1. Introduction

- Review Pathophysiology and Pathology as it relates to surgical treatment strategy
- Review Traditional Treatment
- Discuss the Rationale for a “Minimally Invasive Approach” and its limitations
- Describe the University of Louisville Experience and Results
- Discuss Future Possibilities

2. Epidemiology of Hyperparathyroidism

- Approximately 20,000 new cases of hyperparathyroidism diagnosed yearly (compared to 12,000 cases of laryngeal cancer).
- More common in women (2-3:1)
- 80 percent of cases are isolated/20 percent of cases are familial
- Incidence increases with age

3. Pathophysiology of Primary Hyperparathyroidism

- Autonomous activity of one (90 percent) or more (10 percent) of the parathyroid glands
- Microleaks of calcium in the proximal renal tubules is noted early in the process and is implicated
- Parathyroid tumors exhibit genetic aberrancies in the prad-1 oncogene (cyclin D1)
Effects of Parathyroid Hormone on End-Organs *(William’s Textbook of Endocrinology)*

\[
\begin{align*}
\text{Ca} & \quad \text{ECF Ca} \\
\text{PTH} & \quad 1.25 D
\end{align*}
\]

Indications for Surgery in Hyperparathyroidism *(NIH Consensus Statement)*

- **TABLE 26-1** – Indications for Surgery in Primary Hyperparathyroidism
  
  1. Overt clinical manifestations of primary hyperparathyroidism
  - a. Radiographic nephrolithiasis or otherwise documented kidney stone(s)
  - b. Reduced creatinine clearance (not otherwise explained)
  - c. Radiographically evident hyperparathyroid bone disease
  - d. Classical hyperparathyroid neuromuscular disease
  - e. Symptoms attributable to hypercalcemia per se
  - f. Previous episode of life-threatening hypercalcemia
  2. Serum calcium concentration greater than 12 mg/dL (2.99 mM)
  3. Urinary calcium excretion greater than 400 mg/day (9.98 mmol/day)
  4. Low or declining bone mineral density
    - a. Less than 2 SDs below age/sex-matched controls (any site) or
    - b. Vertebral osteopenia
    - c. Declining vertebral bone density
  5. Age younger than 50 years
  6. Uncertain prospect for successful medical monitoring
    - a. Patient requests surgery
    - b. Consistent follow up seems unlikely
    - c. Coexistent illness that may contribute to, or confound detection of, disease progression

“Traditional” Surgical Approach

- Based on poor localization studies (“The best test to locate the parathyroid glands is to ‘locate’ and experienced parathyroid surgeon...”)
- Bilateral exploration with identification of four glands to define the process as adenoma or hyperplasia
- Unilateral exploration, based on luck or some localization (i.e., Technetium-Thallium subtraction scan or U/S) with identification of a diseased gland and at least one suppressed gland

Finding the Gland can be less than Straightforward

- Related to blood supply-Inferior thyroid artery from the thyrocervical trunk a branch of the first segment of the subclavian artery.
- Ectopic locations
- Variable relationships to Recurrent (inferior) laryngeal nerve
Ectopic Parathyroid Location

Parathyroid Adenomas at Reoperation

What has changed the tradition?

- Improved understanding of the incidence, etiology and pathophysiology of the parathyroid glands and the predilection for single gland disease
- Improved localization studies
- "Sentinel" lymph node technology with wider accessibility to surgeons
- Biotechnology with ability to use radioisotopes and gamma probes and/or cameras in the operating room
Parathyroid Localization Studies: successes and failures

- Gold Standard: Experienced Surgeon
- Moderately Helpful:
  - Technetium-Thallium Subtraction Scan – unacceptable false negative rate
  - Ultrasound – useful, but user experience dependent
- Disappointments:
  - Computed Tomography (selective use, mediastinal)
  - Magnetic Resonance Imaging

The Technetium-99m Sestamibi Scan (Parathyroid scan)

- Based on the affinity of the colloidal form of the isotope for mitochondria
- Based on the high density of mitochondria in the chief cell (oncocyes) of a parathyroid adenoma
- Superior ability to localize parathyroid adenomas to the previous subtraction scan
- 90% for single adenomas, 55% for abnormal glands in patients with multiglandular disease and 75% for recurrent hyperparathyroidism; the specificity for primary adenomas has been shown to be as high as 98%

Parathyroid-Sestamibi Scan and Ultrasound

Demonstrating a “Double adenoma.”
Evidence of a Positive Sestamibi Scan with both early and late increased uptake in the right inferior parathyroid gland. Surgical extirpation demonstrated a single adenoma.

Example of an equivocal Tc99m Sestamibi scan with evidence of assymetrical uptake at 90 minutes being greater on the right side.

Primary Hyperparathyroidism: Treatment Algorithm in Evolution

Case Example

- 46 year old woman with the symptoms:
  - Fatigue
  - Bone pain
  - History otherwise non-contributory
  - No family history of endocrinopathies

- Laboratory
  - Calcium 11.5 mg/dl (8.2-10.8 mg/dl)
  - iPTH 289 microIU/ml (ref.: 15-90)
Primary Hyperparathyroidism (n=427)

Positive Tc99m Sestamibi Scan (n=240)
Equivocal Tc99m Sestamibi Scan (n=105)
Negative Tc99m Sestamibi Scan (n=82)

Single adenoma (n=235)
Multiple adenoma (n=3)
Negative Exploration (n=2)

Multiple adenoma (n=10)
Hyperplasia (n=10)
Negative Exploration (n=2)

Normocalcemia (n=208)
Persistent Hypercalcemia (n=1)
Recurrent Hypercalcemia (n=2)
Persistent Hypocalcemia (n=3)
Normocalcemia with elevated PTH (n=25)
Normocalcemia with low PTH (n=1)

Normocalcemia (n=89)
Persistent Hypercalcemia (n=2)
Recurrent Hypercalcemia (n=1)
Persistent Hypocalcemia (n=1)
Normocalcemia with elevated PTH (n=5)
Normocalcemia with low PTH (n=2)

81 of 465 patients (as of 8-1-05) had a positive clinical and biochemical diagnosis of primary hyperparathyroidism and negative Tc99m Sestamibi scans (17.4%)

Calcium Outcomes
- Less than 8.5 mg/dl (low) – 2/50 (4%)
- 8.5-10.2 mg/dl (normal) – 43/50 (86%)
- 10.3 mg/dl or higher – 5/50 (10%)
Table 1. Summary of Complications based on preoperative Tc99m sestamibi scan cohort

<table>
<thead>
<tr>
<th>Category</th>
<th>Positive Tc99m sestamibi Cohort</th>
<th>Equivocal Tc99m sestamibi Cohort</th>
<th>Negative Tc99m sestamibi cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>240 (56%)</td>
<td>105 (25%)</td>
<td>82 (19%)</td>
</tr>
<tr>
<td>Temporary Hypocalcemia</td>
<td>1 (0.4%)</td>
<td>18 (17%)</td>
<td>15 (18%) (p&lt;0.01)</td>
</tr>
<tr>
<td>Permanent Hypocalcemia</td>
<td>3 (1.3%)</td>
<td>1 (1%)</td>
<td>2 (2.4%)</td>
</tr>
<tr>
<td>Temporary recurrent laryngeal nerve paralysis</td>
<td>3 (1.3%)</td>
<td>1 (1%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Permanent recurrent laryngeal nerve paralysis</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Wound seroma</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Wound infection with drainage</td>
<td>2 (0.8%)</td>
<td>0 (0%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Summary of Findings

- Equivocal Scans (ones with increased focal uptake, but in the face of increased background) are amenable to MIBI, but confidence is increased with use of intraoperative assessment of PTH (96%) can be rendered normocalcemic with a unilateral exploration with intraoperative PTH. Improvements in imaging technology may help drive more of these patients into the “positive scan,” cohort.
- Negative Scans provide a greater challenge to the surgeon. 62 percent still have single gland disease, but radioguidance and intraoperative PTH are less definitive in minimizing surgical exploration. Even with bilateral exploration, 10 percent of this population may remain hypercalcemic. Surgeon-driven V/S and enhanced imaging may make more patients amenable to unilateral exploration.

Advantages

- Focused minimal dissection in cases of primary hyperparathyroidism with single gland disease (adenoma-90 percent)
- Shorter operative time
- Decreased admissions
- Fewer cases of hypocalcemia
- Excellent long-term control of calcium in the context of limited exploration where possible
- Recurrent nerve injury comparable to the rate reported in the literature for parathyroid surgery.
Limitations/Challenges

- Smaller abnormal adenomas are less likely to have a positive Sestamibi scan.
- Resolution
- Sensitivity
- Patients who are taking Serotonin reuptake inhibitors for Depression are at a significantly higher risk (p<0.01) for developing postoperative neurological sequelae with the use of methylene blue infusion for enhanced gland localization (Otalaryngology—Head and Neck Surgery, Vol 135, No 5, November 2006.)
- Postoperative Normocalcemia with persistent elevation of PTH represents a challenging and frankly poorly understood entity; proponents and opponents to the role of hypervitaminosis D have emerged and the literature is full of debate. Persistent disease and hypervitaminosis D are our current best explanations for this finding.
- Optimal integration of preoperative imaging techniques and refinement of IOPTH incorporation into a surgical algorithm have yet to be defined.

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Suggested Selected Reading

1. Bumpous JM, Goldstein RE, Flynn MB: Surgical and calcium outcomes in 427 patients treated prospectively in an image-guided and intraoperative PTH (IOPTH) supplemented protocol for primary hyperparathyroidism: outcomes and opportunities. Laryngoscope 2008 (Accepted for publication)