Indications for surgery for asymptomatic primary hyperparathyroidism

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Goals

- Describe pathophysiology of primary hyperparathyroidism (PHPT)
- Describe the symptoms of PHPT
- If a patient has asymptomatic PHPT when should they be referred to surgery?
- Role of localization studies for focused parathyroid surgery
- Should intraoperative parathyroid hormone assay measurement be routinely used in parathyroidectomy?
Case

- 66 year old male with PMH of HTN, DM, developmental delay (lives in nursing home), BPH and severe osteopenia had presented with elevated Ca and PTH.
- No PSH
- PE
- Non verbal thin, frail, elderly gentleman with poor dentition
- Pectus Carinatum
- Otherwise normal physical exam
Case

- Ca 10.9
- PTH 123
- Normal Vitamin D level (not provided in medical chart)
- CT scan showed 1 cm mediastinal mass
- Sestimibi showed 9mm foci in anterior mediastinum.
Case

- He underwent left VATs resection of anterior mediastinal mass
- Preoperative PTH 129, no access to intraoperative PTH level testing
- Frozen section showed parathyroid tissue
- Final pathology: parathyroid gland 1.2cm
- POD#2 sent home, PTH 17
Figure 15.11 Migration of the thymus, parathyroid glands, and ultimobranchial body. The thyroid gland originates in the midline at the level of the foramen cecum and descends to the level of the first tracheal rings.
Etiology

- Primary (Increased PTH, Increased Ca, Decreased phos)
- Secondary (Increased PTH in response to low Ca)
  - Renal Failure
  - Vitamin D deficiency
- Tertiary (continued excess PTH secretion to chronic secondary hyperparathyroidism)
Primary Hyperparathyroidism Classification

- Solitary adenoma 80-85%
- Double Adenoma 5-10%
- Four-gland Hyperplasia 5-10%
- Parathyroid carcinoma 1%
## Who Has Hyperparathyroidism?

<table>
<thead>
<tr>
<th></th>
<th>Serum Calcium Normal 8.5-10.4</th>
<th>Serum PTH Normal 10 to 65</th>
<th>Parathyroid disease?</th>
<th>Needs an operation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.4</td>
<td>121</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>10.5</td>
<td>97</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>11.1</td>
<td>55</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>10.3</td>
<td>100</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>5</td>
<td>11.8</td>
<td>158</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>12.1</td>
<td>50</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>7</td>
<td>10.9</td>
<td>40</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>8</td>
<td>11.4</td>
<td>30</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>9</td>
<td>10.2-11.6</td>
<td>85</td>
<td>Y if over 25</td>
<td>Y</td>
</tr>
<tr>
<td>10</td>
<td>9.8-10.2</td>
<td>100</td>
<td>Possibly</td>
<td>Possibly</td>
</tr>
<tr>
<td>11</td>
<td>9.5-10.2</td>
<td>40</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>
Symptomatic PHPT

Nervous System Problems
- fatigue
- depression
- irritability
- worsening short term memory
- worsening concentration
- “brain fog”

Bone and Joint Problems
- weakening of the bones
- joint and bone pain

Kidney Problems
- kidney stones
- urinating more frequently
- kidney disease

Muscle Problems
- weakness
- muscle aches

Digestive Problems
- abdominal pain
- nausea
- vomiting
- constipation
- ulcers
- pancreatitis
Asymptomatic PHPT

- Hypertension
- Left ventricular hypertrophy, valvular or myocardial calcification
- Peptic ulcer disease
- Pancreatitis, gout, pseudogout
- Normocytic normochromic anemia
- Weakness, easy fatigability, Anxiety
- Cognitive difficulties
- Somatic complaints and clinical depression
# Comparison of New and Old Guidelines for Surgery

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Serum Ca greater than upper limit of normal</td>
<td>1-1.6mg/dl (0.25-0.4 mmol/Liter)</td>
<td>1.0mg/dl (0.25mmol/liter)</td>
<td>1.0 mg/dl (0.25 mmol/liter)</td>
</tr>
<tr>
<td>24 hr urine for calcium</td>
<td>&gt;400 mg/d (&gt;10mmol/d)</td>
<td>&gt;400 mg/d (&gt;10mmol/d)</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Reduced by 30%</td>
<td>Reduced by 30%</td>
<td>Reduced by 30%</td>
</tr>
<tr>
<td>BMD</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</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

Bilezikian et al J Clin Endocrin Metab 2009
If a patient has asymptomatic PHPT when should they be referred to surgery???

- Age <50
- No ability for appropriate follow up
- Serum Ca >1 mg/dl above normal
- Urine Ca >400 mg/24 hr or above high normal lab limit
- 30% decrease in renal function
- Complications of PTHP, nephrocalcinosis, osteoporosis, or severe psychoneurologic disorder

Udelsman et al J Clin Endocrin Metab 2009
Benefits to Parathyroidectomy

- Resolution of neuropsychiatric symptoms
- Improved quality of life
- Prolongs survival
- Reduced cardiovascular incidents
- Improved renal and bone density
- Cost of parathyroidectomy at 5 years is less than the cost of surveillance
Sestimibi Scan

- Two approaches dual radionuclide with subtraction imaging (I-123 or Tc-99m pertechnetate)

- Single radiotracer with early and delayed imaging (dual phase)

- Limitations of thyroid pathology or other metabolically active tissue can be overcome with double tracer subtraction technique
Ultrasound

- Abnormal parathyroid tissue exhibits hypoechogenic pattern

- Operator dependant
4D CT

- Relies on the vascularity of the parathyroid glands and their relative enhancement with contrast compared to the surrounding structures.

- 4D shows changes in perfusion of contrast over time to the 3D anatomic CT images.
Selective Venous Sampling and Arteriography

- Selective arteriography in conjunction with venous sampling for PTH
  - Requires catheterization of multiple veins in the neck and mediastinum, from which blood samples are obtained with rapid PTH measurement in angio suite
  - Parathyroid adenomas have increased vascularity, demonstrating a characteristic blush on arteriography
  - Indicated for patients requiring re-exploration with negative or discordant imaging studies

Figure 4. Selective venous sampling for intact PTH measurement around the parathyroid. SVC: Supra Vena Cava. IVC: Inferior Vena Cava.
Intraoperative Radioguidance

The procedure involves giving a small injection of Tc-99m sestamibi (the same agent used for the sestamibi scan, just a smaller dose) the morning of surgery. A gamma intraoperatively to guide incision placement as well as to direct the dissection, allowing the surgeon to focus in on the location of the abnormal parathyroid tissue.
<table>
<thead>
<tr>
<th>Imaging</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sestamibi</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Safe</td>
</tr>
<tr>
<td>Sestamibi SPECT</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td>Safe</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Safe</td>
</tr>
<tr>
<td>4D-CT</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Radiation</td>
</tr>
<tr>
<td>MRI</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Safe</td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Very High</td>
<td>Hematoma, CVA, nephropathy</td>
</tr>
<tr>
<td>Venous Localization</td>
<td>High</td>
<td>High</td>
<td>Very High</td>
<td>Hematoma, nephropathy</td>
</tr>
<tr>
<td>US guided Biopsy</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td>Hematoma, Infection</td>
</tr>
</tbody>
</table>
Should intraoperative PTH measurement be routinely used in all cases of parathyroidectomy?

Table 1. Relationship Between Imaging Findings and Surgical Outcome for Parathyroidectomy in Patients With Primary Hyperparathyroidism

<table>
<thead>
<tr>
<th>Imaging Findings</th>
<th>Patients, No. (%)</th>
<th>Patients With Correct Localization, No. (%)</th>
<th>Patients With Incorrect Localization, No. (%)</th>
<th>Patients With Surgical Failure, No. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIBI and US imaging positive for same site (concordant)</td>
<td>322 (57)</td>
<td>319 (99)†</td>
<td>3 (1)†</td>
<td>3 (1)‡</td>
</tr>
<tr>
<td>MIBI and US imaging discordant</td>
<td>201 (35)</td>
<td>125 (62)</td>
<td>76 (38)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>MIBI and US imaging negative (no localization)</td>
<td>46 (8)</td>
<td>NA</td>
<td>46 (100)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>569 (100)</td>
<td>444 (78)</td>
<td>125 (22)</td>
<td>10 (2)</td>
</tr>
</tbody>
</table>

Abbreviations: MIBI, technetium Tc 99m sestamibi; NA, not applicable; US, ultrasonography.

*Surgical failure indicates persistent hypercalcemia after parathyroidectomy.

†P < .001 vs discordant imaging.

‡P = .08 vs discordant imaging.
Sestamibi –
SPU +
(n = 38)

IOPTH falls
(n = 27)

True Positive
(n = 27)

False Positive
(n = 0)

IOPTH does not fall
(n = 11)

True Negative
(n = 10)

False Negative
(n = 1)

Sestamibi +
(n = 242)

IOPTH falls
(n = 221)

True Positive
(n = 220)

False Positive
(n = 1)

IOPTH does not fall
(n = 21)

True Negative
(n = 3)

False Negative
(n = 18)

Question

- A 45 year old perimenopausal woman is referred for possible parathyroidectomy. Her serum calcium has ranged from 9-9.5mg/dl for the last 12 months. Additional lab values include chloride=100, PO4 3.4, PTH= 90. Bone density confirms osteopenia of the femoral neck. Sestamibi does not localize. Which of the following would you recommend?
Question

- A. parathyroidectomy
- B. Hormone replacement therapy
- C. Cinacalcet
- D. Bisphosphonates
- E. Measure vitamin D levels
During neck exploration for symptomatic primary hyperparathyroidism in a 68 yr old woman, normal bilateral superior and inferior parathyroid glands are identified. They are confirmed by frozen section to be parathyroid tissue. The left inferior parathyroid cannot be identified, despite careful examination of the lower pole of the thyroid and surrounding tissue. Which of the following is the most likely location for the missing inferior parathyroid?
Question

A. Carotid

B. Posterior to the inferior thyroid artery

C. Intrathyroidal

D. Thymus