

## REVIEW ΑΝΑΣΚΟΠΗΣΗ

# A modern approach to the diagnosis and management of primary hyperparathyroidism

Primary hyperparathyroidism (pHPT) is currently being diagnosed with increased frequency. This short review demonstrates why surgery is the only curative treatment for patients with pHPT, and why intra-operative measurement of parathyroid hormone (PTH) may not be necessary in all cases of parathyroidectomy. The majority of parathyroid adenomas can be detected by pre-operative localization with  $^{99m}\text{Tc}$ -sestamibi and or neck ultrasound (US). The development of focused parathyroidectomy and other minimally invasive techniques has rendered day-case parathyroidectomy a safe and feasible procedure. Parathyroidectomy, either unilateral or bilateral, when considered necessary, should be performed by an experienced parathyroid surgeon.

## 1. INTRODUCTION

The profile of the surgical patient with primary hyperparathyroidism (pHPT) referred for parathyroidectomy has changed during the last century since the operation was first performed.<sup>1</sup> This condition has largely moved from a symptomatic disorder, with classic symptoms at presentation, towards an almost asymptomatic biochemically detected condition. pHPT has an annual incidence of approximately 0.1%, and diagnosis has recently been facilitated by development of a new whole molecule parathyroid hormone (PTH) assay. The population groups with the highest incidence are middle-aged and elderly women, with a rate of 188 per 100,000 population, and it is in these groups that the disorder is often associated with medical comorbidities.<sup>2</sup>

The diagnosis of pHPT requires detection of hypercalcemia together with detectable circulating PTH levels. The PTH can be either normal or elevated, but inappropriately elevated for the level of calcium. This mode of presentation is the usual scenario, based on routine screening of patients with general symptoms such as fatigue, depression, and weakness. Detection in the context of investigation for osteopenia or nephrolithiasis, the two main complications of pHPT, is less common.

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Περίληψη στο τέλος του άρθρου

## Key words

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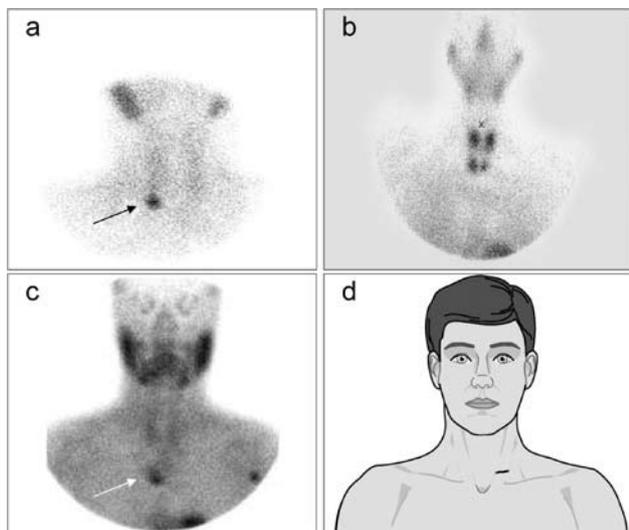
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The vast majority of cases (85–90%) of pHPT are due to a solitary parathyroid adenoma (fig. 1a). In 10% of cases multiglandular hyperplasia (fig. 1b) is present, which may be associated with multiple endocrine neoplasia (MEN) Type I (pancreatic tumors, pituitary tumors, pHPT), sporadic, or induced by long term lithium intake. Carcinoma and double adenoma are very rare and each occurs in approximately 1% of cases of pHPT.

## 2. THRESHOLD FOR SURGICAL INTERVENTION

In the recent past, surgery for pHPT was mainly restricted to patients with symptoms or complications of the disease. In Great Britain this guideline was adopted following a National Institute of Health (NIH) consensus conference in 1990<sup>3</sup> which concluded that many patients did not require surgery as they were asymptomatic and their disease was not progressive.<sup>3</sup>

Two leading articles have now questioned this conservative approach, suggesting that surgery should be considered at the time of the initial diagnosis.<sup>4,5</sup> This policy is supported by two quality of life studies, which have shown that patients with even mild hypercalcemia have physical



**Figure 1.**  $^{99m}\text{Tc}$ -sestamibi scan showing: (a) right inferior parathyroid adenoma; (b) four gland parathyroid hyperplasia; (c) mediastinal parathyroid adenoma. (d) Skin incision for focused parathyroidectomy.

or neuropsychological disabilities that improve following parathyroidectomy.<sup>6,7</sup> In addition, the overall mortality among untreated patients with pHPT is increased, which is thought to be due mainly to heart disease.<sup>8</sup>

The shift in the threshold for surgical intervention led to a second NIH consensus conference that reviewed the indications for surgery in pHPT.<sup>9</sup> These guidelines go a small way towards supporting earlier surgical intervention but, in the opinion of the authors, they may not go far enough. It is evident that surgery is the only curative treatment for pHPT and the introduction of unilateral or focused parathyroidectomy, together with more accurate pre-operative imaging, gives the opportunity for surgery be performed in day surgery, thus limiting the length of hospital stay and the cost. In practice, this modern surgical approach now means that the cost of parathyroid surgery is actually cheaper than any single hospital admission for complications of the disease. There is thus good reason to support this move to earlier surgical intervention purely on the grounds of health economics.

### 3. PROBLEMS IN THE DIAGNOSIS OF PHPT

#### 3.1. Familial hypocalciuric hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is a rare disorder that can also present with hypercalcemia and mildly elevated or inappropriately normal PTH levels, and as a result it must be carefully distinguished from pHPT. FHH is autosomal dominant in inheritance and in

the majority of cases is due to a heterozygous mutation in the calcium-sensing receptor (CaSR) gene, the main regulator of parathyroid cell response to calcium.<sup>10</sup> In cases where the defect is homozygous, with two mutated CaSR genes, severe neonatal HPT results and emergency total parathyroidectomy is required.

The diagnosis of heterozygous FHH is confirmed by urinary calcium concentration assay plus the measurement of the calcium/creatinine clearance ratio (Ca/Cr) in the patient and family members with hypercalcemia. In FHH the Ca/Cr clearance ratio is usually less than 0.01. In pHPT the Ca/Cr clearance ratio is typically greater than 0.02.<sup>9</sup>

#### 3.2. Normocalcemic hyperparathyroidism

Hypercalcemia is not always present in all patients with pHPT. For some patients the serum calcium may be at the upper end of the normal range in association with inappropriate elevation of the PTH. This condition is called normocalcemic or subclinical HPT.<sup>9</sup> It often becomes apparent when PTH is measured during the investigation of osteoporosis or intermittent hypercalcemia. There is some evidence to suggest that the upper limit of normal for vitamin D-adequate patients should be redefined at up to 30% lower than current values.<sup>11</sup> The present definition is based on the belief that the normal range for PTH was derived from healthy adult volunteers, many of whom may have been vitamin D-inadequate. This may also explain why a number of patients have persistent elevation of PTH, despite normocalcemia, following parathyroidectomy for pHPT.<sup>12</sup>

In the differential diagnosis of patients with normocalcemia and elevation of PTH, potential causes of secondary hyperparathyroidism should also be ruled out. Thus, the possibilities of renal insufficiency, vitamin D deficiency or hypercalciuria must be evaluated. If vitamin D deficiency is suspected a trial of calcium and vitamin D supplements can markedly reduce PTH levels<sup>13</sup> and may preclude unnecessary surgery.

### 4. PARATHYROIDECTOMY

#### 4.1. In general

Traditionally, parathyroid surgery for many years relied on experienced surgeons to distinguish an adenoma from hyperplasia by direct visualization of all four glands. As a result bilateral cervical exploration remained the preferred surgical approach, with cure rates of up to 95% in experienced hands.<sup>14</sup> Supporters of this technique have

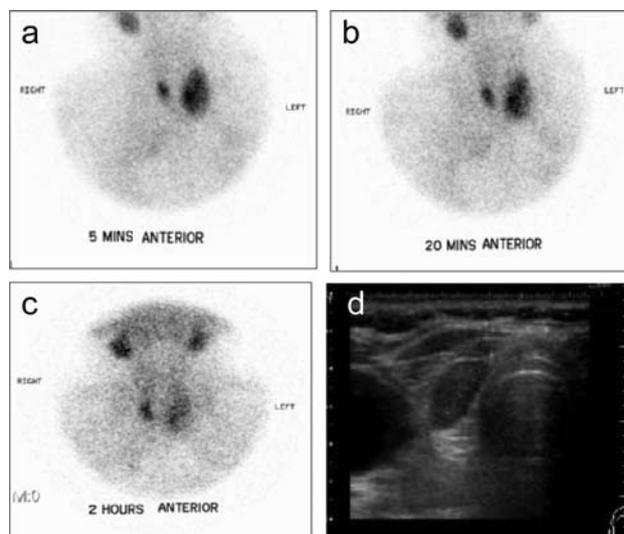
suggested that cases of hyperplasia or double adenoma are easier to recognize if bilateral neck exploration is performed. In addition, frozen section was often previously performed on one or more parathyroid glands and until very recently it was performed routinely by at least 73% of endocrine surgeons in the UK.<sup>15</sup>

In approximately 80–85% of cases, however, pHPT is caused by a single adenoma and improved reliability in preoperative imaging techniques, specifically high resolution neck ultrasound (US) and <sup>99m</sup>Tc-sestamibi scan, along with the development of intra-operative assays to confirm normalization of PTH levels, have led to changes in the modern surgical approach. Today, more surgeons are becoming familiar and comfortable with unilateral exploration, which allows for a smaller incision and shorter operative time.<sup>16</sup> An alternative strategy involves the use of minimal access surgery using video assisted or endoscopic techniques to facilitate parathyroidectomy. Since the first report in 1996 of endoscopic<sup>17</sup> and 1997 of video assisted<sup>18</sup> parathyroidectomy, several series have documented the feasibility of these approaches for both parathyroid and thyroid diseases. The advantages of this minimally invasive approach are reduced postoperative discomfort, improved cosmetic results<sup>19</sup> and reduction in recurrent nerve injuries due to the magnification of the laparoscope.<sup>20</sup>

#### 4.2. Pre-operative localization

The agent of choice for pre-operative parathyroid imaging is <sup>99m</sup>Tc-sestamibi (fig. 1). This can be performed either using a subtraction technique<sup>21</sup> with <sup>123</sup>I or as a sole agent with delayed/dual phase image.<sup>22</sup> The reason why there is uptake and retention of <sup>99m</sup>Tc-sestamibi in parathyroid tissue, allowing identification on delayed imaging, may be partly explained by the large numbers of mitochondria in parathyroid adenomas.<sup>23</sup> Techniques such as the use of collimation and single photon emission computerized tomography (SPECT) allow optimization of the imaging technique and provide sensitivity in excess of 90%.<sup>24</sup> Recent evidence has shown that increased expression of P-glycoprotein, a trans-membrane drug export pump, may explain why some smaller parathyroid adenomas do not show up on <sup>99m</sup>Tc-sestamibi scanning.<sup>25</sup> The combination of neck US and <sup>99m</sup>Tc-sestamibi scanning provides the optimal means of pre-operative localization with a combined sensitivity of 94%.<sup>26</sup> Such high sensitivity provides an ideal instrument for scan-directed selection of patients for either unilateral or bilateral surgery (fig. 2).

There are other methods for parathyroid localization, including CT, MRI and selective venous sampling.



**Figure 2.** Pre-operative imaging in patient with previous right thyroid lobectomy. (a–c) <sup>99m</sup>Tc-sestamibi scan showing delayed washout on right side of neck. (d) Neck ultrasound scan showing 12 mm parathyroid adenoma in right side of neck.

Although they can successfully identify a proportion of adenomas the sensitivity of these techniques is extremely variable and thus their use should be reserved for those patients with persistent hypercalcemia following failed neck exploration.

#### 4.3. Unilateral neck exploration

Since 85–90% of patients with pHPT have single gland disease the operation of choice for the majority of patients with pHPT is unilateral neck exploration (UNE). A meta-analysis of <sup>99m</sup>Tc-sestamibi scanning has revealed sensitivity and specificity of 90.7% and 98.8%, respectively, allowing identification of most adenomas, which may then be treated by unilateral exploration.<sup>21</sup> A series of 184 patients who underwent scan-directed UNE reported a long-term cure rate of 98.4%.<sup>27</sup>

Accurate preoperative localization, however, is not the only prerequisite for successful outcome in UNE. Patient selection is also important, and patients with multigland disease, MEN-related hyperplasia, multinodular goiter and renal disease are clearly not suitable for this limited surgical approach.

#### 4.4. Focused parathyroidectomy (FP)

This procedure, performed following accurate preoperative localization of uniglandular disease, is carried out through a small lateral neck incision (fig. 1d). The patient

is supine with the neck in a neutral position and the head facing away from the operated side. Dissection takes place deep to the sternomastoid muscle and around the lateral border of the strap muscles to reach the retrothyroid space. This operation can be performed as a day-case procedure, under either general or cervical block anesthesia.<sup>28</sup>

This technique has about 50% less complications than bilateral neck exploration, and reduces operating time by half. In addition there is a significant reduction in post-operative stay.<sup>29</sup> A day-case study of 50 patients undergoing focused parathyroidectomy under general anesthesia demonstrated that this procedure is suitable for all age groups, and operating time averaged 30 min. Patients were allowed to go home within two hours of surgery and the postoperative cure rate, defined as normocalcemia, was 100% when FP was combined with intra-operative PTH (iPTH).<sup>30</sup>

#### 4.5. Intra-operative PTH measurement

Measurement of iPTH by rapid PTH assay has replaced the need both for visualization of all glands and for intra-operative frozen section. This innovation has encouraged many surgeons to adopt the focused parathyroidectomy approach. It has previously been shown that a 50% reduction in baseline pre-excision PTH within 5–10 min of adenoma excision can predict post-operative normocalcemia with a high degree of accuracy.<sup>30,31</sup> There is always room for improvement with this technique and there will always be some uncertainty about its reliability. It is, for instance, difficult to explain why a number of cases can take up to 30 min for the PTH to fall by 50%.<sup>29</sup> The technique

nevertheless can guide intra-operative decision making about further exploration, since failure to achieve a 50% drop in baseline PTH does appear to predict the presence of multigland disease or a second adenoma. It is, however, of note that intra-operative PTH measurement is not necessary for all cases of focused parathyroidectomy. For the cases where there is concordance between pre-operative <sup>99m</sup>Tc-sestamibi and US scanning, the false-positive rate for adenoma localisation may be negligible, and as a result iPTH measurement may not be necessary or cost-effective for these patients.

## 5. CONCLUSIONS

- Primary hyperparathyroidism is a disease with a high incidence in the general population
- The need for surgery has shifted to include patients early in the natural history of the disease, including so-called “asymptomatic patients”
- Pre-operative localization with <sup>99m</sup>Tc-sestamibi and or neck US is effective in the vast majority of cases
- Use of focused parathyroidectomy, and other minimally invasive techniques have rendered day-case parathyroidectomy safe and feasible
- Intra-operative PTH measurement obviates the need for frozen section and confirms cure when combined with unilateral surgery
- Parathyroidectomy, either unilateral or bilateral, should be performed by an experienced parathyroid surgeon.

## ΠΕΡΙΛΗΨΗ

### Μια σύγχρονη προσέγγιση στη διάγνωση και την αντιμετώπιση του υπερπαραθυρεοειδισμού

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Ο πρωτοπαθής υπερπαραθυρεοειδισμός διαγιγνώσκεται με όλο και μεγαλύτερη συχνότητα στη σημερινή εποχή. Στην παρούσα σύντομη ανασκόπηση παρουσιάζονται οι λόγοι για τους οποίους η χειρουργική αντιμετώπιση αποτελεί τη μόνη θεραπεία ίασης για ασθενείς με πρωτοπαθή υπερπαραθυρεοειδισμό, καθώς και γιατί η διεγχειρητική μέτρηση της παραθορμόνης δεν είναι αναγκαία σε όλες τις περιπτώσεις παραθυρεοειδεκτομής. Η μεγάλη πλειονότητα των αδενωμάτων του παραθυρεοειδούς μπορεί να ελεγχθεί με προεγχειρητική εντόπιση με <sup>99m</sup>Tc-sestamibi σε συνδυασμό με υπερηχογράφημα της αυχενικής χώρας. Η ανάπτυξη της τοπικής παραθυρεοειδεκτομής, καθώς και των άλλων τεχνικών μικροχειρουργικής, έδειξε ότι η παραθυρεοειδεκτομή είναι ένα ασφαλές και εφικτό χειρουργείο

μίας ημέρας. Η παραθυροειδεκτομή, όταν αυτή πραγματοποιείται αμφοτερόπλευρα ή ομόπλευρα, πρέπει να διεργείται από έμπειρο χειρουργό ενδοκρινών αδένων.

**Λέξεις ευρητηρίου:** Εντοπισμένη παραθυροειδεκτομή, Πρωτοπαθής υπερπαραθυροειδισμός

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