Primary Hyperparathyroidism: Surgeons’ Perspective

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Disclosures

• Speaker Bureau
  • Veracyte
  • Castle Diagnostics
Objectives

• Brief review of history
• Compare the available guidelines
• Identify patients who will benefit from surgical intervention and make some referral recommendations
• Discuss the role of imaging in the treatment of primary hyperparathyroidism (PHPT)
• Review surgical approaches
Brief History

• ~1850 Sir Richard Owen, Royal College of Surgeons of England describes parathyroid glands Indian Rhinoceros

• 1880 Ivar Sansdström, Swedish medical student University of Uppsala identified the glands in humans

• 1891 von Recklinghausen reported on a pt who had multiple atraumatic fractures, long bone ‘bending’ and fibrosis, brown tumors and cysts—osteitis fibrosa cystica of von Reckinghausen

• 1925 in Vienna, Felix Mandl first parathyroidectomy
Captain Charles Martel

• 1926 Martel admitted to NYC metabolism clinic; referred to MGH
  • First person dx’d in US
  • 9th surgery tumor in chest cured his disease
• 1977 Noble Prize for PTH assay
• 1991 PTH mediated surgery
Primary Hyperparathyroidism
Guidelines

• Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop 2014

• The AAES Guidelines for Definitive Management of Primary Hyperparathyroidism 2016
Definitions

- Classic primary hyperparathyroidism
  - Elevated Ca and PTH

- Normohormonal primary hyperparathyroidism
  - Ca elevated, PTH in the normal range but inappropriately suppressed

- Normocalcemic primary hyperparathyroidism
  - Ca normal range and PTH elevated
  - In the absence of secondary causes
2016 AAES
Guideline Panel Findings (1)

• Initial evaluation should include:
  • 25-OH Vitamin D, 24-hour urine calcium, serum creatinine or Estimated GFR, and DEXA

• Parathyroidectomy (PTX) is indicated for:
  • all symptomatic patients and
  • should be considered for most asymptomatic patients.

• PTX is more cost-effective than observation or pharmacologic therapy
Common Secondary Causes of Elevated PTH

- Chronic kidney disease: Creatinine clearance <60 ml/min
- Medications (calcium normal or high): Thiazide and loop diuretics, lithium
- Medications (calcium normal or low): Foscarnet, citrate (banked blood/plasma), EDTA, bisphosphonates, denosumab, cisplatin
- Hypercalciuria secondary to renal leak: Renal hypercalciuria
- Malabsorption syndromes: Celiac disease, inflammatory bowel disease, gastric bypass surgery, cystic fibrosis
- Vitamin D (25-OH) deficiency/insufficiency: Deficiency commonly defined as <20 µg/L Insufficiency commonly defined as 20-30 µg/L
Asymptomatic disease: Indications for surgery

- Age <50 \( (is \ 70 \ the \ new \ 50?) \)
- Osteoporosis (distal 1/3 radius most sensitive)
- Calcium > than upper limits nl
- Compression fractures
- Renal insufficiency, GFR <60
- Urine Ca >400
- Renal stones—silent stones on renal imaging
Asymptomatic PHPT: other candidates

Recommendations 3-8, 3-9, 3-10

• Unable or unwilling to comply with observation protocols
• Neurocognitive and/or neuropsychiatric symptoms that are attributable to PHPT
• Surgical candidates with cardiovascular disease who might benefit from mitigation of potential cardiovascular sequelae other than hypertension
• Nontraditional symptoms of muscle weakness, functional capacity, abnormal sleep patterns, gastroesophageal reflux and fibromyalgia symptoms should be considered in the decision for parathyroidectomy
### Table 1. Guidelines for Surgery in Asymptomatic PHPT: A Comparison of Current Recommendations With Previous Ones

<table>
<thead>
<tr>
<th>Measurement(^b)</th>
<th>1990</th>
<th>2002</th>
<th>2008</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium ((&gt;) upper limit of normal)</td>
<td>1–1.6 mg/dL (0.25–0.4 mmol/L)</td>
<td>1.0 mg/dL (0.25 mmol/L)</td>
<td>1.0 mg/dL (0.25 mmol/L)</td>
<td>1.0 mg/dL (0.25 mmol/L)</td>
</tr>
<tr>
<td>Skeletal</td>
<td>BMD by DXA: Z-score (&lt;-2.0) (site unspecified)</td>
<td>BMD by DXA: T-score (&lt;-2.5) at any site(^b)</td>
<td>BMD by DXA: T-score (&lt;-2.5) at any site(^b)</td>
<td>A. BMD by DXA: T-score (&lt;-2.5) at lumbar spine, total hip, femoral neck, or distal 1/3 radius(^b)</td>
</tr>
<tr>
<td>Renal</td>
<td>A. eGFR reduced by (&gt;30%) from expected</td>
<td>A. eGFR reduced by (&gt;30%) from expected</td>
<td>A. eGFR (&lt;60) cc/min</td>
<td>B. Creatinine clearance (&lt;60) cc/min</td>
</tr>
<tr>
<td></td>
<td>B. 24-h urine for calcium (&gt;400) mg/d ((&gt;10) mmol/d)</td>
<td>B. 24-h urine for calcium (&gt;400) mg/d ((&gt;10) mmol/d)</td>
<td>Previous fragility fracture(^c)</td>
<td>B. 24-h urine for calcium (&gt;400) mg/d ((&gt;10) mmol/d) and increased stone risk by biochemical stone risk analysis(^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT</td>
</tr>
</tbody>
</table>

| Age, y           | \(<50\)                      | \(<50\)                      | \(<50\)                      | \(<50\)                      |

Abbreviations: eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging. Patients need to meet only one of these criteria to be advised to have parathyroid surgery. They do not have to meet more than one.
### Monitoring Recommendations

<table>
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<tr>
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<tbody>
<tr>
<td>Serum calcium</td>
<td>Biannually DXA, annually</td>
<td>Biannually DXA, annually (3 sites)</td>
<td>Annually DXA, every 1–2 y (3 sites)(^a)</td>
<td>Annually Every 1–2 y (3 sites),(^a) x-ray or VFA of spine if clinically indicated (eg, height loss, back pain)</td>
</tr>
<tr>
<td>Skeletal</td>
<td>(forearm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>eGFR, annually; serum</td>
<td>eGFR, not recommended; serum creatinine,</td>
<td>eGFR, not recommended; serum creatinine,</td>
<td>eGFR, annually; serum creatinine, annually. If renal stones suspected, 24-h biochemical stone profile, renal imaging by x-ray, ultrasound, or CT</td>
</tr>
<tr>
<td></td>
<td>creatinine, annually</td>
<td>annually</td>
<td>annually</td>
<td></td>
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</tbody>
</table>

\(^a\) The number of sites should be determined based on the specific indication and clinical setting.
4th Int. Panel Surgical Indications (2)

- Include imaging for occult renal stones as part of initial work up

- Surgery is also indicated for patients if surveillance is not possible or for patients who wish to proceed with surgery as long as the patient does not have prohibitive medical risk factors

- Surgery is always an option because it is the only definitive therapy for PHPT.
Special considerations

- Lithium induced disease
- MEN1
- MEN2
- Hyperparathyroidism-jaw tumor syndrome
- Familial isolated hyperparathyroidism
- Parathyroid cancer

- All need to be considered prior to intervention as this can affect the planning and intervention in regards to surgery
Parathyroid imaging

- Ultrasound
- Nuc med
- 4D CT
  - Nuc Med fused with CT
- Limited value
  - MRI (some promise?)
  - Venous sampling
Guideline Panel Findings (2)

- Cervical ultrasonography or other high-resolution imaging is recommended for operative planning.

- Imaging only ordered once decision for surgery made. Patients with non-localizing imaging remain surgical candidates.

- Preoperative parathyroid biopsy should be avoided.

- Surgeons who perform a high volume of operations have better outcomes.
Surgical approach

- Gold standard has been bilateral 4 gland exploration
  - Many use in combination with imaging and IOPTH
- Focused minimally invasive approach: should employ IOPTH
  - Less invasive
  - Should result in fewer complications
  - Need low threshold to convert to BE
  - Same day discharge safe and encouraged
- Both with excellent rates of cure 95-99%
Surgical Complications

• Failed operation
• Hypocalcemia—transient
• Hypoparathyroidism
• Hematoma
• Infection
• Injury to the recurrent laryngeal nerve
Guideline Panel Findings (3)

• Both focused, image-guided surgery (minimally invasive parathyroidectomy) and bilateral exploration are appropriate operations that achieve high cure rates.

• For minimally invasive parathyroidectomy, intraoperative parathyroid hormone monitoring via a reliable protocol is recommended.

• Minimally invasive parathyroidectomy is not routinely recommended for known or suspected multigland disease.
Guideline Panel Findings (4)

- *Ex vivo* aspiration of resected parathyroid tissue may be used to confirm parathyroid tissue intraoperatively.

- Clinically relevant thyroid disease should be assessed preoperatively and managed during parathyroidectomy.

- Familial pHPT, reoperative parathyroidectomy, and parathyroid carcinoma are challenging entities that require special consideration and expertise.

- The possibility of multigland disease should be routinely considered.
Guideline Panel Findings (5)

- Devascularized normal parathyroid tissue should be autotransplanted.
  - Arm vs Neck

- Postoperatively:
  - Calcium supplementation may be indicated
  - Patients should be observed for hematoma
  - Patients should be evaluated for hypocalcemia and symptoms of hypocalcemia
Definition of Cure

• Surgical cure of PHPT is defined as a return to enduring normocalcemia.

• Initial postoperative results (serum calcium) may be misleading, thus the 6 month time point is the accepted standard for defining cure vs. failure of operative intervention.

• Although normalization of iPTH is desirable, it is NOT a required or defined component of cure.
Normocalcemic PHPT

- **Normocalcemic PHPT** is defined as normal serum calcium levels with elevated iPTH levels in the absence of secondary causes of HPT.
  - The definition of cure must be modified when compared to classic PHPT.

- **Recommendation**: In normocalcemic PHPT, the classic definition of cure as normocalcemia > 6 months after surgery should also include normalization of iPTH > 6 months. *(Insufficient evidence)*
Normocalcemic PHPT
Secondary causes to exclude

- Vitamin D deficiency: inverse relationship between PTH and 25-hydroxyvitamin D.

- Reduced creatinine clearance: PTH begins to rise with a GFR <60 cc/min.

- Hypercalcuria as a primary renal abnormality can be associated with a secondary rise in PTH levels

- Gastrointestinal disorders associated with calcium malabsorption (eg bypass surgery)

- Medications: HCTZ and lithium (hold for 3 months)
Management Normocalcemic Disease

• In some will see progression of the disease leading to consideration for surgery despite normocalcemia
  • worsening bone density, a fracture, or a kidney stone

• Others will develop hypercalcemia that then can enter classic guideline driven management

• Consideration to intervene surgically with caution.
  • Typically multigland disease at time of surgery.

Reoperative parathyroid surgery

- Operation on any pt with previous procedure that put the RLN at risk
- Work up biochemically and confirm indication for surgery
- Many instances surgery not recommended unless at least one image positive
- Success rates 80% in expert hands (compared with 95-99% for initial procedures)
- Referral to expert surgeon recommended
Algorithm for the Evaluation and Management of Persistent or Recurrent PHPT

Patient with suspected persistent or recurrent pHPT

Confirmation of diagnosis

No

Continue routine follow-up

Review previous images, operative reports, pathologic test results, and vocal cord function examination results

Meets criteria for subsequent operation

No

Continue routine follow-up and nonoperative management

Patient is an operative candidate

Noninvasive imaging studies

Does not localize

Consider invasive imaging

Localizes

Subsequent parathyroidectomy (IPM suggested)
Anatomical Relationships of Eutopic & Ectopic Parathyroid Glands
Parathyroid Cancer (PCA)

• Presenting signs and symptoms overlap with benign disease

• Skeletal and renal symptoms may or may not be present

• Labs are more severe (but not always)
  • Serum calcium typically >14.0 mg/dL

• Symptoms of mass effect or invasion

• Palpable neck mass

• Imaging may reveal an irregular, invasive lesion
PCA Recommendations

Strong recommendation, moderate-quality evidence

• The diagnosis should be considered in patients with markedly elevated PTH or serum calcium levels.

• When PCA is suspected before surgery, diagnostic percutaneous biopsy should not be performed.

• Complete resection enhances the likelihood of cure and may require en bloc resection of thyroid tissue or the recurrent nerve.

• Prophylactic central or lateral neck dissection should not be performed.
PCA Recommendations

Strong recommendation, moderate-quality evidence

• Adjuvant external beam radiation should not be routinely given after surgical resection.

• External beam radiation should be used only as a palliative option in patients with locally advanced and inoperable disease.

• Patients with functional cancers should under regular surveillance by serum calcium and PTH testing following attempted curative surgery.
I am an Endocrine Surgeon: AAES

http://www.endocrinediseases.org
Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop

The AAES Guidelines for Definitive Management of Primary Hyperparathyroidism

Summary:

• Diagnosis of hyperparathyroidism should prompt a surgical referral

• Imaging should be ordered only after the decision for surgery is made--best directed by the surgeon

• Surgical intervention minimally invasive and outpatient for many

• In expert hands cure rates are excellent with low risk of complication
Appendix
Case example

- 50 yr old presented with:
  - palpable mass left neck,
  - symptoms of compression,
  - TSH nl

- Ultrasound:
  - complex cystic thyroid left mass 7 cm with calcifications,

- FNA: Bethesda IV (no molecular sample obtained)

- Pre op labs:
  - elevated calcium and PTH—final work up confirmed pHPT

- Nuclear imaging obtained; compared with US
  - Suggested right parathyroid adenoma
Nuclear medicine scan

15 Minute Delay

2 Hour Delay
Surgical and Path Findings

- Surgical exploration for parathyroid
  - 800 mg adenoma, rt superior position; PTH no drop
- Further exploration:
  - rt inferior gland nl, left superior nl, left inferior not identified
- Completed left lobectomy as planned and checked PTH which dropped by 50%, no further exploration
- Final path:
  - double adenomas, left mass cystic parathyroid adenoma
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