Optimizing Parathyroid Surgery

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Objectives

• Diagnosis
• Operative indications
• Goals to Guide Optimal Care
  – Surgical Planning
  – Anatomy and Pathology
Unequivocal Diagnosis

• **Essential tests:**
  – Calcium
  – PTH
  – 24 hour urinary calcium
    • <50 mg/24 hr pathognomonic for FHH

• **Important tests:**
  – Ionized calcium
    • Often elevated with normal total calcium even with a normal albumin

**Normohormonal hyperparathyroidism**
**Normocalcemic hyperparathyroidism**
Operative Indications

• Signs/symptoms
  – Renal stones
  – Bone pain
  – Pancreatitis
  – Constitutional Symptoms
    • Fatigue
    • Loss of focus
1. Unequivocal Diagnosis
2. Decision regarding surgical candidacy

Yes Imaging

No Observation*

*(25-33% disease progression)
Goals of Initial Parathyroid Surgery for Primary Hyperparathyroidism

• 1. Efficacy – **High rate of cures** which should be achievable in this benign disease
• 2. Safety – **Low morbidity** and low complication rate including cosmesis
• 3. Cost – **Cost effective** procedure to achieve the above goals
Goal #1 : Efficacy

• Dependent on the ability to correctly identify and resect all abnormal parathyroid tissue
  – Pre-operative imaging
  – Intra-operative tools

• Operative Failures
  – Single adenoma not found
  – Multi-gland disease not appreciated
Goal #1: Efficacy

Major challenges in parathyroid surgery

- Ectopic gland locations including supranumery glands
- Multi-glandular disease

- Single adenoma - 84.0% (1404)
- Double adenomas - 8.7% (132)
- Hyperplasia - 7.3% (120)

*n=1656
Goal # 1 : Efficacy - Localization

“In my opinion, the only localizing study indicated in a patient with untreated primary hyperparathyroidism is to localize an experienced parathyroid surgeon”

John Doppman, MD 1986
Chief of Radiology, NIH

• Knowledge
  – Experience (>20, >50/year)
  – Lessons from re-operative surgery

• SestI-MIBI
• Neck Ultrasound
• 4-D CT SCAN
Normal Superior Glands
A – near cricothyroid posteriorly
B – behind the upper pole of the thyroid
C – behind the junction of the upper esophagus and lower pharynx in the midline

Normal Inferior Glands
1 – inferior pole of the thyroid
2 – intrathymic
3 – along the carotid artery

## Location of Ectopic Parathyroid Glands

<table>
<thead>
<tr>
<th>Inferior</th>
<th>Superior</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thymus <em>(38%)</em></td>
<td>1. TE groove</td>
<td>1. Carotid bifurcation*</td>
</tr>
<tr>
<td>2. Thyroid <em>(18%)</em></td>
<td>2. Retroesophageal region <em>(31%)</em></td>
<td>2. Posterior triangle of the neck</td>
</tr>
<tr>
<td>3. Thyrothymic ligament</td>
<td>3. Posterosuperior mediastinum <em>(6%)</em></td>
<td>3. Within the vagus nerve</td>
</tr>
<tr>
<td>4. Submandibular*</td>
<td>4. Paraesophageal region</td>
<td>4. Within the hypoglossal nerve</td>
</tr>
<tr>
<td>5. Thyroid gland <em>(18%)</em></td>
<td>5. Pericardium</td>
<td></td>
</tr>
<tr>
<td>6. Carotid sheath <em>(3%)</em></td>
<td>6. Right dome of the diaphragm</td>
<td></td>
</tr>
<tr>
<td>*Undescended <em>(6%)</em></td>
<td></td>
<td>7. Supraclavicular region</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracheo-esophageal groove</td>
<td>27</td>
</tr>
<tr>
<td>Intra-thymic</td>
<td>18</td>
</tr>
<tr>
<td>Normal upper</td>
<td>13</td>
</tr>
<tr>
<td>Normal lower</td>
<td>12</td>
</tr>
<tr>
<td>Intrathyroidal</td>
<td>10</td>
</tr>
<tr>
<td>Undescended</td>
<td>8.4</td>
</tr>
<tr>
<td>Carotid Sheath</td>
<td>3.7</td>
</tr>
<tr>
<td>Retro-esophageal</td>
<td>3.3</td>
</tr>
<tr>
<td>Aorto-pulmonary window</td>
<td>1.4</td>
</tr>
<tr>
<td>Strap muscles</td>
<td>1.4</td>
</tr>
<tr>
<td>Other</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Table 3. Selected Cited Estimates for Accuracy of First-line Imaging Modalities for a Patient with De Novo 1°HPTH

<table>
<thead>
<tr>
<th></th>
<th>Sestamibi Scintigraphy</th>
<th>Ultrasound</th>
<th>4D-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI) (16)</td>
<td>78.9% (64–90.6%)</td>
<td>76.1% (70.4–81.4%)</td>
<td>89.4%</td>
</tr>
<tr>
<td>Positive predictive value (95% CI) (16)</td>
<td>90.7% (83.5–96.0%)</td>
<td>93.2% (90.7–95.3%)</td>
<td>93.5%</td>
</tr>
<tr>
<td>Localization–correct side (single adenoma)</td>
<td>68% (27)</td>
<td>74% (27)</td>
<td>93.9% (57)</td>
</tr>
<tr>
<td>Localization–correct quadrant (single adenoma)</td>
<td>50% (27)</td>
<td>72% (27)</td>
<td>85.7% (57)</td>
</tr>
</tbody>
</table>

Figure 4. Imaging approach in an unexplored patient with a de novo diagnosis of primary hyperparathyroidism. Either scintigraphy or ultrasound may be the initial study of choice depending on local expertise and imaging quality; performing both ultrasound and scintigraphy as an initial evaluation is an acceptable alternative.

Comparison of advantages of focused neck exploration versus bilateral neck exploration

Advantages of FNE
- Smaller incision
- Shorter operative time
- Reduced cost compared with BNE
- Outpatient surgery
- Lower complication rate compared with BNE
- Reduced postoperative pain
- Cure rate equals BNE

Advantages of BNE
- May be done through small incision
- Shorter operative time
- Reduced cost compared with FNE
- May be done in outpatient setting
- Detects multigland disease better than FNE
- Does not require localization or IOPTH

Table 1. Comparison of Traditional Surgery to Minimally Invasive Parathyroidectomy

<table>
<thead>
<tr>
<th></th>
<th>Traditional Surgery</th>
<th>Minimally Invasive Parathyroidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation/workup</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Indications for surgery</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Preoperative imaging</td>
<td>Not required, often obtained</td>
<td>Always obtained</td>
</tr>
<tr>
<td>Operative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General anesthesia</td>
<td>Almost always</td>
<td>Not required</td>
</tr>
<tr>
<td>Bilateral exploration</td>
<td>Always</td>
<td>Not required in most cases</td>
</tr>
<tr>
<td>Extent of surgery</td>
<td>Moderate</td>
<td>Limited</td>
</tr>
<tr>
<td>Visualize all parathyroid glands</td>
<td>Always</td>
<td>Not required in most cases</td>
</tr>
<tr>
<td>Intraoperative PTH assay</td>
<td>May be used</td>
<td>Essential</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient admission</td>
<td>Often</td>
<td>Rare</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Economic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cost (including intraoperative PTH, imaging, stay length, etc.)</td>
<td>Decreased; mean savings of $1471/case vs traditional approach (2)</td>
<td></td>
</tr>
</tbody>
</table>

Note that traditional bilateral cervical exploration may be required in patients with a history of prior neck surgery or remedial, recurrent, or multigland parathyroid disease.


Multigland Disease

- Pre-operative Imaging
- Gamma probe during surgery
- Intra-operative PTH monitoring
South Florida series

- Conversion of unilateral approach to bilateral approach associated with an increased cure rate
- Recurrence rate over time for unilateral vs bilateral neck exploration
Intra-operative PTH Monitoring

- Half-life of PTH is 3 to 3.5 minutes
- Rapid (20-30 min) and accurate commercial assays available
- Initial guidelines (Miami rules):
  - Obtain baseline, “gland manipulation level” and 5-10 minutes and 20 minutes post-resection
  - Cured if > 50% decrease from maximal level
523 patients with IOPTH after removal of a single adenoma

- 439 pts >50% decrease to normal range
  - All cured with single adenoma excision
- 31 pts >50% decrease but above the normal range
  - 22 single adenoma
- 53 pts <50% drop in initial PTH
  - 17 single adenoma
  - 36 multi-gland disease
  - 9 multi-gland disease, 8 double adenoma, and 1 hyperplasia
IOPTH Monitoring and Final Pathology

- Single Adenomas: 60%
- Double Adenomas: 35%
- Hyperplasia: 5%

No. of patients

Glandular Pathology

Single Adenomas
Double Adenomas
Hyperplasia
IOPTH Monitoring and Final Pathology

• Most patients whose IOPTH decreases by greater than 50%, even with failure of levels to return to normal range, will have single adenomas.

• Adherence to the “50% rule” of IOPTH drop as indicative of cure when levels fail to normalize however can lead to an appreciable number of unrecognized cases of multi-glandular disease.

• Failure of IOPTH to return to normal range even with >50% drop from baseline should raise suspicion for additional abnormal glandular tissue, particularly in patients with normal renal function and lower level baseline IOPTH values.
Intra-Operative PTH Assay

• Penn rules:
  – Obtain pre-op baseline PTH level
  – Obtain post-resection PTH level 12-15 minutes after clipping pedicle
  – Post-resection level must decrease by at least 50% and be in the normal range for that assay
  – If not, re-draw level and consider re-exploration
  – All blood drawn from peripheral veins
Use IOPTH for Venous Mapping/Localization

• Unable to find one or more glands and no abnormal gland identified
  – Draw PTH from inferior RIJ, LIJ, and peripheral
  – If lateralizes to one side (>2-fold gradient) then do directed exploration
  – Consider high IJ versus low IJ for undescended glands
  – If no lateralization and RIJ=LIJ=Peripheral consider transcervical thymectomy for mediastinal gland
Goal # 2: Safety

- Potential morbidities
  - Recurrent laryngeal nerve
  - Fracture of gland and “parathyromatosis”
  - Incomplete excision of adenoma
  - Cosmetically important area
Goal # 2: Safety - Recurrent Laryngeal Nerve (RLN)

- The incidence of RLN injury should be 0%.
- Often close to superior parathyroid adenomas particularly when they are located in the deep T-E groove.
Goal # 2: Parathyromatosis

• Fracture of a parathyroid adenoma can lead to implantation with diffuse disease
• More common with secondary HPT
• Must be treated like parathyroid cancer with extensive local resection
Goal # 2: Local Recurrence

- NIH review of parathyroid cancers
  - N=22
  - 15 of 22 re-classified as a locally recurrent adenoma
  - Time interval 6 to 240 months
  - No pathologic evidence of carcinoma; evidence of scar/old suture
  - Bilobed glands

Minimally Invasive Parathyroidectomy (MIP)

- Pre-operative localization (nuclear scan and ultrasound)
- If solitary abnormal gland *can* use conscious sedation
- Use IOPTH with “Penn” rules
- Make 2-3 cm incision in non-tension skin line
- To allow bilateral exploration through a 3 cm incision raise long subplatsymal flaps in all directions
- Local anesthetics are given at the end of the procedure and patients have minimal discomfort
Goal # 3: Cost-Effectiveness

### Table 2. Comparison of Features, Radiation Dose, and Cost for Parathyroid Imaging

<table>
<thead>
<tr>
<th>Method</th>
<th>Relative Advantages</th>
<th>Relative Disadvantages</th>
<th>Calculated Effective Radiation Dose (Ref.)</th>
<th>Medicare Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical ultrasound</td>
<td>Widely available, no radiation</td>
<td>User-dependent interpretation, limited evaluation ectopic glands</td>
<td>None</td>
<td>$125.10</td>
</tr>
<tr>
<td>Sestamibi scintigraphy</td>
<td>Ease of interpretation, assessment for ectopic glands</td>
<td>Radiation, cannot assess thyroid</td>
<td>Sestamibi/SPECT, 6.7–7.8 mSv (58, 71); SPECT/CT, +.9 mSv (72)</td>
<td>$546.76; sestamib alone, $262.53</td>
</tr>
<tr>
<td>CT</td>
<td>Assessment for ectopic glands</td>
<td>Radiation, limited sensitivity</td>
<td>~3–6 mSv (71); varies by protocol</td>
<td>$371.85</td>
</tr>
<tr>
<td>4D-CT</td>
<td>Increased anatomical detail, assessment for ectopic glands</td>
<td>Significant radiation to thyroid, not widely available</td>
<td>10.4 mSv (58)</td>
<td>$424.51</td>
</tr>
<tr>
<td>MR Catheter-based localization</td>
<td>Assessment for ectopic glands Less affected by prior interventions, wide assessment for ectopic glands</td>
<td>Limited sensitivity High level of expertise required</td>
<td>None ~.8–19.6 mSv (71); varies by case</td>
<td>$644.33 $2,310.85</td>
</tr>
</tbody>
</table>

Cost figures listed are current aggregate Medicare reimbursement rates for technical and professional fees. Note that effective total radiation dose is not reflective of absorbed dose to an individual organ or tissue (see Axial Imaging). For comparison, average natural background radiation in the United States is approximately 3.1 mSv/y.
## Cure Rates for Initial HPT Surgery in Current Series

<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>% cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Florida</td>
<td>2200</td>
<td>97.5</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>916</td>
<td>98.3</td>
</tr>
<tr>
<td>University of Wisconsin</td>
<td>254</td>
<td>98.0</td>
</tr>
<tr>
<td>Yale</td>
<td>980</td>
<td>98.1</td>
</tr>
<tr>
<td>Penn</td>
<td>1410</td>
<td>99.6</td>
</tr>
</tbody>
</table>
Algorithm for Surgical Approach to HPT

1. Patient with biochemical diagnosis of HPT and meets criteria for surgery
   - Office-based ultrasound or Sestamibi / ultrasound
     - Solitary imaged abnormal parathyroid
       - MIP
     - Negative Imaging
       - Outpatient neck exploration under general anesthesia
     - Multiple abnormal glands

Re-Operative Parathyroid Surgery

• Wait as long as possible
• Localization is a MUST
  – High volume parathyroid surgeon
  – Imaging
    • 4D
    • Selective venous sampling
Case Report

49 yo man with h/o depression for 4y.

Mild HPTH.

+localized NM
(-) localization US

→ Exploration
2/14/20XX.
Conclusions

• Minimally invasive parathyroidectomy appropriate for the majority of patients
• Utilize sestamibi and intra-operative PTH
• Respect multi-gland disease
• Always localize for re-operative surgery
• Every patient with PHPT should be offered the opportunity to discuss risks and benefits of surgery with an endocrine surgeon