Leaves remainder of neck pristine.</td>
</tr>
<tr>
<td>Duh QY, Uden P (43 refs)</td>
<td>1993</td>
<td>Mt Zion, UCSF</td>
<td>Mathematical model to explore numbers required for unilat. exploration trial</td>
<td>N/A</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Would require 684 pts – 1 side and 684 bilat. to have 80% stat. power of detecting a difference between 5 -10% of missing an adenoma.</td>
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<tr>
<td>Worsey MJ, Carty SE, &lt;i&gt;et al&lt;/i&gt; (25 refs)</td>
<td>1993</td>
<td>Uni Pittsburgh USA</td>
<td>Case series</td>
<td>125 patients</td>
<td>No localisation used</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Found 1 side = shorter. 99.2% cure in one-sided exploration only.</td>
</tr>
<tr>
<td>Petti G, Chonkich G, &lt;i&gt;et al&lt;/i&gt; (9 refs)</td>
<td>1993</td>
<td>Loma Linda, Uni Calif</td>
<td>Case series</td>
<td>50+ scan 45- no scan 5 no localisation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50+</td>
<td>80% of localised scans → unilat. Exploration negative scan alerts to other pathology.</td>
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<tr>
<td>Robertson J, Johnson P, &lt;i&gt;et al&lt;/i&gt; (36 refs)</td>
<td>1996</td>
<td>Lancaster Royal Infirmary, UK</td>
<td>Case series</td>
<td>57 unilat. exploration from 80 patients</td>
<td>→ Research</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Comparable results to bilat exploration.</td>
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<tr>
<td>Author</td>
<td>Time</td>
<td>Setting</td>
<td>Study Type</td>
<td>No. of Patients</td>
<td>Successful Localisation</td>
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<td>Sestamibi</td>
<td>Outcome</td>
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<tr>
<td>Ryan JA, Eisenberg B (3 refs)</td>
<td>1997</td>
<td>Virginia Mason Clinic, Seattle</td>
<td>Case series</td>
<td>100 consecutive 1991-96; 43 unilat, 57 bilat. Unilat only if localisation correct</td>
<td>-</td>
<td>43</td>
<td>-</td>
<td>-</td>
<td>59% ✓ (together with thallium 73%). - 75% ✓ Reduced op. time 75%, success. Similar to bilateral exploration.</td>
</tr>
<tr>
<td>Roe SM, Preston WB, et al (36 refs)</td>
<td>1998</td>
<td>Uni Tennessee, Chatanuga Campus</td>
<td>Case series 1991-97</td>
<td>67 no imaging 28 imaging 64/67 (95.5%) without, 27/28 (96.4%) with.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>- ✓ - 75% ✓ No stat. difference in outcome between imaging or not. Not recommended.</td>
</tr>
<tr>
<td>Zmora O, Phinas P, et al (23 refs)</td>
<td>1995</td>
<td>Tel. Hashoma, Israel</td>
<td>Case series 79 patients 58 Unilat.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✓ ✓ - -</td>
<td>Questions cost effectiveness False + 1.3% u/s, 13% scan.</td>
<td></td>
</tr>
<tr>
<td>Vogel M, Lucas R, Czako P (8 refs)</td>
<td>1998</td>
<td>William Beaumont Hosp, Royal Oak, Michigan</td>
<td>Retrospective case study 106; 99( 93.4%) single adenoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✓ - - -</td>
<td>- 90% accuracy for u/s, endorses unilateral approach.</td>
<td></td>
</tr>
<tr>
<td>Wen S, Sabemci U, et al (28 refs)</td>
<td>1997</td>
<td>Mt Zion Hosp, UCSF</td>
<td>Case study 40 patients preop sestamibi</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>- ✓ - -</td>
<td>✓ 71% correct 20/28 adenomas Relying on sestamibi alone ➔ greater failure on single side exploration.</td>
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</table>
3. Minimally Invasive Parathyroidectomy

Introduction

Although bilateral neck exploration provides a satisfactory approach to the management of PHPT, there still remain 2-5% of patients uncured after primary surgery who may require further and more difficult surgery.

The 1991 Consensus Development Panel declared bilateral neck exploration to be the gold standard in managing PHPT and that preoperative localisation measures were not cost effective. This remains the case when surgeons plan to undertake bilateral neck exploration to manage PHPT\textsuperscript{1}.

However, the field of parathyroid surgery has always been dynamic and as might be expected, researching surgeons have continuously probed the conventional boundaries\textsuperscript{2}. Unilateral parathyroidectomy occupied the attention of these surgeons for over a decade, following the introduction of the technique by Tibblin and colleagues\textsuperscript{3}. However, the results of unilateral surgery have been very satisfactory when all their criteria have been met. The extent of the surgery and serendipitous element of choosing the correct side of the neck to explore in the first instance left many research-minded surgeons dissatisfied with the uncertainty of the approach. They wanted more precision in selecting the location of the affected parathyroid gland, or they would continue with bilateral neck exploration\textsuperscript{4,5}.

Researchers have not followed a single path in their progress. However the introduction of an agent that could specifically identify pathological parathyroid tissue with a high degree of accuracy was a milestone in their endeavours. The radiolabelled isotope technetium 99m sestamib\textsuperscript{4,6} set a number of surgeons on a new path. At the same time, other localising techniques were employed and various operative approaches explored. A significant interest in cost effectiveness was concurrently engendered. To many long-experienced surgeons, cure of their patient had become regarded as being a highly cost effective activity. Attitudes amongst those interested in reducing the extent of parathyroid surgery were moving to embrace the view that accurate localisation, minimal surgical dissection, possibly under local anaesthesia, followed by day of operation discharge would establish new milestones in terms of patient and hip pocket wellbeing.

Traditionalists have realised that change is afoot, they clearly do not wish to lower their standards in any way, but wish to ensure that patients are treated in a highly appropriate and effective manner, and they wish to remain in this intriguing field of surgery\textsuperscript{1,4,5,7}.

To date there has been no randomised trial reported in the papers reviewed that relate to the newer approaches. Each group seems set on carefully modifying its approaches and borrowing ideas from others to provide high level results.

Most available papers represent case series and are evaluating a particular approach to localisation as an aid to facilitating lesser surgery for hyperparathyroidism. Some such papers have already been reviewed in relation to unilateral neck exploration, (see section 2, The Unilateral Cervical Approach to the Management of Primary Hyperparathyroidism).
Ultrasound

Ultrasound has been used quite widely and a recent paper by van Vroonhoven and van Dalen 1998, reported on the use of preoperative Doppler ultrasound together with spiral CT as the basis of a protocol, for precise localisation of single parathyroid adenoma and management by minimally invasive surgery. Of 66 patients studied, 51 had only one parathyroid adenoma identified preoperatively and underwent minimally invasive surgery. This was successful in 49 and was converted to conventional bilateral neck exploration in two patients. A small incision was used to explore the localised adenoma and operative time was about 15 minutes. Van Vroonhoven and van Dalen point out that the high sensitivity of preoperative imaging does not of necessity presage an easy operation “by the occasional parathyroid surgeon”. The small incision imposes some physical restriction and the approach differs from unilateral neck exploration already discussed in this report, (see section 2, The Unilateral Cervical Approach to the Management of Primary Hyperparathyroidism). All 51 patients were cured. Six of the remaining 15 patients undergoing conventional surgery as no distinct single lesion had been identified, had multiglandular disease and nine of them had a single adenoma. All were cured. These authors demonstrated that a carefully selective approach with a defined protocol can lead to a significantly lesser procedure, in this series in 49 of 66 (73.4%).

Another study approached unilateral parathyroid exploration using high-resolution sonography to localise adenomas preoperatively, 37 patients were studied. Ultrasound correctly localised 27 adenomas, there were three false positives, two being thyroid nodules and one a lymph node. Of five false negative patients, three had multinodular goitre and one a parathyroid adenoma in the “silent” low tracheo-oesophageal groove area. Two patients with negative studies had negative neck exploration. The side on which the lesion was observed on sonogram was the first explored. The sensitivity of the study was 84%, the accuracy of sonographic localisation was 90% and the operative success rate 97%. A true positive ultrasound reduced the operating time by 40 minutes and reduced operative charges to the patient.

High-resolution ultrasound has been shown to yield very satisfactory localisation of parathyroid adenomas. The published papers reveal a sensitivity value ranging from 70-80+% for sonographic localisation, the surgeons involved in the cases studied have remained prepared to go on to bilateral exploration where imaging has been deficient. Thyroid nodules have been shown to be a significant distracting influence when ultrasound alone is used as an imaging agent.

Gofrit et al, made this very clear by reporting that in a case series of 52 patients with PHPT, directed at the evaluation of ultrasound, that a sensitivity of 83% for preoperative ultrasound could be increased to 90% in the absence of multinodular thyroid disease. The conclusion of this study, which was 98% successful, was that a positive ultrasound study for a parathyroid adenoma should allow unilateral surgical exploration of the neck. Conversely, if multinodular goitre was present, bilateral neck exploration should proceed. This was the first paper apart from van Vroonhoven to make a feature of this point.

To achieve the results reported above requires excellence in the use of ultrasonography, a technique recognised as requiring a high level operator with skill and commitment to parathyroid localisation when the diagnosis of PHPT has been established, as reported by Pearl et al. This degree of skill should clearly be a given in all imaging procedures, especially if a minimally invasive approach is planned. It is notable that Pearl's study was
done in the milieu of a conventional bilateral approach, before the unilateral approach was being embraced more widely.

**Isotopes**

Scanning the neck with sestamibi was an innovation commenced later than the NIH Consensus meeting 1 at which it was decided that imaging had little if any role in surgery for PHPT. Preoperative localisation now has very wide acceptance in managing PHPT.

Sestamibi scanning seems to have brought preoperative imaging to a level of accuracy beyond other imaging techniques and has been the base upon which newer techniques have been developed and probably even more adventurous proposals will be built 11-15.

The move towards sestamibi followed careful approaches by a number of surgeons involving a range of techniques that they believed would:

(i) improve accuracy of localisation of parathyroid adenomas;
(ii) reduce surgical time;
(iii) improve cosmesis; and
(iv) be more cost effective.

Following ultrasound in technological development for location of parathyroid pathology, thallium – 201 and technetium – 99m subtraction scanning became quite widely used to meet the criteria already stated. Tsukamoto and Russell et al 16 using this technique on 160 patients found 96 (60%) positive preoperative scans, 81 (84.4%) of which were accurate predictors of adenoma location. They noted a strong correlation between the weight of parathyroid adenomas and scintigraphic positivity. Where unilateral surgery was carried out, operative times were materially decreased. Unilateral neck exploration was carried out only when there was unequivocal scintigraphic positivity suggesting presence of parathyroid adenoma. Renaut et al 17 reported reversing the order in which the isotopes were used in 60 patients, with 100% specificity for localising parathyroid adenomas. They concluded that the success of this approach strongly supported scan directed neck exploration in PHTP with single adenoma.

A discordant point of view was put by Sinha et al 5, who reported on parathyroid exploration in 60 patients, 21 of who had sestamibi scanning and ten had technetium-thallium scanning. The results of scanning were said to have no overall effect on operative time, this depends on the surgeon’s experience. They noted the cost of scanning exceeded costs saved in relation to time saved in unilateral exploration. The authors felt isotope scanning to be insufficiently sensitive to move towards it being the basis for unilateral neck exploration. The numbers of patients studied are probably too small to justify the conclusions made on scanning, while observation on experience of surgeons and operative time would appear appropriate.

Thompson et al 18, discuss the use of ultrasound and thallium technetium subtraction scanning. Their conclusion was that if either or both modalities identified and lateralised a lesion, it was likely to be found at that location and therefore supported unilateral exploration. They state however that neither method exceeds the accuracy of an experienced surgeon, particularly stressing that posterior glands may not be visualised, and that single or multiple thyroid nodules are significant distracters. This paper is not very discriminatory but does outline the advantages and disadvantages of imaging factors in a concise way.
The above studies indicate the increasing acceptance of unilateral parathyroidectomy and although it has not made universal inroads, there has been an increasing acceptance of the approach, a move towards local anaesthesia becoming more accepted and newer methods of localisation being tested. Chapuis\textsuperscript{11} and his group, looking for more accurate localisation and also assessing intraoperative hormonal monitoring of parathormone (parathyroid hormone, PTH), to increase the precision of the whole procedure have made a significant contribution.

Chapuis set very strict criteria in patients planned for unilateral neck exploration “(1) a presumed solitary adenoma detected by ultrasonography; (2) no thyroid disease; and (3) no family history of PHPT or multiple endocrine neoplasia”. Most importantly, all patients consented to conversion from unilateral to bilateral exploration if surgically, or biologically necessary. Sensitivity of ultrasound studies was 82.5% and 80% in the 70 patients who had sestamibi scanning. Persistence of PHPT was accurately demonstrated by intraoperative measurement of UcAMP or 1-84 PTH, so allowing for further appropriate exploration.

This approach provided for unilateral exploration of 200 patients, of 447 patients studied. In the total group the sensitivity of ultrasound localisation was 76%, but for the 200 patients undergoing unilateral exploration it was 92.5%. Chapuis et al\textsuperscript{11} stress the need for significant skill in the execution of ultrasound localisation. Having such skill available, having strict criteria applied to unilateral neck exploration and the use of local anaesthesia for unilateral neck exploration, further established the acceptability of unilateral approach to the management of PHPT.

Okada\textsuperscript{19} and his group approached 37 patients with PHPT using ultrasound, CT and subtraction scanning (technetium and thallium); the studies were successful, 76.7%, 76.4% and 61.3% respectively. A combination of all three modalities provided a true location of parathyroid in 96% and suggests local excision or unilateral exploration of the neck for parathyroid adenoma could follow the use of multi-modality imaging. Okada and co-workers included patients with parathyroid hyperplasia in their study and probably lowered the overall accuracy of their localisation studies on this account.

It is clear from the available papers that the introduction of sestamibi provided a possibly more defined way forward for those surgeons clearly committed to both imaging and performing what they believed to be less invasive surgery for PHPT.

In 1996, Borley et al\textsuperscript{12} reported on 56 patients upon whom they had operated for PHPT. Only 48 had complete data and in these there was 96% sestamibi scan accuracy. For single adenoma the sensitivity of imaging was 97% and specificity and positive predictive value were 100%, the laterality of such lesions being correct was 100%, and site correctly identified in 94%. When there was multiple gland pathology, laterality and location were 82% and 79% accurate respectively. These were clearly seminal observations, which provided sound sensitivity, and sufficient positive predictive value and accuracy in single gland disease to allow scan directed unilateral neck exploration.

This paper was published while others were clearly pushing at the boundaries of parathyroid surgery, aiming to reduce it to localisation and “keyhole” extraction where appropriate.

Sestamibi was to lead the way to an even more minimal surgical approach in the management of PHPT.
There are already a significant number of papers reviewed in which sestamibi was a component in making decisions for a unilateral approach to a parathyroid adenoma. However, it seems to this reviewer that Borley’s paper led to surgeons concentrating on the location of the adenoma and its being locally rather than unilaterally approached, i.e. a precise surgical approach.

Carty et al\textsuperscript{13} appear to have taken this forwards, comparing two approaches to “concise” parathyroidectomy. Driven in the author’s words by “pressure to improve outcome and resource utilisation”.

In a longitudinal prospective cohort study comparing two approaches, neck structures were palpated after opening the median fibrous raphe, and the side with “nodule” explored first, or the right hand side first if nothing is palpable. If an adenoma was located and resected and a “normal” gland biopsied, the neck was closed and the patient was ready for discharge in eight hours if appropriate. The second approach was directed to unilateral exploration following single photon emission computed tomography (SPECT) 99m Tc-sestamibi imaging and intraoperative quick parathormone (QPTH) measurement. Sestamibi imaging is the prime director of neck exploration. After opening the median raphe of the neck, venous blood is drawn for QPTH estimation and this is repeated 15 minutes later after the adenoma has been excised and a normal gland biopsied. Reduction of PTH to 50% or less of baseline level and below the normal upper limit of 65 pg/ml leads to completion of the operation. If the hormone level does not drop, further exploration and excision of parathyroid tissue continues until repeat PTH levels meet the criteria. One assumes some other “cut off” arrangement if the criteria are not met in a reasonable time.

The authors report 93.1% sensitivity for SPECT sestamibi scanning with 97.4% accuracy in patients with adenoma compared to 61.1% and 65% respectively for hyperplastic disease. Sestamibi studies on patients referred from elsewhere had lesser levels of accuracy, 88.9% for adenomas and 50% for hyperplasia. SPECT was clearly favoured, as opposed to two positional static scans. Intraoperative QPTH determination added a further opportunity for ensuring that the active parathyroid pathology has been removed. This report represents a step towards greater precision in selecting the correct side when planning unilateral excision. The authors also demonstrate how valuable intraoperative performance of QPTH measurement can be in multiple gland disease. The discussion of this paper clearly reveals the level of interest in this newer approach to parathyroid surgery by surgeons who have provided leadership in the conventional approach to PHPT.

A further paper based on sestamibi scanning has been reported by Norman, Chheda and Farrell\textsuperscript{14}, 18 patients with a positive sestamibi scan underwent neck exploration through a 2.5cm incision. They were compared with the 25 parathyroid explorations immediately preceding them, which followed the conventional procedure of bilateral neck exploration. There were no complications in either group, but length of incision and length of hospital stay of the minimally explored group were significantly less (P<0.01) than for the conventional group. Steps were being taken to lessen the extent of surgery and capitalise further on sestamibi scanning.

The papers addressing sestamibi scanning began to present smaller groups of patients, concentrating on exactitude of localisation so as to allow the least surgery possible in a safe and efficacious manner. A further report by Norman and Chheda\textsuperscript{20}, outlines a protocol in which all patients with PHPT have a sestamibi scan, those with a positive scan enter the
study. Fifteen consecutive patients with PHPT, in whom a single adenoma was demonstrated, were studied. Operation was commenced about 2.2 hours after scanning and the “hottest” area (area of greatest radioactivity detected in the neck by a handheld Neoprobe gamma counter, Neoprobe Corp. Dublin Ohio USA) after all four quadrants of the neck were scanned, was approached. A two-cm incision was made at this location, it being based on the sestamibi scan and measurement of gamma emissions with the probe. Norman and Chheda were of the view that false positive results could be avoided by nuclear mapping several hours after scanning with sestamibi, at a time when the parathyroid tissue has the greatest level of background radiation. This was clearly demonstrated in their paper by comparing simultaneous counting of lymph node, fat and parathyroid tissue. Norman and Chheda also discuss radiation exposure hazard and note that in the 15 cases it represented 1% of acceptable yearly exposure (five rem) as determined by the Nuclear Regulation Commission.

A significant feature of this paper is to be found in the discussion where Dr Norman tells Dr Carty that no biopsy was made of a normal parathyroid gland. Up until that time, most papers reported excision of an adenoma and biopsy of a normal gland when unilateral exploration was undertaken. The approach taken by Dr Norman and his colleagues was clearly dependent on the expected level of accuracy achieved with sestamibi scanning and the level of confidence the surgeons were prepared to place in it.

A further paper from the Norman group, Denham and Norman 1998\textsuperscript{15}, was in the form of a meta-analysis designed to assess the collective sensitivity and specificity of sestamibi scanning, aiming to check on the utility of such scanning in relation to unilateral cervical exploration for PHPT. Denham and Norman also tested the view that all patients should undergo preoperative scanning with a view to improving cost effectiveness, a factor not considered in the Consensus Statement\textsuperscript{1}, because it was presented later in time. In some 6331 cases, 87% had solitary adenomas and with a scan sensitivity of 90%, as many as 78% of all patients having sporadic PHPT become candidates for unilateral exploration. As confidence and familiarity with the method has grown it is clear that more focussed procedures under local anaesthesia were ready to be introduced\textsuperscript{20}. Furthermore, as positive scans are found in excess of 51% patients\textsuperscript{15}, the procedure is cost effective and on these grounds the authors feel that all patients with PHPT should have a sestamibi scan before advancing to surgery, not all however will qualify for a lesser operation. Denham and Norman report approximately equal numbers of studies\textsuperscript{15} where subtraction scanning was used as compared to dual phase sestamibi.
Conclusions

- The 20 papers reviewed in this section are essentially retrospective case studies. Papers\textsuperscript{7-9} followed protocols developed to test imaging processes and the unilateral approach and papers\textsuperscript{13,14} each compared two case series comparing the more conventional approach with imaging assistance. Paper\textsuperscript{15} is a meta-analysis of publications in English relating to sestamibi scanning.
- The quality in terms of sensitivity of imaging studies varies, and in the case of ultrasound\textsuperscript{7-11,19} the need for definitive skill on the part of the operator is both demonstrated and emphasised.
- The problems associated when thyroid nodules are present in patients with PHPT are clearly stated\textsuperscript{9-11}.
- Some authors were clearly not influenced by their studies to shift to the newer approach\textsuperscript{4,5}. The remainder supported the change to unilateral or local surgery.
- There has been a strong concentration on single gland disease and it seems to the reviewer that interest in multiglandular disease appears to be diminishing. As few papers report results beyond six months, multiglandular disease may yet have its day at the ball game.
- Morbidity is reported to be minimal and no mortality is recorded. No group reports anxiety in these areas. Van Vroonhoven\textsuperscript{8} reports one case of transient recurrent nerve palsy.
- Quick parathyroid estimation\textsuperscript{12} and intraoperative nuclear mapping following sestamibi scanning\textsuperscript{13,20}, together with use of local anaesthetic introduce further moves towards more local surgery.
- The groups carrying out the studies all appear to have significant background in parathyroid surgery. This factor may be important in the ultimate success of this more localised type of parathyroid surgery\textsuperscript{5,8,18}.
- In these papers criteria are being developed for unilateral and more focussed surgery\textsuperscript{11}. These criteria aimed to avoid failure and ensure patient safety.

Comment

The authors of the papers reviewed in this segment of the report have clearly taken the Tibblin et al\textsuperscript{3} approach much further. For a lesion clearly demonstrated on sestamibi scan, authors have shown that in a number of groups that focused, minimal surgery can be done with a success rate exceeding 90% if sound criteria are followed. The criteria are demanding and are as reported by Chapuis (Table III, Minimally Invasive Parathyroidectomy) a minimum set.
Reference List

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Setting</th>
<th>Study Type</th>
<th>No. of Cases</th>
<th>SPECT.</th>
<th>U/Sound</th>
<th>Rapid PTH</th>
<th>Isotope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wei JP, Burke GJ (13 refs)</td>
<td>1997</td>
<td>Medical College of Georgia, Augusta General Hosp, USA</td>
<td>Case cost utility analysis.</td>
<td>22</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✔ 22 dual phase study. 20+ scans 2 – scans 16 true pos 4 false pos 1 true neg 1 false neg (mediastinum).</td>
<td>Of 22 patients surgery was not altered to affect outcome. The negative scans contributed nothing to surgery. Scan not necessary or cost effective in bilat. neck exploration.</td>
</tr>
<tr>
<td>Koslin DB, Adams J, et al</td>
<td>1997</td>
<td>Oregon Health Science Uni, Portland, Oregon USA</td>
<td>Prospective case study using high-resolution ultrasound. Study op time and cost.</td>
<td>37 previously untreated patients.</td>
<td>-</td>
<td>✔</td>
<td>-</td>
<td>-</td>
<td>Sensitivity u/s – 84% operative time reduced 40 mins and cost $564.00. Note interference by thyroid nodules.</td>
</tr>
<tr>
<td>Gofrit ON, Lebensent PO, Pikarsky A, et al (8 refs)</td>
<td>1997</td>
<td>Hadassah Med Centre, Jerusalem, Israel</td>
<td>Case series, U/sound study.</td>
<td>52</td>
<td>-</td>
<td>✔</td>
<td>-</td>
<td>-</td>
<td>50 patients single adenoma. 98% success at op, u/s sensitivity 83%. Multi-nodular thyroid creates a problem.</td>
</tr>
<tr>
<td>Pearl AJ, Chapnik JS, Freeman JL, et al (32 refs)</td>
<td>1993</td>
<td>Mt Sinai Hospital, Toronto, Ont, Canada</td>
<td>Prospective case studies.</td>
<td>25</td>
<td>-</td>
<td>✔ CT &amp; MRI confirmation</td>
<td>-</td>
<td>-</td>
<td>U/s accurate 92% (100% in the neck).</td>
</tr>
<tr>
<td>Tsukamoto E, Russell CFJ, et al (15 refs)</td>
<td>1995</td>
<td>Royal Victoria Hospital, Belfast, Ulster, Ireland</td>
<td>Case series and scintigrams selected for unilateral – exploration on protocol.</td>
<td>160 studied 96+ scans 81+ prediction of location of adenoma.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Thallium and technetium. 84.4% accurate site prediction. Suggest with subtraction scintigraphy to accurately predict location of adenoma in high % of cases.</td>
<td></td>
</tr>
<tr>
<td>Renaut AJ, Georgimmos SN (11 refs)</td>
<td>1996</td>
<td>Royal London Hospital, (Whitechapel) Academic Surgical Unit, UK</td>
<td>Case series.</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Tc99 m + thallium - 201.</td>
<td>All bilateral neck exploration; 61 adenomas – one pt had one right one left. 100% cure – one pt transient hypocalcaemia.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Setting</td>
<td>Study Type</td>
<td>No. of Cases</td>
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<td>Isotope</td>
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<tr>
<td>Sinha CK, Hamaker R</td>
<td>1997</td>
<td>Otolaryngology, Head and Neck Service, Walter Reed Hospital, Washington DC, USA</td>
<td>30 cases scanned in a series of 60. Operative times observed against experience.</td>
<td>60 patients 10 Tc-Th scan 21 sestamibi</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>21 sestamibi 10 Tcqq and Th</td>
<td>Found little value for scanning contra op time and cost. Preferred bilat. neck exploration.</td>
</tr>
<tr>
<td>Thompson CT, Bovers J, Broadie TA</td>
<td>1993</td>
<td>Indiana School of Medicine, Indianapolis, USA</td>
<td>Case studies Technology Review.</td>
<td>69</td>
<td>-</td>
<td>62</td>
<td>-</td>
<td>Thallium – technetium 45</td>
<td>Ultrasound +35/62 TTss +27/45 Both 29/42 = positive. Supported unilateral approach to PHPT.</td>
</tr>
<tr>
<td>Okado Y, Mizutani Y, Takeuchi H, et al</td>
<td>1997</td>
<td>Depts Urol and Nuclear Med, Fac. Medicine, Kyoto, Japan</td>
<td>Retrospective study with u/s or Tc99m and Th subtraction in PHPT.</td>
<td>37</td>
<td>CT</td>
<td>32</td>
<td>-</td>
<td>Tc99m and Th 29</td>
<td>Using all 3 modalities – 96% accuracy and recommend same.</td>
</tr>
<tr>
<td>Borley NR, Collins RE, et al</td>
<td>1996</td>
<td>Surgery and Nuclear Med, Kent and Canterbury NHS Trust</td>
<td>Retrospective case study.</td>
<td>56</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>All 48 pts. Scan accuracy 96% 97% for single lesions. Specificity 100% PPV 100%</td>
<td>Side identified 100% in single gland disease. 94% correct site. Multiple 82 + 79% respectively. Results indicate single side and possibly first author to indicate site approach. Could be effective.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Setting</td>
<td>Study Type</td>
<td>No. of Cases</td>
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<tr>
<td>Norman J, Chheda H, Farrel C</td>
<td>1998 (presented Feb 1997)</td>
<td>Dept Surgery and Nuclear Med, Uni Sth Florida, Florida, Tampa</td>
<td>Comparison two case series.</td>
<td>25 conventional approach 18+ sestamibi and 2.5 cm incision.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✓ (18)</td>
<td>No morbidity either group. Sestamibi group = less operative time and smaller incision P&lt;0.01.</td>
</tr>
<tr>
<td>Denham DW, Norman J</td>
<td>1998</td>
<td>Dept Surg, and Nuclear Med., Uni Sth Florida, Tampa, Florida USA</td>
<td>Meta-analysis of all papers in English on sestamibi scanned patients.</td>
<td>6331</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6331 patients</td>
<td>Localisation of PT path sensitivity 90.7%. Specificity 98.8%. 87% patients had solitary adenomas. 78% of all patients with sporadic PHPT (90% of 87% with solitary adenoma) are candidates for unilat operation with &lt;1% expected failure.</td>
</tr>
</tbody>
</table>
4. **Endoscopic Approach to Minimally Invasive Surgery for Primary Hyperparathyroidism**

When highly localised and focused studies were achievable for the surgery of PHPT, endoscopic surgeons soon saw it as having a role for them to demonstrate their skills.

The papers available for review in this area are few in number, no randomisation, small numbers in studies, frequent repetition between papers. The interest that has awakened in this area has seen some very slim papers published. This reviewer in no way sells skill or competence short, but the small amount of relatively limited literature has been outstripped by the interest it has aroused in practice before it has been well tried and tested.

There has been a limited amount of experimental work published in relation to the development of an endoscopic approach to neck exploration and parathyroidectomy. The significant element of the surgery being the development of appropriate operating space in a limited area. Brunt and his co-workers\(^1\) pioneered this work in dogs. He used a 2.5cm incision in the lower neck to access the pretracheal space and expanded the space with a balloon dissector, maintaining access with the assistance of an external lift device, this was used as in both canine and porcine models. When carbon dioxide (CO\(_2\)) insufflation was employed at 15 and 20 mm Hg pressure pneumomediastinum and subcutaneous emphysema was encountered. The approach that Brunt and colleagues developed allowed for very satisfactory visualisation of parathyroid glands and other vital structures in the neck in dogs and human cadavers.

Following this report there was correspondence to the journal from Dr John Norman\(^2\). He confirmed the work of Brunt\(^1\) in both dogs and cadavers. He commented on the fact that dissection in the neck of the dog was more readily achieved, because of the amount of loose connective tissue present. The author also reported on achieving hemithyroidectomy in some animals. On transferring the technique to patients, he found that bleeding and tissue staining with blood reduced visibility of parathyroids and that the operative space was limited\(^3\). Norman and his team moved to radio-guided parathyroidectomy and intraoperative mapping\(^4\), pointing out that the incision used is no greater than that for the endoscopic approach and that the success rate is high.

A reply by Brunt\(^5\) agreed with Norman’s observations and stated that he and his group had done further work on cadavers to simulate the limited anatomical conditions encountered in the endoscopic approach before moving on to clinical work. When involved in clinical procedures they moved to using 4 mm ports for lateral access and used a 1.5 cm access wound into which was inserted a small external lift ring to maintain exposure in the pretracheal space. Two procedures were reported with successful removal of single parathyroid adenomas and good visualisation of the recurrent laryngeal nerve, although cramped space and bleeding do slow safe dissection and visualisation of parathyroids. While agreeing that Dr Norman has a good approach with scintigraphic mapping, Brunt and group doubt that the method of isotope mapping and 2.5 cm incision provides better visualisation than endoscopic instrumentation. They also chide the Norman group for not visualising and biopsying a normal gland on the side of exploration. Improvement in technology and wider involvement in the clinical application of the endoscopic method is predicted.

In 1996, Gagner\(^6\) undertook parathyroid exploration in a 37 year-old male with resolving pancreatitis and family history of hypercalcaemia in whom four areas of abnormal uptake of
sestamibi were demonstrated on isotope scanning. Ultrasound studies of the neck were not rewarding. Using four 5 mm trocars under the platysma muscle, CO$_2$ insufflated at 15 mm Hg provided space above the strap muscles. Four parathyroids were demonstrated and 3½ glands removed, together with a benign thyroid nodule. The patient suffered extensive subcutaneous emphysema, but was discharged from hospital in four days. Gagner was impressed with the magnificent view of the structures and predicted the development of better instrumentation and mediastinal exploration.

In a report on endoscopic parathyroidectomy in which subcutaneous emphysema and severe hypercarbia resulted, the patient appears to be the same as in the previous paper, essentially reporting the hypercarbia and subcutaneous emphysema in greater detail. Gottlieb and co-workers noted that creating a subplatysmal space required 20 mm Hg pressure, this is a higher pressure than that required in intraperitoneal insufflation. It was further noted that a plateau level of CO$_2$ tension or elimination was not reached during extraperitoneal insufflation, unlike that observed during intraperitoneal insufflation. This patient had no respiratory problems after his seven-hour procedure and was discharged on the fourth postoperative day with no further complications. The same case was reported again. In this paper the authors further outline possible introduction of endoscopic cervical surgery. Further data supporting endoscopic surgery have come from Hong Kong. A clear field is stressed as essential, blood staining obscures the view and suction and irrigation disturb the small space, fog lenses and render the procedure more difficult. The techniques and results of endoscopic parathyroidectomy are clearly described in two papers. There are four patients and they are reported in both papers. Yeung also reports on eight endoscopic thyroidecomies. The authors only approached parathyroids that were clearly viewed on all investigative techniques. They were well able to demonstrate normal parathyroid glands by their endoscopic approach. Furthermore, they suggest large prospective studies may be necessary if they are comparing the efficacy of this approach with the conventional approach.

A rapid communication by Miccoli and colleagues provides a larger series of cases, all had proven PHPT and ultrasound located single adenomas. The video-assisted and intraoperative QPTH methods were used. A two cm incision one cm above the sternal notch provided access to trocar (12 mm) on the side of the tumour, under the strap muscles, CO$_2$ was insufflated for three to four minutes at 12 mm Hg and a 5 mm – 30° endoscope introduced. The arterial blood gas was checked at this time. The adenoma was visualised and dissected free and haemostasis secured. The skin was then sutured. The QPTH was carried out after induction of anaesthesia and at five and ten minutes after adenoma excision, a decrease of PTH concentration by 50% was the criterion used to assure that all patients did well and that there was no morbidity.

In April 1998 at the American Association of Endocrine Surgeons, Miccoli et al, reported on 31 of 50 patients who were selected for endoscopic parathyroidectomy. The same approach was followed as already described, seven superior and 24 inferior glands were removed, all were cured and pain was determined as being of less intensity than in patients undergoing hemithyroidectomy. Miccoli et al noted that more than 60% of patients referred to an Endocrine Unit were suitable for the endoscopic procedure. A later paper from Miccoli and his group from Pisa has only been sighted in abstract form, the paper not yet being available in Australia. The same methods of investigation have prevailed, Miccoli having relied on ultrasonic imaging and insisting on the absence of goitre and no previous surgery in the neck. The paper represents 30 endoscopic operations in 65 consecutive patients with
PHPT, over a 13 month period. All patients have normal PTH and serum calcium at up to six months.

This group of papers represent a progressive series depending on accurate diagnosis through 1-84 immuno parathormone estimation, defined ultrasonic localisation of a single parathyroid adenoma, the absence of goitre and no previous surgery in the neck. The operative surgery is assisted by QPTH estimations, which allows the operator to know when hyperfunctional tissue has been excised. This has proven to be a useful process whereas jugular venous sampling at the commencement of surgery was found to be of little value in adenoma localisation\(^5\). This paper carries further the recommendations of Chapuis et al (see Table III, Minimally Invasive Parathyroidectomy), in establishing criteria to avoid becoming involved in multiglandular disease. Some of these papers, however, refer to surgical activity that would embrace all four parathyroids and possibly the thyroid gland\(^1,4,6-11\).
Comment

- This series of papers is a patchwork, being made up of sound laboratory work of one group.\textsuperscript{1,2,4,5}

- Two brackets of papers used what appears to be repetitive reporting, of endoscopic parathyroidectomy aimed at total neck exploration.\textsuperscript{6-11}

- i. A series of ultrasound located single parathyroid adenomas submitted successfully to endoscopic parathyroidectomy and QPTH monitoring with 100% success. The series being expanded at each report.\textsuperscript{12-14}
  
  ii. It would appear that in the reports of Miccoli \textit{et al.}\textsuperscript{12-14}, only clearly defined single adenomas were offered endoscopic surgery.

Conclusion

Each of these papers offers a progressive approach. It would appear that Norman\textsuperscript{2,4} and Miccoli\textsuperscript{12-14} have adopted an approach that will deal with PHPT identified almost without doubt as being due to single gland disease. It would further appear that rather than risk being in error they submit all other patients to classical bilateral neck exploration. Norman’s approach of sestamibi and QPTH mapping appearing to have a slightly higher yield of defined single gland disease, although Miccoli \textit{et al.} have 100% yield in the cases they choose to operate upon.
Reference List


## Table IV

**Endoscopic Approach to Minimally Invasive Surgery for Primary Hyperparathyroidism**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Location</th>
<th>Study Type</th>
<th>No. of Cases</th>
<th>Endoscopy</th>
<th>Problems</th>
<th>Benefits</th>
<th>Morbidity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norman J, Chheda H (from Table III)</td>
<td>1997</td>
<td>Dept Endocrine Surgery, Uni Sth Florida, Tampa Fl.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Gagner M (4 refs)</td>
<td>1996</td>
<td>Dept Gen Surg. Cleveland Clinic</td>
<td>Clinical case.</td>
<td>1</td>
<td>✓</td>
<td>Difficulty monitoring space with CO₂</td>
<td>All four glands exposed.</td>
<td>Subcutaneous emphysema.</td>
<td>Satisfactory.</td>
</tr>
<tr>
<td>Yeung GCH, Ng WT (9 refs)</td>
<td>1998</td>
<td>Dept Minimally Invasive Surg. Tan Chai Hosp, Hong Kong</td>
<td>Case study.</td>
<td>4</td>
<td>✓ with other imaging methods</td>
<td>Need for absolute haemostasis.</td>
<td>▼ cosmesis.</td>
<td>Nil.</td>
<td>Can show normal glands.</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>Location</td>
<td>Study Type</td>
<td>No. of Cases</td>
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<tr>
<td>Yeung GCH (6 refs)</td>
<td>1998</td>
<td>Dept Minimally Invasive Surg. Tan Chai Hosp, Hong Kong</td>
<td>Case study. 4 the same</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>Nil.</td>
<td>Promote prospective study.</td>
<td></td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>Location</td>
<td>Study Type</td>
<td>No. of Cases</td>
<td>Endoscopy</td>
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<tr>
<td>Pattou F, Oudar C, et al (21 refs)</td>
<td>1998</td>
<td>Dept Surg, University Hospital, Lille France</td>
<td>Case studies.</td>
<td>175</td>
<td>Nil. Used sestamibi Tetrofosmine and bilat. jugular samples for PTH.</td>
<td>PTH performed once intra-operatively → little assistance in imaging.</td>
<td>Isotopes satisfactory.</td>
<td>-</td>
<td>Unilateral approach would have missed excision of pathology in multiglandular disease.</td>
</tr>
</tbody>
</table>
5. Safety of Minimally Invasive Procedures in the Management of Primary Hyperparathyroidism

Mortality

Throughout this review no evidence of mortality was located in any report, in relation to bilateral or unilateral neck exploration, or to any of the described “minimally invasive” procedures.

Morbidity

In the papers reviewed, none but minimal morbidity was reported.

Transient recurrent laryngeal nerve palsy was reported when a two-cm incision was used to remove a unilateral ultrasound located parathyroid adenoma\(^1\).

Two patients had transient recurrent nerve palsy in 18 cases undergoing minimally invasive surgery, none occurring in 56 concomitant conventional cases\(^2\). There was one case of bleeding leading to conversion of the procedures to a conventional approach.

The removal of a parathyroid adenoma from the neck, when the exit wound is very small, or when an adenoma is being removed through an endoscopy port or cannula, provides a situation of risk for rupture of the adenoma. Cell spillage, leading to parathyromatosis could be a complication of this process. Great care should be exercised in removing parathyroid lesions through very limited exits, even in a specimen bag.

A more immediately serious problem was reported in association with endoscopic parathyroidectomy, in association with CO\(_2\) insufflation\(^2-4\) where extensive subcutaneous emphysema of the “eyelids to the scrotum and anteriorly on the thorax and abdomen”, neck radiography revealed CO\(_2\) in intramuscular planes, while the chest radiography was clear. Hypercarbia and tachycardia persisted throughout the rather long (five hours) procedure. The problem resolved in three days. The insufflation pressure was recorded as 15 mm Hg\(^2\), 20 mm Hg\(^3\) and 15 mm Hg\(^4\), (yet all appear to be the same patient).

Miccoli and associates\(^5-7\) have used carbon dioxide insufflation under the strap muscles for three to four minutes at 12 mm Hg without complication. No patient had an elevation in CO\(_2\) pressure with this short insufflation phase, using what Miccoli et al describe as a “gasless” approach\(^6\). There has been no recorded instance of CO\(_2\) embolism in any of the published case reports or case series. Adherence to Miccoli’s\(^5-7\) approach should ensure a low risk for this possible complication.

As the Miccoli group have had no problems with CO\(_2\) insufflation in 37 consecutive endoscopic parathyroidectomies, it would appear from their reports\(^5-7\) that the method they have employed is safe. This method should be considered by all those intending to undertake this type of surgery who plan to use CO\(_2\) insufflation.

\(^\star\) Personal communication; Professor L Delbridge, Sydney.
Comment on Safety

As seen from papers published in this review, the newer technical approaches require a sound knowledge of parathyroid pathology and anatomy and the vagaries of both. This knowledge is built on sound surgical training and ongoing experience, or surgery by trainees under close supervision of experienced surgeons. Surgeons undertaking parathyroid surgery would be expected to have such a background if successful outcomes and not moderately morbid procedures are to be expected.
Reference List


6. Efficacy of Minimally Invasive Surgery for Parathyroidectomy for Primary Hyperparathyroidism

The classical surgical approach to PHPT has provided very satisfactory results (see Table I, Bilateral Neck Exploration). These have resulted from meticulous attention to diagnosis and operative care. In Australia, the surgery has been performed by surgeons well trained and experienced in the field.

To focus attention on the surgery only, overlooks the importance of clearly establishing the diagnosis prior to operation. Surgeons caring for patients with PHPT should be expected to have a good understanding of the disease and its pathological and anatomical vagaries. A clear decision should be taken prior to surgery as to what approach should be taken and clearly discussed with the patient.

While patient wishes and requests deserve clear consideration, they should not be allowed to overrule sound surgical decision-making.

The choice of surgical approach to parathyroid pathology will depend on a number of factors. A specific operation should be offered on the basis of its suitability for the patient, not simply because it can be done.

The original approach offers:

- 95-98% success rate at initial operation
- a cost effective procedure without need for routine localisation studies
- hospital stay of one to two days
- a major complication rate of <1%
- a cosmetically acceptable “collar” scar.

(Royal Australasian College of Surgeons document).

The desire to cause less pain, to provide a smaller scar and leave one side of the neck pristine after surgery, has been worked at by devoted endocrine surgeons for nearly 20 years, starting with Tibblin et al. Their dedication and skills have led to two groups of approaches.

One group aim to clearly define the cause of PHPT and if clearly definable, approach it by a lesser surgical approach. When not definable in this manner, patients are recommended to have the conventional bilateral neck exploration.

In terms of review, it is necessary to see if lesser procedures measure up to the efficacy of the conventional approach.

Those surgeons who have reported a localising approach have reported satisfactory results, see Table II, Unilateral Neck Exploration and Table III, Minimally Invasive Parathyroidectomy. They have depended on identifying the single cause of the disease and approached the site either by direct limited incision and their dissection over the lesion and in some instances using a nuclear probe to map the isotope sestamibi in neck and lead them to the lesion. This is reported as an effective approach yielding very satisfactory results.
Another group isolates the unitary pathology by ultrasound and approaches it endoscopically. One such group monitors the situation with QPTH and reports 100% success. Others use an endoscopic approach only. The reviewer has been reliably informed that the addition of QPTH has occurred in one such major group. Yet another approach is to localise the unitary pathology and approach through a mini-incision and use a lateral probe to provide “superior visualisation” through video assistance. The extra visual information may have significant value during dissection, especially in relation to the recurrent laryngeal nerve. Although bleeding can still cause difficulty.

Commentary

From this review it has been observed that the most effective role for minimally invasive surgery is for the management of unitary parathyroid pathology. This would in effect mean that when all matters concerning the clinical presentation are considered, about 65% of patients with PHPT at most, would be suitable for consideration of a minimalist approach, but other criteria would need to be taken into account.

To achieve results that parallel those of conventional neck exploration requires very careful selection.

Selection criteria have been advanced from the serendipitous in relation to the early unilateral approach to criteria aimed at producing 100% outcomes from highly focussed approaches. To not take notice of the following criteria may increase the risk of failure when performing minimally invasive parathyroid surgery.

The following criteria have been gleaned from the literature, personal enquiry, personal observation and hearsay.

Criteria to be taken into account when planning minimally invasive surgery for PHPT.

- It is an assumption as well as a recommendation, that patients will have had an appropriate and informative discussion with the surgeon. It is also assumed that they will be made aware that they may be progressed from whichever minimal approach is planned, to open surgery if required.

- Identification of a presumed solitary adenoma. To be unequivocal at a single site. Means of identification:
  
  i. Sestamibi scanning
  
  ii. Ultrasonic scanning

- Exclude all patients with apparent multiple gland disease.

---

* Personal communication; Dr A Aufses, New York.
‡ Personal communications; Professor L Delbridge, Sydney; Dr A Aufses, New York; Dr O Clark, San Francisco; Dr N Thompson, Ann Arbor.
• Exclude as far as possible, all likelihood of hyperplasia of parathyroids or multiple gland disease of any kind:
  - Renal Disease
  - Family history of parathyroid disease
  - Suspected MEN syndrome

All the above would lead to exclusion from a minimalist approach.

• Exclude all patients with goitre.

• Exclude all patients with previous neck surgery.

• Exclude all patients with previous irradiation of the neck.

• Exclude all patients with lithium associated PHPT.

• Exclude all patients with abnormal neck structure (skeletal or soft tissue).

• One group excludes patients with significant heart disease because of the use of CO$_2$ in some endoscopic techniques*. The reviewer questions this and would suggest that patients with significant heart disease could benefit from the minimal approach. It is probably better to exclude CO$_2$ and use a lifting device in this situation.

• A surgeon experienced in the conventional technique, who can readily progress to it during a minimalist operation if necessary, should be present at surgery.

• The use of QPTH is promoted by some as being a useful adjunct in improving specificity.

Observation of the above criteria would lead to a significant number of patients being candidates for one of the approaches being put forward at this time, probably 15-25% of all patients referred for parathyroid surgery. No doubt patient demand will cause this to increase over time.

As the techniques are as yet in the unproven mould, it is suggested that the techniques be espoused in trial mode across Australia.

It would seem that each major unit that is already involved in parathyroid surgery should set up a trial to assess minimally invasive surgery. While Australia is significant in quality of surgery, it is a small contributor in overall numbers for PHPT. It would seem appropriate that if physicians and surgeons agree, patients meeting the criteria already elaborated could be considered for such surgery.

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* Personal communication; Dr A Aufses, New York.
Reporting and Evaluation

In order to obtain a wide review of the methods in a reasonable time, individual units could adopt different techniques. Randomisation would be the ideal, but it may take a large number of patients than are available to complete a study in reasonable time\textsuperscript{12}.

It would be valuable if data were accrued to a register on a quarterly basis, the data to include the following:

- Total number of patients referred for parathyroidectomy.
- Number of patients meeting criteria for minimally invasive parathyroidectomy.
- Total number undergoing minimally invasive surgery.
- Newer exclusion criteria developed on the basis of ongoing experience should be reported.
- Operative complications to be recorded and reported, being bleeding or haematoma, infection, recurrent laryngeal nerve injury (transient and permanent), temporary or permanent hypocalcaemia (a highly unlikely complication), persistent or recurrent hyperparathyroidism or death.
- The wound and its length should be recorded.
- Cosmetic result to be noted.
- The type of anaesthesia used during surgery.
- Length of hospital stay.
- The surgeon’s views about the procedure, its safety and its efficacy.
- Patient satisfaction.

The careful (graded) collection and comparison of this data against known Australian data for the conventional procedure should assist in determining the rightful role of these newer approaches, providing a minimal data set of information.

The reviewer believes that Dr David Roder of the South Australian Cancer Registry would be most helpful in developing such a register.

The reviewer further suggests that one group use sestamibi mapping and another Quick Serum Parathyroid Hormone estimation in their protocols. Both techniques are coming into wider use in USA and Europe and pilot studies would allow Australian surgeons to have local information rather than be “flat-footed” at the next level of assessment.

Until such nationwide review and evaluation is completed, the procedure should be put on hold as far as its performance in the community generally is concerned. The Royal Australasian College of Surgeons and its Section of Endocrine Surgery could assist in this development as part of ongoing audit and evaluation process.
In consultation with the Review Group, the recommended ASERNIP-S classification is 3; safety and efficacy of the procedure is not yet established. Procedure requires further evaluation and may be used only as part of systematic research; comprising either an observational study or a controlled clinical trial.

Emeritus Professor Tom Reeve AC CBE
Reference List


Methodological Assessment Report for the Review of Minimally Invasive Parathyroidectomy for Primary Hyperparathyroidism

Dr Wendy Babidge
ASERNIP-S Research Co-ordinator

February 1999
**Background**

To assess a new technique one must compare it with the technique it is proposed to replace, generally being the current gold standard treatment for that condition. Where surgery is indicated for treatment of patients with primary hyperparathyroidism (PHPT), the “gold standard” technique is bilateral open neck exploration by an experienced endocrine surgeon.

The possible complications for this kind of endocrine surgery include damage to the recurrent laryngeal nerve, potentially resulting in permanent hoarseness and permanent hypocalcaemia due to injury of the parathyroid glands\(^1\). The risks associated with these complications are reported to be less than 1% to 2\(^2\)-\(^3\). Transient hypocalcaemia occurs more frequently but is generally resolved soon after surgery, with no major consequences\(^4\). Other minor complications such as haematoma, seroma and keloid formation have also been reported to occur\(^1\).

A recent report by Edis\(^5\) emphasised the need for experienced endocrine surgeons for parathyroid surgery, but stressed the current safety and high success rate. There are however, potential pitfalls that can lead to failure of the current operation, requiring the patient to undergo further costly investigations and a potentially hazardous re-operation\(^5\).

It is now common in bilateral open neck exploration for surgeons to sight all glands but only to biopsy one normal gland, to reduce the risk of damage to others and thus lower the incidence of hypoparathyroidism\(^6\). Despite the success of the bilateral operation there has been a steady push towards a more limited and focused cervical exploration under local anaesthesia. This has arisen due to the increased availability of the QPTH assay and the emergence of more sensitive imaging modalities, for example, Tc-sestamibi. Imaging has been used in the past prior to re-operation but is now thought to be useful for initial surgery in cases of single gland disease\(^7\).

The NIH Consensus Development Statement\(^8\) suggested that imaging of parathyroid glands before initial surgery was not necessary and that the usefulness of such non-invasive methods was diminished by their unreliability and that they were not proven to be cost-effective. A variety of localisation studies have been used; ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), thallium-technetium (Th-Tc), sestamibi radionuclide scans, and selective venous sampling for PTH assay. Sestamibi and MRI are the newest techniques and all imaging requires expert radiologists and state-of-the-art equipment. These have not been considered cost-effective in the past prior to initial operation\(^1\).

Use of preoperative imaging techniques is expanding as their accuracy improves. They are theoretically able to distinguish uni- from multi-gland disease and also to direct the initial surgical exploration to the predicted side of the offending gland\(^9\). Experience with the localisation technique is of paramount importance as the operator has a great influence on the results. Unilateral neck exploration for PHPT has been controversial due to concern for missing multiglandular disease. However, patients with localisation of an adenoma on one side of the neck have a high success rate for unilateral surgery\(^6\). A single adenoma is found in approximately 85% of cases of PHPT\(^6\). Support for unilateral neck exploration has been based on the premise of increased cost-effectiveness and reduced complications such as decreased risk of permanent hypoparathyroidism, as one side of the neck is left untouched. The drawbacks are of missing double adenomas and hyperplasia\(^6\).
Concern was expressed over localisation, in that a positive result may engender inappropriate confidence in a less experienced surgeon, thus resulting in a higher operative failure rate. For second explorations the role of localisation is undisputed, since re-operation is technically more difficult and hazardous with respect to recurrent laryngeal nerve injury \(^1\).

None of the reviews used as background for the report have discussed the endoscopic approach to parathyroid surgery, therefore the topic will be discussed later in this report when assessing the current literature on the endoscopic technique. The articles describing the endoscopic technique encompass developmental animal studies and case studies in patients, who have had either image localised adenomas or total endoscopic neck exploration.
Assessment of Articles for Review

Of the 41 articles for the review of new minimally invasive surgical techniques in PHPT, 32 relate to unilateral neck exploration. Included in this group are ten case controlled studies of which details regarding safety and efficacy are provided in the assessment table (see page 61). The remainder of studies are case series reports and relevant safety issues will also be described from these. There are nine articles discussing the endoscopic technique, none of which were controlled studies and are therefore not included in the assessment table. A narrative discussion on safety and efficacy issues of the endoscopic technique arising from these is included in this report. One publication is in the form of a letter and reply discussing the unilateral and endoscopic techniques.

The studies included in the assessment table are of the highest quality. The study by Denham and Norman is a meta-analysis of the English literature over the last ten years. Sestamibi imaging was assessed and found on average to be 91% accurate and considered cost-effective when performing unilateral surgery. Two other studies suggested that sestamibi imaging was a good technique for identifying a single adenoma and thus performing unilateral surgery, with a concomitant reduction in operating time. Thallium-technetium radionuclide scanning was found to be a good imaging technique if adenomas were of sufficient size, with subsequent unilateral surgery having reduced operating times and was also thought to be cost-effective. Ultrasound was reported to be useful, especially when there was a single adenoma. Two studies used Oil Red O and/or Haematoxylin and Eosin staining to differentiate between adenomatous or hyperplastic tissue, allowing some cases to undergo unilateral exploration. One study assessed unilateral parathyroid surgery and compared only the results from one dedicated sonographer to base decisions for unilateral surgery. Any patient results imaged by others were excluded. This reporting is considered to be biased and as such the results of this study have not been considered further.

The accuracy of imaging is thought to be the most important factor in determining the success of unilateral surgery. This depends on the type of imaging and whether it is used to detect a single adenoma or hyperplasia. The cost-effectiveness of unilateral surgery is dependent on decreased operating times and lengths of hospital stay in offsetting the cost of the scan(s). Overall in the ten studies assessed there was a lower rate of adverse outcomes with the unilateral procedure than was found with the bilateral procedure.
<table>
<thead>
<tr>
<th>Level</th>
<th>ID#</th>
<th>Adenoma/All</th>
<th>Scan type</th>
<th>Magnitude of effect (Unilateral vs Comparator)</th>
<th>Adverse Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Type</td>
</tr>
<tr>
<td>I 11</td>
<td>All (87% adenoma)</td>
<td>Sestamibi</td>
<td>Operative time: U 46', C 109' (P&lt;0.0001)</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Costs: U $1773 C $1123</td>
</tr>
<tr>
<td>III-2 18</td>
<td>Adenoma</td>
<td>No Scan</td>
<td>Operative Success: 100%</td>
<td>Transient Hypocalcaemia</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Operative time: U 93', C 115'-164'</td>
<td>Hospital stay mean 5.6 days (nsd)</td>
<td></td>
</tr>
<tr>
<td>III-2 16</td>
<td>Adenoma</td>
<td>Thallium</td>
<td>Operative success: U 97.5%, C 93%</td>
<td>Persistent hypercalcaemia</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Operative times: U 55', C 74' (P&lt;0.01)</td>
<td>Operative time: U 15', C not stated</td>
<td>Transient hypocalcaemia</td>
</tr>
<tr>
<td>III-2 17</td>
<td>All (77% adenoma)</td>
<td>US and CT</td>
<td>Operative success: U 96%, C 100%</td>
<td>Transient vocal cord paralysis</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Hospital mean 5.6 days (nsd)</td>
<td>Operative time: U 15', C not stated</td>
<td>Transient hypocalcaemia</td>
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<tr>
<td>III-3 12</td>
<td>Adenoma</td>
<td>Sestamibi</td>
<td>Operative success: U 100%, C 96%</td>
<td>None found</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hospital Stay: U 15hr, C 30hr (p&lt;0.01)</td>
<td>Incision length: U 3cm, C 9.6cm (p&lt;0.001)</td>
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<td>III-3 14</td>
<td>All (86% adenoma)</td>
<td>Thallium</td>
<td>Operative Success: S 100%, NS 92% (scan =U, no scan =C)</td>
<td>Persistent hyperparathyroidism</td>
<td>0%</td>
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<td></td>
<td></td>
<td></td>
<td>Costs: S $4917 NS $6070 (US$)</td>
<td>Temporary hypoparathyroidism</td>
<td>22%</td>
</tr>
<tr>
<td>III-3 15</td>
<td>All (94% adenoma)</td>
<td>US and Thallium</td>
<td>Operative time: U 105', C 151' (P&lt;0.001)</td>
<td>Recurrent Hypercalcaemia</td>
<td>2.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hospital stay: S 5.7 d, NS 7.2 day</td>
<td>Equivalent costs (U + scan vs C)</td>
<td>Persistent Hypercalcaemia</td>
</tr>
<tr>
<td>III-3 20</td>
<td>All (93% adenoma)</td>
<td>US</td>
<td>Operative time: U 77', C 98-106' (P&lt;0.001)</td>
<td>Transient Hypocalcaemia</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Transient Hoarseness</td>
<td>Temporary Vocal Cord Injury</td>
<td>0%</td>
</tr>
<tr>
<td>III-3 13</td>
<td>Adenoma</td>
<td>Sestamibi</td>
<td>Operative success: all 100%</td>
<td>None found/stated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Operative time: U 88', C 118' (P=0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-3 19</td>
<td>All (87% adenoma)</td>
<td>Various</td>
<td>Operative success: U 99%, C 93%</td>
<td>Temporary Hypocalcaemia</td>
<td>9.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Operative time: U 69', C 92' (P&lt;0.001)</td>
<td>Temporary Vocal Cord Injury</td>
<td>0%</td>
</tr>
</tbody>
</table>

* biased reporting for single operator
Adenoma/All: refers to whether all cases of Primary Hyperparathyroidism assessed or just selected patients with an adenoma
NS- no scan, S - scan, US - ultrasound, CT - computed tomography
Level - as per NH&MRC assessment guidelines (see page 62); For ID# see attached reference list (page 65)
NH&MRC Assessment Guidelines: Hierarchy of Evidence

I Evidence obtained from a systematic review of all relevant randomised controlled trials.

II Evidence obtained from at least one properly designed randomised controlled trial.

III-1 Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).

III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.

III-3 Evidence obtained from comparative studies with historical control group, two or more single arm studies or interrupted time series without a parallel control group.

IV Evidence obtained from case series; either post-test or pre-test and post-test.
Safety Issues Arising from Controlled Studies of Imaging/Unilateral Neck Exploration

No mortality was reported. Transient hypocalcaemia was a feature of most studies, varying from 3% to 22% for unilateral surgery\textsuperscript{14,17,18} and 13% to 39% for bilateral surgery\textsuperscript{14,18,19}. In three studies no adverse outcomes were reported; none being found in one study\textsuperscript{12} and not assessed in the others\textsuperscript{11,13}. Transient vocal cord injury or associated hoarseness was reported in two controlled studies; for unilateral surgery the occurrence of this complication was nil versus 1.6% for bilateral cases in one study\textsuperscript{19} and 1.5% for unilateral surgery in the other study\textsuperscript{17}.

Conclusions

Resolution of hypercalcaemia is a major measure of operative success and this was the case in most of the controlled studies. In one study persistent hypercalcaemia was found in 2% of unilateral surgery cases compared with 7% of bilateral surgery cases\textsuperscript{16} and in 5.3% of unilateral surgical cases in another study\textsuperscript{15}. Ryan and co-workers\textsuperscript{15} also found recurrent hypercalcaemia in about 2% of cases following unilateral or bilateral surgery. Overall operative success rates were stated for most studies and these ranged from 92% to 100% for bilateral surgery and 96% to 100% for unilateral surgery. Operative times were shorter for unilateral compared with bilateral surgery and the difference was statistically significant\textsuperscript{11,13,15,16,19}. Based on the current evidence from controlled studies it appears that the unilateral technique is at least as good as the “gold standard” of bilateral parathyroid resection in all aspects of safety and efficacy.

Safety Issues Arising from Case Studies of Imaging/Unilateral Neck Exploration

No mortality was reported. No further major safety issues arose from the case studies relating to the potential use of unilateral neck exploration. Many of the case studies assessed the success of imaging by performing bilateral surgery and as such, if adverse outcomes were stated, they did not relate to unilateral surgery.

Conclusions

There were 22 case studies overall. In about 60% of these, unilateral surgery was recommended, following a positive scan (by various radionuclide scan techniques and ultrasound) for a single adenoma. Other case studies (32%) reported an opposing view that imaging was neither accurate nor cost-effective enough for first time parathyroid surgery. One study recommended combining three imaging modalities to achieve a 96% diagnostic accuracy for both adenomas and hyperplasia, while one study did not use imaging prior to unilateral exploration.

Safety Issues Arising from Case Studies of Endoscopic Parathyroid Surgery

No mortality was reported. Adverse outcomes were transient and generally related to high insufflation pressures and lengthy operating times. The operative complications relating to these were pneumomediastinum and subcutaneous emphysema. Other recorded complications were of a cut laryngeal nerve and tachycardia.
Description of Endoscopic Studies

Of the nine papers reviewed, three were from one research group and appeared to be reports on the same patient\textsuperscript{22-24}. Three papers came from a second group, and included one technique development report and two reports, which may possibly relate to the same patients\textsuperscript{25-27}. Two other papers described technique development in dogs\textsuperscript{28,29} and cadavers\textsuperscript{28} and another study reported videoscopic-assisted surgical success in six and thirty-nine patients with a single adenoma\textsuperscript{30,31}.

Conclusions

The endoscopic technique was reported by most as feasible but technically difficult. The totally endoscopic technique\textsuperscript{25-27} required very long operating times, while the videoscopic-assisted technique\textsuperscript{30,31} was considerably shorter.

Overall Conclusions

In general the quality of studies in the area of minimally invasive parathyroid surgery has been poor. It is understood that difficulties associated with performing randomised controlled trials may preclude their use for this procedure. It is important however, for both unilateral neck exploration and endoscopic parathyroid surgery, that an appropriate assessment by well designed studies is made prior to the widespread introduction of this technique in Australia.
Reference List


