Parathyroid Imaging: A Surgical Perspective

Brendan C. Stack Jr, MD, FACS, FACE

(1) Department of Otolaryngology-Head and Neck Surgery, (2) UAMS Thyroid Center
University of Arkansas for Medical Sciences, Little Rock, Arkansas
• provides educational presentations for Shire pharmaceuticals.
• Editor of “Medical and surgical treatment of Parathyroid disorders: an evidence based approach”
• Editor of “Neck Dissection”
• Research Support:
  Oncovision (loan of Sentinella device)
  Co-PI, ECOG/ACRIN 6685, U01 CA80098
  Co-investigator, 2R44CA168100-03A1 (Dynasil/RMD)
• SNNMI panel developing “Appropriate Use Criteria for Nuclear Medicine in the Evaluation and Treatment of Differentiated Thyroid Cancer”
Parathyroid Imaging

• What Do I need?
  – Shows precise anatomic (quadrant) location in 3 orthogonal planes
  – Projects onto a flat screen in the OR

• What can I live with?
  – Directs me to the correct side of the neck

• What would be my ideal parathyroid imaging tool?
  – Intraoperative, real-time, visualization of the offending adenoma(s) (excision) and visualization of normal glands (protection)
Work-up of Elevated Calcium

• **Parathyroid Fun Facts:**
  – Last endocrine gland discovered (1863)
  – Function of gland discovered 20 years later by a medical student
  – Not under pituitary control (CaSR)
  – Parathyroid surgery has less than a century tradition in the US
  – Last gland for which hormone replacement was clinically available/approved (2015)
Work-up of Elevated Calcium

• Pillars of Hypercalcemia
  – Outpatient
    • Hyperparathyroidism
      – Primary
        » Early presenting variants (normohormonal, normocalcemic)
  – Inpatient
    • Skeletal related events
      – Solid tumor metastases
Investigating the Potential Under-Diagnosis of Primary Hyperparathyroidism at UAMS

R.J. Quallap, Brendan Slack Jr., M.D., Melody Penning, PhD
Departments of Otolaryngology and Biomedical Informatics, University of Arkansas for Medical Sciences, Little Rock, AR

ABSTRACT

Primary hyperparathyroidism (PHPT) is a condition in which one or more parathyroid glands secrete excess amounts of parathyroid hormone (PTH). In short, PHPT is characterized by hypercalcemia/hyperparathyroidism with concurrent elevated PTH levels. This condition is known to increase the risk of cardiovascular disease, osteoporosis, psychiatric disturbances, and renal complications.1 As of now, the disease typically runs a long course before being identified and treated. Consequently, surgery is often the only viable treatment option for patients with this disease. Publications from other tertiary centers have identified a large-scale under-diagnosis of PHPT.2,3 To evaluate for potential similar under-diagnosis at UAMS, all patients from 2006-2018 with hypercalcemia and/or hyperparathyroidism (excluding those with known malignancies or other possible causes of excess calcium) were identified in electronic medical records. Subsequent investigation indicates that 72% of hypercalcemic/hyperparathyroidic patients did not receive follow up of their PTH levels.

RESULTS

From 2006-2018 at UAMS, 28,831 patients were identified to have hypercalcemia and/or hyperparathyroidism not explained by other medical conditions. Of these 28,831, only 7,994 subsequently had PTH levels tested. This finding leaves 20,847 that never had PTH levels drawn for follow up.

CONCLUSIONS

These data may indicate a massive under-diagnosis of primary hyperparathyroidism at UAMS. Literature review has show that other U.S. tertiary institutions have reported similar large-scale lack of follow up for the potential diagnosis of PHPT.

METHODS

All UAMS patients from 2006-2018 with hypercalcemia (total calcium > 10 mg/dL or ionized calcium > 1.33 mmol/L) and/or diagnosis of hyperparathyroidism were identified. Patients with pre-existing malignancy, vitamin D toxicity, hypermagnesemia, hyperphosphatemia, acute pancreatitis, active infection, heredodegen exposures, familial hypocalciuric hypercalcemia, Bartels syndrome, milk-alkali syndrome, and toxicity due to rifampin, aminoglycosides, bisphosphonates, or proton pump inhibitors were excluded. Then, it was determined what portion of the remaining patients were subsequently tested for PTH level abnormalities.

References

2. Chen et al., University of Alabama at Birmingham. Follow-Up Diagnosis: The Management of 31,742 Patients with Suspected Primary Hyperparathyroidism: Opportunities for System-Level Intervention to Increase Surgical Rates and Outcomes. 3. Fees et al., Cleveland, OH. The prevalence of undiagnosed and untreated primary hyperparathyroidism: a population-based analysis from the electronic medical record.
Work-up of Elevated Calcium

• Confirmation of Hypercalcemia
  – EMR search
  – Outside records
  – 2 or more episodes of elevated calcium
  – Repeat your own laboratories

• Confirmation of Primary Hyperparathyroidism
  – 1-2 paired Ca/PTH elevated values
  – Repeat your own laboratories
Work-up of Elevated Calcium

- What are the essential/desired laboratories?
  - Serum Calcium
  - Intact PTH
  - Ionized calcium
  - Albumin
  - Urine calcium (if concern for FHH, borderline serum values)
  - Chloride
  - Creatinine/EGFr
  - Vitamin D
  - Bone specific alkaline phosphatase

Table 3. Patient Cost for “B-Pack” and Intraoperative Parathyroid Hormone (PTH) Laboratory Testing.

<table>
<thead>
<tr>
<th>Test</th>
<th>Costs (US Dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative PTH</td>
<td>4.10</td>
</tr>
<tr>
<td>Intact PTH</td>
<td>4.10</td>
</tr>
<tr>
<td>Ionized calcium</td>
<td>2.41</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>0.54</td>
</tr>
<tr>
<td>Magnesium</td>
<td>4.10</td>
</tr>
<tr>
<td>Chloride</td>
<td>4.10</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.41</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.51</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D</td>
<td>4.10</td>
</tr>
</tbody>
</table>

*Cost reflects charge for patients at the University of Arkansas for Medical Sciences.
*Run in 15 minutes.
*Run in 30 minutes.


$26.34
Work-up of Elevated Calcium

• What laboratory values confirm the diagnosis of primary HPT?
  – Calcium > 10.2 mg/dL
  – Intact PTH > 88 pg/mL
  – Ionized calcium > 1.33 mmol/mL
  – 24 hour urinary calcium > 150 mg/24 hours*
  – Chloride > 107 mmol/L

Our current challenge is that due, in part, to widespread calcium testing in medical care, more cases of borderline HPT are being seen.
Work-up of Elevated Calcium

• Non Parathyroid Tumor Causes for Hypercalcemia:
  – Vitamin D toxicity
  – CaSR mutation
  – Skeletal metastases
  – Magnesium abnormalities
  – Hyperphosphatemia
  – Chelation therapy
  – Acute pancreatitis
  – Sepsis
  – Herbicides
  – PPI use
  – Rifampin
  – Anticonvulsants
  – Bisphosphonates
  – Aminoglycosides
**N=20,225**

<table>
<thead>
<tr>
<th>Parathyroid histopathologies</th>
<th>Prevalence (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary adenomas</td>
<td>88.90</td>
<td>88.89–88.92</td>
</tr>
<tr>
<td>Multiple gland disease</td>
<td>9.84</td>
<td>9.84</td>
</tr>
<tr>
<td>Multiple gland hyperplasia disease</td>
<td>5.74</td>
<td>5.33–6.15</td>
</tr>
<tr>
<td>Double adenomas</td>
<td>4.14</td>
<td>3.74–4.53</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>0.74</td>
<td>0.53–0.95</td>
</tr>
</tbody>
</table>

Ruda et al., Otolaryngol Head Neck 2005
Once the diagnosis of hyperparathyroidism has been established, and perhaps confirmed in office by ultrasound, the patient should be referred for surgery so the surgeon can select the preferred imaging modality to prepare the patient for surgery. This might vary based on local resources and practice patterns.
Imaging

Many endocrine or head and neck surgeons will confirm ultrasound findings with their own ultrasound exam. This might be done in clinic and/or in the operating room. They will either proceed to surgery on ultrasound findings alone or order additional preferred pre operative imaging.
Figure 1. Four-dimensional computed tomography coronal (A) precontrast and (B) early postcontrast phases reveal the avidity of adenoma enhancement as compared with surrounding soft tissues.
4D CT

History

• 75 yo female with a 2.5 yr. history of hypercalcemia
• Ca 11.1, PTH 60
• LS by ultrasound
Intraoperative Events

Radioguidance

• Baseline 1: 3300
• Baseline 2: 7000
• Fat: 50
• LS (low lying): 2850

IOPTH

• Baseline: 61
• Post excision 1: 26
• Post excision 2: 18
Final Results

Pathology
• 470 mg LS hypercellular parathyroid

Laboratory
• PTH: 21.3
• Ca: 9.2
• iCa: 1.35
• 25OH vit. D: 26.3
• GFR: 37 (>59)

http://www.youtube.com/watch?v=Xect3GWHj9Q
AHNS Series: Do you know your guidelines? Optimizing outcomes in reoperative parathyroid surgery: Definitive multidisciplinary joint consensus guidelines of the American Head and Neck Society and the British Association of Endocrine and Thyroid Surgeons


First published: 02 August 2018 | https://doi.org/10.1002/hed.25023

AHNS Endocrine Surgery Section – https://endocrine.ahns.info
Re-operative Parathyroid Surgery

The greatest challenge in parathyroid localization is to localize a good parathyroid surgeon

- John L Doppman, MD

Re-operative Parathyroid Surgery

Repeat parathyroid exploration is associated with more complications and fewer cures compared to the initial explorations and should only be undertaken by an experienced surgeon in a center that can provide expert preoperative localization, adjunctive intra-operative tools, and cryopreservation when necessary.

Orlo Clark, MD 2004
Re-Operative Surgery: Reasons for failure

- Careful review of previous operative note, pathology report (slides), images, and rapid PTH results if available.
- Approach patient without pre-conceptions

<table>
<thead>
<tr>
<th>S</th>
<th>R</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>35mg</td>
<td>Excised</td>
<td>Found, judged normal, no biopsy</td>
</tr>
<tr>
<td>Not found</td>
<td>Found, biopsied, hypercellular</td>
<td></td>
</tr>
</tbody>
</table>
Reasons for Surgical Failure

• Inexperience
• Difficulties from anatomy or previous surgery (thyroidectomy, parathyroidectomy, ACDF)
• Ectopic
  – Carotid sheath and retro-esophageal
  – Intra-capsular vs. intra-parenchymal thyroid (1%)
  – Thymus
• Unrecognized multiple gland disease (10%)
• Supernumerary (1%)
Recommendation 5a

- Preoperative imaging of reoperative parathyroid surgical patients is mandatory.
- Level of evidence: 1-3, level of recommendation: strong.
Re-Operative Surgery

Case 1
• 59 yo female with the following history:
  – 1st Surgery:
    • Failed parathyroid exploration on right
    • “Exploratory” right hemi thyroidectomy
    • Incidental micro papillary cancer
  – 2nd surgery:
    • Failed parathyroid exploration on left
    • Completion thyroidectomy for “thyroid cancer”
  – 3rd surgery:
    • Failed revision left neck exploration
Clinical Presentation

- Fatigue, somatic complaints, depression
- Labs: PTH 97, Vit D 24.8, iCa 1.34, Ca 10.1
- Imaging:
  - non localizing on u/s
  - “Non-localizing” on SPECT CT sestamibi
  - Not visualized on TEE (u/s)
CT: 2HR FUSION CT
NM: RECON TOMO / TRANS-AC-2HR
CT: 9/18/2013
NM: 9/18/2013

CT: Series: 3 / Slice: 90
NM: Series: 0 / Slice: 138

Width: 350 Level: -35
LL: 0 UL: 848
Intraoperative Events

**Radioguidance**
- Baseline 1: 1950
- Baseline 2: 2900
- Fat: 80
- R superior “ectopic” parathyroid adenoma: 4200

**Intraoperative PTH**
- Baseline: 110
- Post op #1: 17
- Post op #2: 14
Pathology: 690 mg parathyroid adenoma

Laboratory:
- PTH: 41.3
- iCa: 1.03
- Ca: 7.6
Re-Operative Surgery

Case 2
Re-Operative Parathyroid Surgery

- 70 yo female with history of right hemi-thyroidectomy in the past
- The patient was diagnosed with pHPT in 2007.
- Adenoma localized on sestamibi
- Underwent a negative exploration March 2008
- Repeat sestamibi unchanged after surgery
Re-Operative Parathyroid Surgery

Oct 2007

April 2008
Re-Operative Parathyroid Surgery

- Patient was given a preoperative injection
- An MIRP was performed
- A lateral approach modification was employed through a midline incision
- 75% drop in rapid PTH assay 5 minutes post op
Re-Operative Parathyroid Surgery

- Right superior parathyroid gland weighing 1.14 grams (20x enlarged by weight)
- Post op Ca 9.0
Intraoperative gamma imaging
Intraoperative gamma imaging (HPT w/ prev. L HT)

Pre-incision

Post-excision
Synchronous Thyroid Ca and PHPT (DA)

Pre excision
Thyroid cancer and HPT.
Breast cancer and GBM survivor

s/p Total
Thyroidectomy
Remaining
RI parathyroid
adenoma

Incidentally
discovered LI
double (second)
parathyroid
adenoma

Completion of
operation

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES
Future?
Future?
The Cost-Effectiveness of Fluorodeoxyglucose 18-F Positron Emission Tomography in the N0 Neck

Christopher S. Holmes, M.D., M.S.1
Val J. Love, M.D.2
Brendan C. Stack, Jr., M.D.3

1Department of Surgery and Health Evaluation Sciences, Penn State College of Medicine, Hershey, Pennsylvania
2Department of Otolaryngology, Mayo Clinic, Rochester, Minnesota
3Division of Otolaryngology-Head and Neck Surgery, Penn State College of Medicine, Hershey, Pennsylvania

BACKGROUND: Although surgery and radiation are effective treatments for patients with regional lymph node involvement, patients with N0 disease who are shown to have negative N0 nodes by computed tomography may have their treatment options limited. Positron Emission Tomography (PET)/CT is emerging as an imaging modality that may be useful in this setting.

METHODS: We conducted a cost-effectiveness analysis comparing PET/CT with standard imaging in the setting of N0 disease. Results: PET/CT is cost-effective in the setting of N0 disease.

RESULTS: When compared to the standard of care, PET/CT is cost-effective and offers additional information that may guide treatment decisions.

CONCLUSIONS: PET/CT is a cost-effective imaging modality in the setting of N0 disease.


Multicenter Trial of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging of Head and Neck Cancer and Negative Predictive Value and Surgical Impact in the N0 Neck: Results From ACRIN 6685

Multicenter Trial of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging of Head and Neck Cancer and Negative Predictive Value and Surgical Impact in the N0 Neck: Results From ACRIN 6685

Multicenter Trial of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging of Head and Neck Cancer and Negative Predictive Value and Surgical Impact in the N0 Neck: Results From ACRIN 6685

Multicenter Trial of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging of Head and Neck Cancer and Negative Predictive Value and Surgical Impact in the N0 Neck: Results From ACRIN 6685
Lessons I have Learned from Parathyroid Surgery

- 1. Know the disease
- 2. Know imaging and review your own images
- 3. Quality control of ultrasound
- 4. The parathyroid Laboratory battery (8-pack)
- 5. Don’t forget about vitamin D
- 6. Radioguidance is my preferred technique
- 7. IOPTH is a mixed blessing
- 8. The only thing worse than Hyperpar...
- 9. Frozen sections are not required
- 10. Cost-efficiency
- 11. The non-localizer
- 12. How to avoid failure
- 13. Intellectual honesty
- 14. the importance of long-term follow up