Current Investigation for Primary Hyperparathyroidism

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Quan-Yang Duh, Professor of Surgery, UCSF
What Causes Primary Hyperparathyroidism?
What Causes Primary Hyperparathyroidism?

- Menin (MEN 1)
- Cyclin D1 (PRAD1)
- Radiation
  - RAI for thyroid
- Parafibromin (HRPT-2)
**HRPT2 Mutations:**
Parathyroid cancer & (HPT-JT) syndrome

- *HRPT2* (1q25–q32) encodes parafibromin.
- Hyperparathyroidism–jaw tumor (HPT-JT) syndrome: 1 HPT, ossifying fibromas of the maxilla and mandible, renal cysts and solid tumors.
- Germ-line inactivating mutations of *HRPT2* found in about half the kindreds with HPT-JT syndrome
- Somatic and germ-line mutations in 2/3 (10 of 15) of sporadic parathyroid carcinomas.

NIH Consensus Conference on the Indications for Parathyroidectomy for Primary Hyperparathyroidism: 1990, Revised 2002
NIH Consensus Statement: Indications for Parathyroidectomy

- Markedly elevated serum calcium
- Episodes of life-threatening hypercalcemia
- Reduced creatinine clearance
- Kidney stone(s) by radiography
- Markedly elevated 24 hr urinary calcium excretion
- Substantially reduced bone mass


- Serum calcium > 11.4-12.0 mg/dl (>11.4)
- Creatinine clearance reduced by 30%, (abnl cr)
- 24 hr urinary calcium excretion > 400 mg (not)
- Bone density Z score, age match < -2 (to T score)

NIH Consensus Statement: Indications for Parathyroidectomy

- Patients request surgery
- Consistent follow-up is unlikely
- Coexisting illness complicates management
- Patient is young (< 50 years old)

Why Parathyroidectomy?
Primary Hyperparathyroidism: Symptoms & Associated Conditions

- “Stones, Bones, Moans and Groans”
- Bone: osteitis fibrosa cystica, osteoporosis
- Kidney: stones, renal failure
- Abdominal pain: PUD, pancreatitis,
- Fatigue, weakness, lethargy
- Depression, memory loss
- Hypertension, gout, pseudogout
Increased Risk of Death from Untreated Primary Hyperparathyroidism

- Increased risk of death
  - Mainly from CV disease and cancers
  - Actuarial curve like smoking 1 pack per day
- Risk correlated with tumor size
  - But not serum calcium level
- Reverse the risk by parathyroidectomy
  - in younger patients.

Primary Hyperparathyroidism: Symptoms in Screened Patients

- Swedish screening mammography study
- More psychic complaints
  - lassitude, fatigue, irritability
  - lack of sexual and emotional interests.
- Lower bone density, visited physicians more often
- More sick leave used (odds ratio 12) for the 5 years before diagnosed, due to cardiovascular diseases.

Bone Disease in Postmenopausal Women with Primary Hyperpara

Minimal Hyperparathyroidism
“asymptomatic hyperparathyroidism”
Minimal Hyperparathyroidism

Minimal Hyperparathyroidism

“Asymptomatic” Hyperparathyroidism

- 5% (7/152) truly asymptomatic
  - prospective questionnaire
  - non-specific symptoms including fatigue, exhaustion, weakness, polydipsia, polyuria, nocturia, joint pain, bone pain, constipation, depression, anorexia, nausea, and heartburn

- 95% have some improvement postop
  - 55% feels better overall (vs 30% thyroid control)

- Serum calcium does not predict improvement.

Minimal Hyperparathyroidism

- Rochester Epidemiology Project: 1965 to 1992, 435 diagnosed with primary hyperpara, only 126 (29%) had parathyroidectomy.
- Maximal serum Ca: an independent predictor of mortality (RR=1.3 per mg/dL) by age-adjusted multivariate analysis.
- Survival not affected in patients with mild primary hyperpara

Improvement after Parathyroidectomy
Improvement after Parathyroidectomy

- Improve strength and fine motor, 1 month.

- Improve psychiatric symptoms, 1 month.

- Improve renal colic (66% to 2%/yr), 1 year.

- Improve LVH, 1 year and continue beyond.
  - Interventricular septum (-6%), posterior wall (-19%)

- Improved health status (SF36), 2 months
Improved Bone Mineral Density (BMD) after Parathyroidectomy

- Improved BMD, 15% (1 yr) 21% (4 yr) postop, in the lumbar spine of those with vertebral osteopenia.
- Improved BMD in spine and hip. Improved serum alkaline phosphatase and osteocalcin.
- Improved BMD to an extent that restores the preoperative bone loss.
Improve Health Status (SF36) after Parathyroidectomy

- SF-36 health status assessment tool
  - (140 pts, 110 followed at 2 m, 82 at 6 m)
- Preop: marked impairment in 7 of 8 domains
- 2 m postop: improvement in 5 of 8 domains
- 6 m postop: improvement in 6 of 8 domains
- Improvement in: limitations caused by physical and emotional role function, social function, bodily pain, and vitality.

Parathyroidectomy: Extent of Exploration

- Bilateral exploration
  - 4 glands or more identified
- Unilateral exploration
  - 1 tumor and 1 normal gland identified
- Focused exploration
  - “limited”, “targeted”, “concise”
  - 1 tumor identified
  - Adenomaectomy without full exploration
Successful Parathyroidectomy: Focused (vs General) Exploration

- **Know where to start**
  - Preoperative localization studies (MIBI or US)
  - *Intraoperative localization studies*

- **Know when to stop**
  - Intraoperative quick assay for hormones
  - Bayesian analysis
  - *Intraoperative radio-guidance*
45 year-old woman, had gastric bypass, Ca 11, PTH 78, Left upper 2.6 cm parathyroid adenoma
Intraoperative PTH for Parathyroidectomy
University of Miami Protocol

Samples taken:
- Pre Incision (skin incision)
- Pre Excision (prior to cross clamping pedicle)
- 5 minutes
- 10 minutes
- 50% decrease from highest Pre value predictor of eucalcemia at ≥6months
University of Miami: 294 consecutive patients

<table>
<thead>
<tr>
<th>Initial Operation</th>
<th>Calcium Level at 6 months</th>
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<tbody>
<tr>
<td></td>
<td>&lt;10.3</td>
</tr>
<tr>
<td>Drop in 10 minute PTH</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>TP: 279/294 (95%)</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>FN: 7/294 (2.7%)</td>
</tr>
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</table>
Double adenomas: more than half of the time IOPTH is wrong

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution</th>
<th>No Patients</th>
<th>&lt;50% drop TN</th>
<th>≥50% drop FP</th>
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<tbody>
<tr>
<td>Gauger</td>
<td>Univ Michigan/ Australia</td>
<td>20</td>
<td>9(45%)</td>
<td>11(55%)</td>
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<tr>
<td>Haciyanli</td>
<td>UCSF</td>
<td>21</td>
<td>8(40%)</td>
<td>13(60%)</td>
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</table>

UCSF billing data

- Neck ultrasound $544
- Sestamibi scan: $1,100
- CT with and without contrast: $2,500
- MRI with gadolinium: $4,100
- PET scan: $4,700
- Selective venous cath: $18,000
  - IR pro fee: $10,000 + $8,000 hospital charge
- IOPTH $318 for 1 pre and post. $284 each addtl post.
- 99Tc Sestamibi for Gamma probe $398
- Serum PTH + Ca: $214 (Ca only: $35)
- Serum Phos: $33
- Surgeon’s fee: $3,473
- Semi-private room: $1,896 per day
- OR cost: base level $2,200. First 30 min $1,800.
  - Each addtl 15 min ~$900
- Anesthesiologist pro fees: 1.5hr $950, 2.5hr $1,250

Total inpatient bill for focused PTX with overnight stay (professional fees and preoperative localization not included)

$16,500
# Charges for Parathyroidectomy

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>US (UCSF’04)</th>
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<tbody>
<tr>
<td>Mibi</td>
<td>$631</td>
<td>($1100)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>$47</td>
<td>($544)</td>
</tr>
<tr>
<td>CT</td>
<td>$118</td>
<td>($2500)</td>
</tr>
<tr>
<td>MRI</td>
<td>$193</td>
<td>($4100)</td>
</tr>
<tr>
<td>IOPTH</td>
<td>$19</td>
<td>($600)</td>
</tr>
<tr>
<td>Surgeon</td>
<td>$1237</td>
<td>($3500+$1900 Hosp)</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>$566</td>
<td>($950+$5800 OR)</td>
</tr>
<tr>
<td>15 more min.</td>
<td>$0</td>
<td>($150+$900)</td>
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</table>

<table>
<thead>
<tr>
<th>Localization + OR + Anesthesia charges only</th>
<th>Focused</th>
<th>Bilateral</th>
<th>Failed Focused</th>
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<tbody>
<tr>
<td>US</td>
<td>$544</td>
<td>$0</td>
<td>$544</td>
</tr>
<tr>
<td>MIBI</td>
<td>$1,100</td>
<td>$0</td>
<td>$1,100</td>
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<tr>
<td>IOPTH (3 samples)</td>
<td>$602</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>OR charge</td>
<td>$5,800</td>
<td>$9,400</td>
<td>$9,400</td>
</tr>
<tr>
<td></td>
<td>(1 hr)</td>
<td>(2 hr)</td>
<td>(2 hr)</td>
</tr>
<tr>
<td>Anesthesia fees</td>
<td>$950</td>
<td>$1,250</td>
<td>$1,250</td>
</tr>
<tr>
<td></td>
<td>(1.5 hr)</td>
<td>(2.5 hr)</td>
<td>(2.5 hr)</td>
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<tr>
<td>Total</td>
<td>$8,996</td>
<td>$10,650</td>
<td>$12,294</td>
</tr>
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1 hr focused (vs 2 hr bilateral) approach saves $3900 in OR and anesthesia fees! (net savings $1,654)

15 min in OR = $1,000

Standard preop localizing studies add $1,644!
Imaging directed parathyroidectomy (imaging selected parathyroidectomy)

- +MIBI alone
  - 90% success with focused approach
- +US alone
  - 85% success with focused approach
- +MIBI and +US
  - 96% success with focused approach

- Positive MIBI and US selected those likely to have a solitary adenoma

“Kebebew Score” of 3 or more predicts single adenoma

- Sestamibi
- Ultrasound
- Concordance
- Ca > 12 mg/dl
- PTH > 2x upper nl

3 or more predicts single gland disease

Recommendations

Primary Hyperparathyroidism
Routine mibi & US

- Mibi+ & US+ & Concordant (Kebebew 3, 4 or 5) 60%
  - Focused expl No ioPTH

- Mibi+ or US+ Ca>12 & PTH > 2x (Kebebew 3) 10%
  - Focused expl No ioPTH

- Mibi+ or US+ less severe Ca/PTH (Kebebew 1 or 2) 10%
  - Focused expl & ioPTH
  - Or
  - Unilateral expl no ioPTH

- Mibi- & US- (Kebebew 0,1 or 2) 20%
  - Bilateral expl +/- ioPTH
Changing Approach for Primary Hyperparathyroidism: Conclusions

- Parathyroidectomy:
  - successful, beneficial, and minimal risks
  - NIH criteria too conservative?
- Routine preoperative sestamibi and ultrasound
  - even for first-time operation and reoperation
  - Save time and money by shorten operation?
- Focused exploration possible in most patients
  - Most are known preoperatively (“Kebebew Score”)
  - Selective use of intraoperative PTH?