Parathyroid Imaging in 2015

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I do not have any relevant financial and nonfinancial disclosures to make.
Incidence of Primary Hyperparathyroidism

- Incidence ~1 per 1,000 in general population in USA
- Incidence increases with age & especially in postmenopausal women (female-to-male ratio 3:1; up to ~21 per 1,000 in post-menopausal women)
- MC in Blacks
- Lower in countries where serum calcium is not yet routinely measured


Most have 2 upper & 2 lower

**Upper (superior):**
- 4\textsuperscript{th} pharyngeal pouch
- Posterolateral to upper thyroid lobes
- Usually 1-2 cm superior to recurrent laryngeal nerve

**Lower (inferior):**
- 3\textsuperscript{rd} pharyngeal pouch
- Anywhere along where thymus travels during development, but usually posterolateral to lower thyroid lobes
16% incidence of ectopic glands

MC ectopic sites mirror routes of descent


Gomes EMS et al. Ectopic and extranumerary parathyroid glands location in patients with hyperparathyroidism secondary to end-stage renal disease
**PTH**

- Regulates free ionized calcium
- Negative feedback system
- Synthesized in parathyroid chief cells & secreted in response to low calcium levels
- Acts on kidneys (absorption), intestines (resorption), bone (resorption) to raise serum calcium levels
- Rapidly metabolized by liver (70%)/kidneys (20%), disappearing from circulation with biologic T1/2 of 2-3 min
**Hyperparathyroidism Signs/SXs**

“stones, bones, abdominal groans, and psychic moans”

<table>
<thead>
<tr>
<th>GI</th>
<th>Dry mouth, thirst, polydipsia, anorexia, nausea, vomiting, constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GU</td>
<td>Polyuria/nocturia, renal stones, nephrocalcinosis, uremia</td>
</tr>
<tr>
<td>MS</td>
<td>Fatigue, muscle weakness, arthralgia, bone pain, osteoporosis</td>
</tr>
<tr>
<td>Neuro</td>
<td>Drowsiness, lethargy, stupor, confusion</td>
</tr>
</tbody>
</table>

- Most (~50%) are asymptomatic at presentation
- Brown tumors, osteitis fibrosa cystica, pathologic fractures, etc.
Lab Investigation

Blood tests
- Calcium
- PTH
- Bone markers (alkaline phosphatase, osteocalcin – marker for bone formation)
- Others (phosphorous, vitamin D)

Urine
- 24-hr urinary calcium
Forms of Hyperparathyroidism

- **Primary**
  
  - **MC form**
  
  - *Intrinsic* parathyroid abnormality
  
  - Characterized by \( \uparrow \text{PTH}, \uparrow \text{Ca}, \downarrow \text{phosphate} \)
Forms of Hyperparathyroidism

**PRIMARY**

- Single adenoma in 80-90%
- Multiple in 10-19%
  - Hyperplasia
  - Multiple Endocrine Neoplasia
  - Multiple Adenomas (2-3%)
- Malignancy < 1%
Hypertrophy of glands as compensation for another dysfunctional organ (i.e. chronic renal failure, Paget’s disease, multiple myeloma)

Elevated PTH *in response* to chronic hypocalcemia
Forms of Hyperparathyroidism

**TERTIARY**

- Usually state of excessive secretion of PTH after a long period of secondary hyperparathyroidism and resulting hypercalcemia
- Irrepressible $\uparrow$ PTH
Many surgeons advocate for 2 concurrent imaging studies for localizing a parathyroid adenoma. US and scintigrapy level II evidence as first-line imaging (US first, then scintigrapy confirmatory).


<table>
<thead>
<tr>
<th>MIBI (planar)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>88%</td>
<td>82%</td>
</tr>
<tr>
<td>MIBI (SPECT)</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>MRI</td>
<td>94%</td>
<td>95%</td>
</tr>
</tbody>
</table>


4DCT - 92% sensitivity, 93% specificity
Chazen JL et al. AJNR. 2012;33:429-33 N = 35

CEUS - Did not improve from US or MIBI
Ultrasound

- Considered a first line modality
- Noninvasive localization
- Supine & neck hyperextended
- Longitudinal and transverse images from carotid bifurcations to sternal notch
- Measurements in 3 dimensions
- Evaluate relationship to thyroid gland; may be intrathyroidal
- May not see PA unless > 1 cm
- Sensitivity 53-88%; Specificity 40-98%

2013 AIUM/ACR Guidelines
Homogeneously hypoechoic to thyroid gland, ovoid

Doppler may show feeding vessel with arc or rim of hypervascularity & entering at one pole of the gland (Polar Vessel Sign)

Increases sensitivity

Lane MJ, Desser TS, Weigel RJ et al. Use of power and color Doppler sonography to identify feeding arteries associated with parathyroid adenomas. AJR; 1998; 171:819-23.
MRI

- Not typically first line

- Surface neck and chest coils for mediastinum

- Hyoid bone to lung apices; 3 mm thickness

- T1 hypointense, T2/STIR hyperintense, avid enhancement (but 30% without this typical pattern)

- Sensitivity 64 – 78%; Specificity 88 – 95%

- Useful for detecting **ectopic** mediastinal glands (sensitivity > 80%)

Medscape

FP: lymph nodes, thyroid nodules (adenomas, exophytic colloid cysts), enlarged cervical ganglia, other neck masses (sarcoid nodules, neurofibromas)

FN: small parathyroid glands, concomitant thyroid disease, anatomic distortion from prior surgery, atypical signal
From Terris Parathyroid Book
Chapter – right inferior parathyroid adenoma (enhances)

Pre and post-contrast T1 MRI
Conventional CT

- Not typically first-line
- More difficult to localize PA’s above shoulders and in neck region
- Sensitivity 46 – 80%; Specificity 88 – 90%

Medscape
4DCT

4\textsuperscript{th} Phase = contrast enhancement with time

NECT followed by 3-phase CECT (75 cc iohexol 300 IV; Imaging at 30, 60, and 90 sec (Philips Brilliance 64-slice scanner (120 kvP, 180-300 mAs, 2.0 mm))

Mandible to carina

NECT – can help distinguish PA from intrinsically dense iodine-rich thyroid gland (esp if intrathyroidal); PA demonstrates attenuation similar to muscle

CECT – demonstrates hypervascular PA (early enhancement) with characteristic early washout

May see an extrathyroidal feeding artery entering one pole of the parathyroid adenoma (Polar Vessel Sign)
Axial CT images in noncontrast (A) early post-contrast (B) and delayed post-contrast (C) phases demonstrate an intrathyroidal lesion with subtle hypodensity on precontrast imaging and delayed enhancement. This enhancement pattern is seen less commonly than early enhancement and washout.
Polar Vessel Sign

**Parathyroid Venous Sampling**

- Introduced in 1970 as outpatient procedure
- Typically performed after other image localization studies have failed

Proceed to surgery if **2 noninvasive studies** (US, CT, MRI, MIBI) identify abnormal parathyroid gland

If equivocal, perform digital arteriography or venous sampling with rapid PTH


- Sensitivity 80 - 90% in experienced hands
- Combined with rapid PTH assay – 100% cure rate when venous gradient demonstrated
- More significant contrast load and radiation exposure
- Invasive
Access femoral vein with Seldinger technique, then fluoroscopically-guided to veins with contrast injected to document catheter position with permanently-recorded image at each site; small amount venous blood collected at each site from multiple veins.

(+) when > 50% gradient (2:1) between PTH concentration at specific sites compared to peripheral blood samples.

<table>
<thead>
<tr>
<th>Site#</th>
<th>Location</th>
<th>Assay result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left Internal Jugular v. - superiorly</td>
<td>143</td>
</tr>
<tr>
<td>2</td>
<td>Left Middle thyroidal v.</td>
<td>102</td>
</tr>
<tr>
<td>3</td>
<td>Left I. J. vein - inferiorly</td>
<td>165</td>
</tr>
<tr>
<td>4</td>
<td>Left Subclavian v.</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>Left Innominate v.</td>
<td>289</td>
</tr>
<tr>
<td>6</td>
<td>Hemiazygos v.</td>
<td>1374</td>
</tr>
<tr>
<td>7</td>
<td>Right Internal Jugular v. - superiorly</td>
<td>128</td>
</tr>
<tr>
<td>8</td>
<td>Right Superior thyroidal v.</td>
<td>190</td>
</tr>
<tr>
<td>9</td>
<td>Right I. J. vein - inferiorly</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>Right Subclavian v.</td>
<td>146</td>
</tr>
<tr>
<td>11</td>
<td>Right Innominate v.</td>
<td>130</td>
</tr>
<tr>
<td>12</td>
<td>Superior vena cava</td>
<td>235</td>
</tr>
<tr>
<td>13</td>
<td>Azygos v.</td>
<td>153</td>
</tr>
<tr>
<td>14</td>
<td>Right atrium</td>
<td>109</td>
</tr>
<tr>
<td>15</td>
<td>Common hepatic v.</td>
<td>87</td>
</tr>
<tr>
<td>16</td>
<td>Inferior vena cava - supra renal</td>
<td>136</td>
</tr>
</tbody>
</table>
Adenoma appears as rounded, densely staining blush

C-11 methionine (MET-PET)

Meta-analysis:

9 studies with 258 patients

Sensitivity - 81%

Detection Rate - 70%

Not recommended as first line

FDG-PET (N=21):

- Sensitivity - 86%
- Specificity - 78%
- Able to detect smaller adenomas
- More FPs
- Higher cost

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Scintigraphic Evaluation of Parathyroid Adenomas: Techniques, Protocols and Interpretation

Twyla B. Bartel, Tracy L. Yarbrough, and Brendan C. Stack, Jr.
Scintigraphy

- Noninvasive localization of PA
  (& minimally invasive surgery)
  - Reduces operating time
  - Limited neck dissection
  - Shorter hospital stay
  - Reduce reoperation incidence
Some Radiotracers/ Methods Used:

- Can be *combined* for **Dual-Isotope Subtraction Scan**
- Or *single* radiotracer for **Single-Isotope Dual-Phase Scan**

- **Tc-99m-sestamibi (MI BI)** – gold standard today;
  thyroid & parathyroid uptake; look at washout pattern; 140 keV, T1/2 = 6 hours

- Tc-99m-tetrofosmin – thyroid & parathyroid; slower washout from thyroid than MI BI; 140 keV, T½ = 6 hrs

- Thallium-201 – thyroid & parathyroid uptake; 70-80 keV, T½ = 73 hrs

- In-111-pentetrotide (Octreoscan) - some parathyroid glands have somatostatin receptors; 173 & 247 keV, T½ = 67 hrs

- I-123 – thyroid uptake only; 159 keV, T1/2 = 13 hrs

- Tc-99m pertechnetate – thyroid uptake only; 140 keV, T1/2 = 6 hrs
Example of Dual-Isotope Subtraction Scan:

\[ {}^{99m}\text{Tc-sestamibi}/{}^{123}\text{I} \]

- MIBI uptake by thyroid & parathyroid
- \(^{123}\text{I}\) uptake by thyroid only
- Administer MIBI, then I-123
- Final image = (I-123 – MIBI)
Coakley incidentally discovered uptake & retention in abnormal parathyroids while doing **myocardial perfusion studies**

*Coakley et al. Nucl Med Commun 1989;10:791-4*

O'Doherty published 1st results of using a MIBI scan for preop localization of PA


Preferred parathyroid imaging agent worldwide

T1/2 = 6 hours, 140 keV
Uptake depends on:
- **Number of MITOCHONDRIA**
  - Hetrakul et al. Surgery 2001;130:1011-18
- Number of oxyphil cells (mitochondria-rich)
- Active growth of gland
- Elevated PTH
- Blood flow
- Gland size
False Positives:
- Thyroid adenomas
- Cervical lymph nodes
- Malignancy

False Negatives:
- Small adenomas
- Displaced/obscured by goiter
- Ectopic adenoma
- Low mitochondrial activity
Advantages over other radiotracers:

- Higher sensitivity (70-100%)/specificity
- Superior image quality
- Single radiotracer

Tc-99m sestamibi
Early Tc-99m Sestamibi Dual-Phase Imaging

- Uptake by thyroid & parathyroid
- Delayed imaging w/ greater washout from thyroid compared to parathyroid adenoma (persistent focal uptake on delayed images)
Can do immediately after planar imaging

Increases sensitivity (91 – 96%)

Adds depth info and topographic correlation w/ anatomic structures

Improves contrast

Aids in evaluation of mediastinum for ectopic adenomas

Helps guide surgeon

_Single Isotope Dual-Phase SPECT Imaging_
Tc-99m Sestamibi Dual-Phase SPECT Imaging

Early Images

Delayed Images
From Terris Parathyroid Book Chapter - SPECT/CT localized to left inferior-posterior parathyroid gland
From Terris Parathyroid Book Chapter - ectopic parathyroid adenoma
From Terris Parathyroid Book Chapter - right inferior parathyroid adenoma & lung cancer
Operative Procedures

- Bilateral Exploration
- Unilateral Exploration
- Radioguided Parathyroidectomy
- Minimally-Invasive Radioguided Parathyroidectomy (MIRP)
- Autologous Transplantation
Radioguided Parathyroidectomy

Intraoperative gamma probe localization

Courtesy, Brendan Stack, MD
Our Protocol

Hyperparathyroidism

Sestamibi Scan

- positive
  - MIRP
    - positive: unilateral exploration with turbo PTH
    - negative: ultrasound
      - positive: bilateral exploration with turbo PTH
      - negative

- negative: ultrasound
  - negative: bilateral exploration with turbo PTH

Courtesy, Brendan Stack, MD
Advantages:

- Local anesthesia (not general)
- Dissection minimal
- Outpatient procedure
- Less post-op pain
- Frozen section pathology
- Perioperative calcium supplementation
- Eliminates post-op blood tests

Eliminates need for intraoperative frozen-section analysis

Measure PTH drop during “safety window” (time between adenoma excision & when other glands start producing PTH)

Venous blood (usually anterior jugular) sample before gland removal & 10 min after excision

> 50% decline in PTH @ 10 minutes from baseline indicates successful removal of adenoma (relying on drop only has 22.4% failure rate)

Adenoma ex-vivo counting rate of at least > 20% higher than thyroid background

Murphy et al. Surgery 1999; 126:1023-9
African American female with an incidental finding of hypercalcemia
Co-morbidities of hypertension and diabetes
No history of stones, neuromuscular symptoms, or gastrointestinal complaints
Post-menopausal

*MIRP Case Example*

*Courtesy, Brendan Stack, MD*
Gamma probe guided external marking
Minimal access incision
Use of *any* localization technique:
- Reduces the risk of RLN injury by 37% to 52%
- Produces a cost-benefit when compared w/ nondirected BNE

Preop MIBI scanning afforded a > $3000 reduction in charges when compared w/ nondirected BNE

Approximately equivalent savings were found if preop MIBI scanning was combined with iPTH

Fahey et al. Arch Surg 2002;137:917-23
Costs based on 2011 Medicare reimbursement schedules:

- **US + 4DCT** least expensive strategy ($5,901)

- **US alone** ($6,028) or **4DCT alone** ($6,110) - 2nd least expensive

- **US + MIBI** ($6,329)

- **4-gland, bilateral neck exploration (BNE)** most expensive strategy ($6,824)

Radiation Dose Comparison of Parathyroid Planar Scintigraphy, Combined SPECT/CT, and Multiphase 4DCT

Bartel TB\textsuperscript{1}, Stack, Jr, BC\textsuperscript{2}, Yarbrough TL\textsuperscript{3}, Medarametla S\textsuperscript{1}, Samant R\textsuperscript{1}, Fitzgerald RT\textsuperscript{1}

**Objective:** Compare radiation doses for planar scintigraphy, SPECT/CT, & 4DCT in cases of difficult-to-detect parathyroid adenomas in pts with primary hyperparathyroidism

**Methods:** 4DCT performed in 5 pts where no lesion was detected by P or S/CT. Dual-phase planar and SPECT/CT (15 min, 2 hr) also performed prior to but no PA detected.

Radiation doses were calculated using Stanford’s RADAR (P, S/CT) and BCM’s effective dose calculator (4DCT) which utilizes DLP (dose-length product) info.
### Results:

Planar or SPECT/CT gives lowest radiation dose.  
Optimized 4DCT alone similar if utilized as initial study.  
Combined radiation dose is nearly doubled or tripled for P+S/CT+4DCT, and multiple localization studies in difficult cases even further increases total dose.  
Prior to 4DCT, Pt 1 had 3 nonlocalizing scintigraphic studies giving a total radiation dose of 35.7 mSv.  
Pt 5 had 3 nonlocalizing scintigraphic studies and 1 CT-neck prior to 4DCT with a total dose of 52.4 mSv.  
All pts were successfully localized and treated surgically.  We are further optimizing our 4DCT protocol.

### Conclusions:  
For PA localization, P alone provides the lowest dose.  Nonlocalized lesions may require S/CT and/or 4DCT.  Given the implications of localization for surgical morbidity, the benefit of additional exams likely outweighs the added radiation dose.

### Acknowledgement:  Martin A. Lodge, PhD, Johns Hopkins Medicine, Dept of Radiology.

<table>
<thead>
<tr>
<th>Tc-99m-MIBI (mCi)</th>
<th>Scintigraphy Only</th>
<th>SP SPECT/CT</th>
<th>DP SPECT/CT</th>
<th>4DCT</th>
<th>SP SPECT/CT &amp; 4DCT</th>
<th>DP SPECT/CT &amp; 4DCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt 1</td>
<td>28.0</td>
<td>9.3</td>
<td>14.1</td>
<td>18.9</td>
<td>30.0</td>
<td>44.1</td>
</tr>
<tr>
<td>Pt 2</td>
<td>24.9</td>
<td>8.3</td>
<td>13.1</td>
<td>17.9</td>
<td>8.9</td>
<td>22.0</td>
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<tr>
<td>Pt 3</td>
<td>28.1</td>
<td>9.4</td>
<td>14.2</td>
<td>19.0</td>
<td>10.0</td>
<td>24.2</td>
</tr>
<tr>
<td>Pt 4</td>
<td>28.1</td>
<td>9.4</td>
<td>14.2</td>
<td>19.0</td>
<td>10.0</td>
<td>24.2</td>
</tr>
<tr>
<td>Pt 5</td>
<td>27.0</td>
<td>9.0</td>
<td>13.8</td>
<td>18.6</td>
<td>18.0</td>
<td>31.8</td>
</tr>
</tbody>
</table>

**More pts to be accumulated prior to presentation**

SP = Early OR Late SPECT/CT  
DP = Early AND Late SPECT/CT
Hyperparathyroidism

Sestamibi Scan

- positive
  - MIRP
    - positive: unilateral exploration with turbo PTH
    - negative: ultrasound
  - negative: ultrasound

- negative: ultrasound
  - positive: bilateral exploration with turbo PTH
  - negative: 4DCT???
Summary

- Pre-op PA image localization is beneficial to the patient.

- MIBI Scintigraphy considered standard for this.

- SPECT/CT esp. useful for difficult cases.

- 4DCT may prove useful for last resort, cost-effective, & if optimized to similar radiation dose.

- This is a team effort!
Thank You!!