Primary Hyperparathyroidism - A Surgeon’s Perspective

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Introduction

Primary hyperparathyroidism (pHPT) had been considered to be a rather rare disorder of calcium metabolism, identified only when signs and symptoms were present. With the advent of the multichannel autoanalyser in the early 1970s, hypercalcaemia became much more common, and the prevalence and incidence of pHPT were found to be much higher than previous estimates. The clinical profile had also shifted from a symptomatic disorder towards a more asymptomatic state. The phenotype of asymptomatic pHPT became the overwhelming predominant form of pHPT in countries where biochemical screening became routine. In countries where biochemical screening was and still is not routine, pHPT continues to be an uncommon disease.

Indications for Parathyroid Surgery

Symptomatic Disease

There is no controversy that all patients with symptomatic biochemically confirmed pHPT should undergo surgical treatment. In these symptomatic patients, following successful parathyroidectomy, improvement in bone density and reduction in fractures, reduced frequency of recurrent kidney stones, improvement in some neurocognitive elements, decreased incidence of cardiovascular complications, and decline in premature death have been well demonstrated.

Asymptomatic Disease

The recommendation of surgical treatment for seemingly asymptomatic patients with pHPT, however, remains controversial. To address this issue, consensus conference was organised by the National Institution of Health in 1990, and subsequently in 2002, and 2008, attempted to define a rational basis for recommending parathyroidectomy for asymptomatic patients (Table 1). However, other authorities have recommended more liberal guidelines in managing these patients based on the inability to determine predictably whether complications or progression of this disease will develop in a specific patient.

Moreover, growing evidences have demonstrated that the disease does not appear to be indefinitely stable. Deterioration of bone density and renal function had been demonstrated in one third of patients on long term follow-up. The bone density and renal concentrating capacity will however show improvement consistently after parathyroidectomy. Patients with ‘asymptomatic’ pHPT were also shown to have more neuropsychiatric symptoms and, in some cases, showed improvement after successful parathyroidectomy. Increased incidence of hypertension, left ventricular hypertrophy, vascular calcification and stiffness, and myocardial events had been demonstrated in patients with mild pHPT. They also appeared to be at risk of premature deaths, due to cardiovascular disease or cancer. All these new data on the natural history of asymptomatic pHPT have favoured surgery. There is growing consensus that prevention of these events, when possible, by earlier parathyroidectomy, rather than treatment of complications might be prudent in patients who can be defined to be at risk, and surgery may eventually be appropriate in the majority of patients with asymptomatic disease.

Another argument advanced to support surgical referral to this disease is the durability and overall cost-effectiveness of surgical treatment over long-term monitoring. Moreover, advances in the effectiveness and safety of new surgical techniques have brought added confidence to its recommendation.

Table 1. Comparison of new and old guidelines for parathyroid surgery in asymptomatic primary hyperparathyroidism.

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<td>Serum calcium (&gt;upper limit of normal)</td>
<td>1.6mg/dl (0.25-0.4mmol/L)</td>
<td>1.6mg/dl (0.25mmol/L)</td>
<td>1.6mg/dl (0.25mmol/L)</td>
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<td>24hour urine for calcium</td>
<td>&gt;400mg/d (&gt;10mmol/d)</td>
<td>&gt;400mg/d (&gt;10mmol/d)</td>
<td>Not indicated</td>
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<tr>
<td>Creatinine clearance (calculated)</td>
<td>Reduced by 30%</td>
<td>Reduced by 30%</td>
<td>Reduced to &lt;60ml/min</td>
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<tr>
<td>Bone marrow density</td>
<td>Z-score &lt;-2.0 in forearm</td>
<td>T-score &lt;-2.5 at any site</td>
<td>T-score &lt;-2,5 at any site and/or previous fracture fragility &lt;50</td>
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<td>Age (year)</td>
<td>&lt;50</td>
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Surgical Treatment of Primary Hyperparathyroidism

Bilateral neck, 4-gland exploration had been the gold standard since the first successful parathyroid surgery in 1925. Through a 6-8 cm lower neck incision, all 4 parathyroid glands are identified after mobilisation of both thyroid lobes and the adjacent structures. It ensures that all glands are visualised and the morphology of the gland determines the need for resection. Intra-operative frozen section is also required to confirm whether the excised gland or tissue is histologically abnormal. The extent of resection (number of glands being removed), and the cure rate, depends on the experience of the operating surgeons and pathologists.
As the vast majority (over 85%) of patients with pHPT have a single adenoma as the cause of their disease, the gold standard, bilateral neck exploration, was theoretically necessary for less than 15% of patients who had multi-gland disease. Thus, the current paradigm has shifted to a limited exploration and excision of the adenoma only by less invasive approaches. The challenge has always been to, preoperatively, or even intraoperatively, categorise individual patients. With the recent technical innovations including improved preoperative localisation, availability of rapid intraoperative parathyroid hormone (PTH) assays, and intraoperative gamma detection probes, various techniques of minimally invasive parathyroidectomy have become applicable with excellent outcomes. However, even if we can identify which patients have a single adenoma and which do not, finding the adenoma can still be challenging as they can be located anywhere from the base of the skull at the jugular foramen down to the level of the heart. It needs to be emphasised that parathyroid surgeries should be performed only by surgeons who are highly experienced in this operation; otherwise failure and complication rates will be unacceptably high.

Preoperative imaging in the setting of pHPT is designed to assist the surgeon in identifying the anatomic location of abnormally functioning or enlarged parathyroid gland(s). Positive imaging studies are not useful for the confirmation of a diagnosis of pHPT whilst a negative scan does not exclude the diagnosis of pHPT. Furthermore, all imaging studies demonstrate both false-positive and false-negative findings that could be misleading. The most commonly employed techniques are radionuclide (sestamibi) scan (Fig.1) and ultrasound (Fig.2). The success of these imaging studies is highly dependent on the operator and the experience of the centres performing the procedures. Computer tomography, magnetic resonance imaging, selective venous sampling for PTH are usually reserved for patients who have previous failed explorations or for whom other localisation techniques are uninformative or discordant. Failure to localise the adenoma preoperatively is generally regarded as a contraindication for minimally invasive parathyroidectomy, the other contraindications include the presence of multiglandular disease, multiple endocrine neoplasia, malignancy, and the presence of concomitant thyroid disease.

Minimally invasive parathyroidectomy is generally described as the removal of parathyroid adenoma(s) through a small skin incision and, most importantly, without four-gland visualisation. Thus intraoperative adjuncts such as quick PTH assay have been employed in some centres to determine the extent of surgery, and to confirm operative cure. Due to the relatively short half-life of PTH (4-5 minutes), a dramatic drop in circulating hormone can be detected once the abnormal gland has been removed. A curative drop in PTH allows the surgeon to terminate the operation and obviate additional exploration, whereas failure of the PTH levels to demonstrate an adequate decrement mandates further exploration due to the presence of presumed additional hyperfunctioning gland.

Approaches of minimally invasive parathyroidectomy can be grouped into four main categories. The choice of these approaches is highly surgeon, or institution specific, and should be based on the expertise and resource availability of the surgeon and the institution.

Focused Parathyroidectomy

This is by far the most widely employed technique. It is performed via a 2-3 cm incision under either local, cervical block or general anaesthesia. This incision can either be made in the midline (Fig.3) of the neck or unilaterally (Fig.4), based on the findings of preoperative imaging or by bed-side ultrasound performed by the operating surgeon. Following the excision of the abnormally enlarged gland(s) (Fig.5), operative cure can be confirmed by rapid intraoperative PTH assay.
exploration and excision of the abnormal gland(s). and most importantly, a lower incidence of postoperative temporary hypocalcaemia 24,25. Shorter operating time largely composed of recurrent laryngeal nerve injury, or success rate (95-98%) and low complication rate (1%), by experienced surgeons, all offer a similarly high by the operative field is magnified to facilitate the dissection of the parathyroid gland(s). This procedure is performed via a 2cm midline or lateral incision, and the use of an endoscopic camera, the operative field is magnified to facilitate the dissection of the parathyroid adenoma. Minimally Invasive Radio-guided Parathyroidectomy (MIRP) This approach requires a preoperative administration of low dose radioactive stentabani. Through a 2-3 cm midline incision, a gamma probe is used to measure the radioactivity of the parathyroid glands, and to guide the exploration and excision of the abnormal gland(s). Minimally Invasive Video-assisted Parathyroidectomy (MIVAP) This procedure is performed via a 2cm midline or lateral incision, and the use of an endoscopic camera, the operative field is magnified to facilitate the dissection of the parathyroid adenoma. Endoscopic Parathyroidectomy It can be performed via the cervical, axillary, or anterior chest wall approaches. Typically, 3 to 4 trochars are inserted under general anaesthesia. Gas insufflation is also required. However, most groups have abandoned this technique because of additional personnel and costs, the longer operating time, need of general anaesthesia and gas insufflation. Research studies suggested that the various techniques of minimally invasive parathyroidectomy, when performed by experienced surgeons, all offer a similarly high success rate (95-98%) and low complication rate (1%), largely composed of recurrent laryngeal nerve injury, or temporary hypocalcaemia24,25. Shorter operating time and hospital stay, decreased pain, improved cosmesis, and most importantly, a lower incidence of postoperative hypocalcaemia have been demonstrated in studies comparing minimally invasive parathyroidectomy to that of the conventional approach 26,27.

Conclusion
Surgery is always considered to be the definitive therapy in primary hyperparathyroidism. There is growing consensus that surgery may eventually be appropriate in the majority of patients, even with asymptomatic disease. Minimally invasive parathyroidectomy, by expert endocrine surgeons, in properly selected patients is safe, cost-effective, and associated with a high cure rate and very low perioperative morbidity.

References