LOCALIZATION STUDIES FOR PRIMARY HYPERPARATHYROIDISM

Marika Russell, MD, FACS
Assistant Professor
UCSF Otolaryngology-Head and Neck Surgery

Overview

- Background
- Review of imaging techniques
  - Ultrasound
  - Sestamibi (MIBI)
  - SPECT
  - SPECT/CT
  - 4D CT
- Diagnostic efficacy
- Adjunctive localization measures

Background: Overview

- Shift over last 10-15 years
- Four gland exploration -> minimally invasive/targeted parathyroidectomy
  - Drivers:
    - Decrease operative time
    - Decrease morbidity
    - Improve cosmesis
  - Effectors:
    - ioPTH
    - Improved imaging techniques
Background: Case Example

- 44 yo M, incidental finding elevated Ca++
- w/u reveals primary hyperparathyroidism
- Sestamibi: “area of persistent focal uptake inferior to left thyroid lobe suggestive of parathyroid adenoma”
- Radiology U/S: “1.9 cm right parathyroid adenoma candidate inferior to the left thyroid lobe. Recommend correlation with nuclear medicine sestamibi scan”
Ultrasound: Advantages

- Non-invasive
- No ionizing radiation
- Inexpensive
- Readily repeatable
- Surgeon performed US: direct, real-time interpretation of images; instrumental component of physical exam
- Surgeon performed US enhances understanding of anatomy and informs surgical plan


Ultrasound: Limitations

- Obese patient, short neck
- Concurrent thyroid pathology
- Intrathyroidal adenoma
- Ectopic glands obscured by bone or air columns
  - Mediastinal
  - Retrotracheal
  - Retroesophageal


US: Imaging Characteristics

- Normal parathyroid glands not typically visualized
- PT adenoma
  - Homogenous, hypoechoic nodule
  - Well circumscribed
  - Ovoid, bilobed, longitudinal
  - Rate of detection increases with size; threshold ~4-8mm
- Hyperplastic glands difficult to detect unless marked increase in size


US: Imaging Characteristics

R superior PT adenoma: transverse
R superior PT adenoma: longitudinal

**US: Imaging Characteristics**

L inferior PT adenoma: transverse

L inferior PT adenoma: longitudinal


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**Parathyroid Scintigraphy**

**Sestamibi (MIBI)**

- First reported in 1989
- Utilizes $^{99m}$Tc sestamibi (MIBI)
- Concentrates in thyroid and parathyroid; washes out more rapidly in thyroid
- Dual phase methodology
- Planar imaging

Sestamibi (MIBI)

First reported in 1989

Utilizes $^{99m}$Tc sestamibi (MIBI)

Concentrates in thyroid and parathyroid; washes out more rapidly in thyroid

Dual phase methodology

Planar imaging
Sestamibi (MIBI)

- **Advantages**
  - Simple, easy to perform
  - Single injection MIBI

- **Limitations**
  - Smaller size
  - Less sensitive for multiglandular disease, hyperplastic PT
  - False positives with thyroid nodule or carcinoma

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SPECT (Single Photon Emission Computed Tomography)

- **3D imaging of MIBI uptake**
- **Localization**
  - Thyroid vs. parathyroid
  - Posterior adenoma (descended superior PT)
  - Anatomic location: ectopic PT adenoma

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SPECT

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SPECT/CT

- **Fuses SPECT and CT images for more precise anatomic localization**
- Typically acquired at single time interval (early vs. late)
- Radiation dose associated with CT scan

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4D CT

- Utilizes time (contrast washout) as "4th dimension (≥2 contrast phases)
- Parathyroid adenoma
  - Peak enhancement on arterial phase
  - Washout in delayed phase
  - Low attenuation in non-contrast images

Diagnostic Efficacy: Ultrasound

- Sensitivity: 27-95%
  - Wide range
  - Varies with experience
- Specificity: 92-97%

Khati N et al. Ultrasound Q 2003;19:162-76
Diagnostic Efficacy: Surgeon-performed US

Otolaryngologist–Head and Neck
Surgeon-Performed Ultrasonography for Parathyroid Adenoma Localization

Thomas A. Garvey, MD; Louis A. Ochoff, MD

<table>
<thead>
<tr>
<th>n</th>
<th>Side (Right vs. Left)</th>
<th>Side and Quadrant (Superior vs. Inferior)</th>
<th>US</th>
<th>MIBI</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>29</td>
<td>90%</td>
<td>71%</td>
<td>0.0578</td>
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</table>

Laryngoscope 2008;118:243-46

Diagnostic Efficacy: Surgeon-performed US

Parathyroid Adenoma Localization: Surgeon-Performed Ultrasound Versus Sestamibi

David L. Stewart, MD; Gregory P. Grestan, MD; Chad R. Afran, MD; Jeffrey A. Walp, PhD

<table>
<thead>
<tr>
<th>n</th>
<th>Side (Left vs right) and Quadrant (Superior vs. Inferior)</th>
<th>US</th>
<th>MIBI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>103</td>
<td>87%</td>
<td>58%</td>
<td>&lt; 0.001</td>
<td></td>
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</tbody>
</table>

Laryngoscope 2006;116:1380-4

Diagnostic Efficacy: Surgeon-performed US

Surgeon-Performed Ultrasound is Superior to 99Tc-Sestamibi Scanning to Localize Parathyroid Adenomas in Patients with Primary Hyperparathyroidism: Results in 516 Patients over 10 Years

Brian R. Uech, MD; Mohamed M. AlAzab, MS; Randall P. Seka, MD; Shuhi; Kusa M. Reznik, MS; Diamond Davis, MA; Christy, Webb, BS; George, M. Leigh Jr, MD; Jack, A. Ochoff Jr, MD; et al

- 392 patients with PHPT underwent SUS
- 357/392 (91%) with positive finding
- 342/392 (87%) were TP
- Sensitivity 91%
- PPV 96%


Diagnostic Efficacy: Surgeon-performed US

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- 32/392 (8%) were FN
  - Deep tracheoesophageal groove (9)
  - Thyrothymic ligament below clavicle (5)
  - Concurrent thyroid goiter (4)
  - Thyroid cancer (1)
  - Normal location, missed (13)

Diagnostic Efficacy: Surgeon-performed US

Surgeon-Performed Ultrasound Is Superior to 99Tc-Sestamibi Scanning to Localize Parathyroid Adenomas in Patients with Primary Hyperparathyroidism: Results in 516 Patients over 10 Years

- 156 pts with SUS before MIBI
- PT candidate in 140/156 (90%)
- TP SUS 131/156 (84%)
- 144/156 (92%) no additional info from MIBI
- Strategy to reserve MIBI for unclear or negative SUS


Diagnostic Efficacy: Surgeon-performed US

Surgeon-Performed Ultrasonography as the Initial and Only Localizing Study in Sporadic Primary Hyperparathyroidism

- 226 patients with PHPT
- 173/226 (77%) localized with SUS
- 53/226 not localized with SUS
  - No parathyroid gland (32)
  - Failed to recognize multiglandular disease (5)
  - Incorrect location of abnormal gland (16)


Summary: Surgeon-performed US

- Inexpensive, non-invasive
- Highly effective in hands of surgeon
- May be more sensitive than MIBI
- Limited in:
  - Ectopic/extra-cervical disease
  - Concomitant thyroid disease
  - Multiglandular disease
- Argument for SUS as primary localizing study; MIBI as adjunct

## Sensitivity: MIBI vs. US

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>US (%)</th>
<th>Tc-Mibi (%)</th>
<th>Combined (%)</th>
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<tr>
<td>Casas</td>
<td>1993</td>
<td>22</td>
<td>67</td>
<td>100</td>
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<tr>
<td>Light</td>
<td>1996</td>
<td>21</td>
<td>57</td>
<td>87</td>
<td></td>
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<tr>
<td>Mazzeo</td>
<td>1996</td>
<td>73</td>
<td>85</td>
<td>82</td>
<td></td>
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<tr>
<td>Sofferman</td>
<td>1996</td>
<td>33</td>
<td>89</td>
<td>91</td>
<td></td>
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<tr>
<td>Ishibashi</td>
<td>1998</td>
<td>20</td>
<td>78</td>
<td>83</td>
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<tr>
<td>Ammori</td>
<td>1998</td>
<td>72</td>
<td>80</td>
<td>100</td>
<td></td>
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<tr>
<td>Purcell</td>
<td>1999</td>
<td>61</td>
<td>57</td>
<td>54</td>
<td>78</td>
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<tr>
<td>Joshua</td>
<td>2004</td>
<td>319</td>
<td>86</td>
<td>70</td>
<td></td>
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<tr>
<td>Hajioff</td>
<td>2004</td>
<td>48</td>
<td>64</td>
<td>83</td>
<td>96</td>
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<tr>
<td>Mekel</td>
<td>2005</td>
<td>146</td>
<td>61</td>
<td>74</td>
<td>83</td>
</tr>
</tbody>
</table>


## MIBI vs. SPECT vs. SPECT/CT

- SPECT generally purported to have better detection capability than planar imaging
  - Studies with mixed results
  - Most utilize single SPECT
- SPECT/CT offers theoretical advantages over MIBI, SPECT
  - Few large series with direct comparisons

## MIBI vs. SPECT vs. SPECT/CT

**Comparison of SPECT/CT, SPECT, and Planar Imaging with Single- and Dual-Phase 99mTc-Sestamibi Parathyroid Scintigraphy**

William C. Lavely, Sibyl Goehle, Kent P. Friedman, Jeffrey P. Leal, Zhe Zhang, Elizabeth Garret-Mayer, Alan P. Dackow, Ralph P. Tufano, Martha A. Zeiger, and Harvey A. Ziesman

- Lavely et al., 2007
  - Prospective comparison
  - 210 pts submitted to protocol
    - 98 with single adenomas at surgery included in analysis


## MIBI vs. SPECT vs. SPECT/CT

- Early and late images obtained for every patient
  - Planar
  - SPECT
  - SPECT/CT
- Every combination of study was generated
  - 2 reviewer groups examined all combinations for adenoma localization
  - Level of certainty measured
  - Compared against surgical localization

MIBI vs. SPECT vs. SPECT/CT

**Table 2**

<table>
<thead>
<tr>
<th>Imaging method</th>
<th>P value</th>
<th>Sensitivity</th>
<th>AUC</th>
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</thead>
<tbody>
<tr>
<td>Planar E vs. planar D</td>
<td>0.004</td>
<td>0.685</td>
<td>0.717</td>
</tr>
<tr>
<td>Planar E vs. planar D (early)</td>
<td>0.002</td>
<td>0.680</td>
<td>0.715</td>
</tr>
<tr>
<td>Dual-phase SPECT vs. planar D</td>
<td>0.001</td>
<td>0.684</td>
<td>0.716</td>
</tr>
<tr>
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<td>0.683</td>
<td>0.715</td>
</tr>
<tr>
<td>Dual-phase SPECT/CT vs. planar D</td>
<td>0.027</td>
<td>0.676</td>
<td>0.712</td>
</tr>
<tr>
<td>Dual-phase SPECT/CT vs. planar D (early)</td>
<td>0.027</td>
<td>0.675</td>
<td>0.711</td>
</tr>
<tr>
<td>Single-phase SPECT vs. planar D</td>
<td>0.001</td>
<td>0.684</td>
<td>0.715</td>
</tr>
<tr>
<td>Single-phase SPECT vs. planar D (early)</td>
<td>0.001</td>
<td>0.683</td>
<td>0.715</td>
</tr>
<tr>
<td>Single-phase SPECT vs. planar D (delayed)</td>
<td>0.001</td>
<td>0.683</td>
<td>0.715</td>
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<tr>
<td>Single-phase SPECT vs. planar D (early)</td>
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<td>0.715</td>
</tr>
<tr>
<td>Early SPECT vs. planar D</td>
<td>0.011</td>
<td>0.685</td>
<td>0.717</td>
</tr>
<tr>
<td>Early SPECT vs. planar D (early)</td>
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<td>0.683</td>
<td>0.715</td>
</tr>
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**MIBI vs. SPECT vs. SPECT/CT**

- Better agreement on certainty for dual-phase studies compared with single-phase studies
- **Planar:** Dual-phase more sensitive than single-phase (early or delayed)
- **SPECT:** Dual-phase more sensitive than single-phase (early or delayed)
- **SPECT/CT:** Dual-phase SPECT/CT more sensitive than single-phase (early or delayed)
  - Early more sensitive than late

**MIBI vs. SPECT vs. SPECT/CT**

- **SPECT vs. Planar:**
  - SPECT (single- or dual-phase) not significantly better than dual-phase planar
- **SPECT/CT vs. Planar:**
  - Single-phase SPECT/CT not significantly better than dual-phase planar
  - Dual-phase SPECT/CT more sensitive than dual-phase planar
  - Early SPECT/CT with delayed planar imaging more sensitive than dual-phase planar

**MIBI vs. SPECT vs. SPECT/CT**

- **Conclusion:**
  - Early SPECT/CT in combination with any delayed imaging (planar, SPECT or SPECT/CT) more sensitive than dual-phase planar


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**4D CT**

- **Kelly et al., 2014**
  - Retrospective series, 208 pts
  - 155 initial; 53 re-operations
  - 233/284 lesions (82%) correctly localized with 4D-CT
  - 46/48 (95.8%) re-operative cases correctly localized unilateral vs. bilateral

  Kelly et al. AJNR 2014

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**4D CT**

- **Hunter et al., 2012**
  - Retrospective study, 143 patients
  - Single adenoma
  - Accuracy of side and quadrant
    - Laterality 93.7%
    - Quadrant 86.6%
  - Median weight 417 mg

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**4D CT vs. US vs. SPECT**

- **Cheung et al., 2012**
  - Meta-analysis
  - 43 studies
  - Initial parathyroidectomy for PTHP

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>76.1%</td>
<td>93.2%</td>
</tr>
<tr>
<td>SPECT</td>
<td>78.9%</td>
<td>98.7%</td>
</tr>
<tr>
<td>4D CT</td>
<td>89.4%</td>
<td>93.5%</td>
</tr>
</tbody>
</table>

Cheung et al. 2012 Ann Surg Oncol
4D CT: Conclusions
- Effective tool, may offer improved accuracy
- Dependent on quality of imaging study
- Should be reserved for select cases

Adjunctive techniques: FNA
- 2005 position statement
- USG-FNA for PTH analysis: sensitive method of localization

USG-FNA: Parathyroid
- Abraham et al., 2007
  - Retrospective review
  - 32 pts with PHPT underwent USG-FNA with PTH washout
    - 30 solitary adenomas
    - 2 multigland hyperplasia
  - Control: 13 thyroid nodule FNA
  - Mean PTH level: ~22,000
    - mean thy nodule PTH level: 9.0, p<0.001

USG-FNA Parathyroid
- Abdelghani et al. 2013
  - 24 pts with recurrent/persistent PHPT
  - USG-FNA PTH washout
cytopathologic analysis
  - 22/24 (91.6%) elevated PTH in washout concentrations
    - PPV 100%
  - 7/24 (29%) positive cytology
  - Conclusion: USG-FNA PTH washout helpful in reoperative setting
USG Interventions: Parathyroid

Intraoperative Tumor Localization with Surgeon-Performed Ultrasound-Guided Needle Dye Injection

William B. Byun, MD, Leen A. Orloff, MD

Laryngoscope 2011;121:11-55

Ultrasound-Guided Methylene Blue Dye Injection for Parathyroid Localization in the Reoperative Neck

Leah Condel • Michael J. Campbell • Wes E. Metz • Jessica E. Courth • Olga H. Clark • Quan-Ying Dinh


Conclusions

- Minimally invasive parathyroidectomy is facilitated by highly sensitive localization studies
- Surgeon performed ultrasound is highly effective in management of PHPT
- MIBI is workhorse of parathyroid scintigraphy; should be used in combination with or as an adjunct to US
- SPECT questionable value over MIBI
- SPECT/CT and 4D CT may be valuable in select cases
- Identify what works well at your institution

Thank you