# Parathyroid Imaging in 2015

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GLOBAL ADVANCED IMAGING, LLC

*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

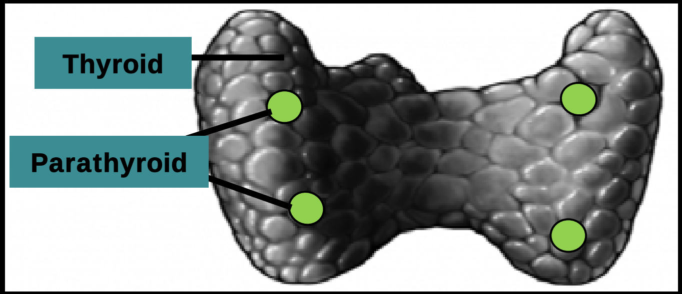
*Deshmukh RG et al. Primary hyperparathyroidism presenting with pathological fracture. J Royal Coll of Surg. 1998;43:424-7.*

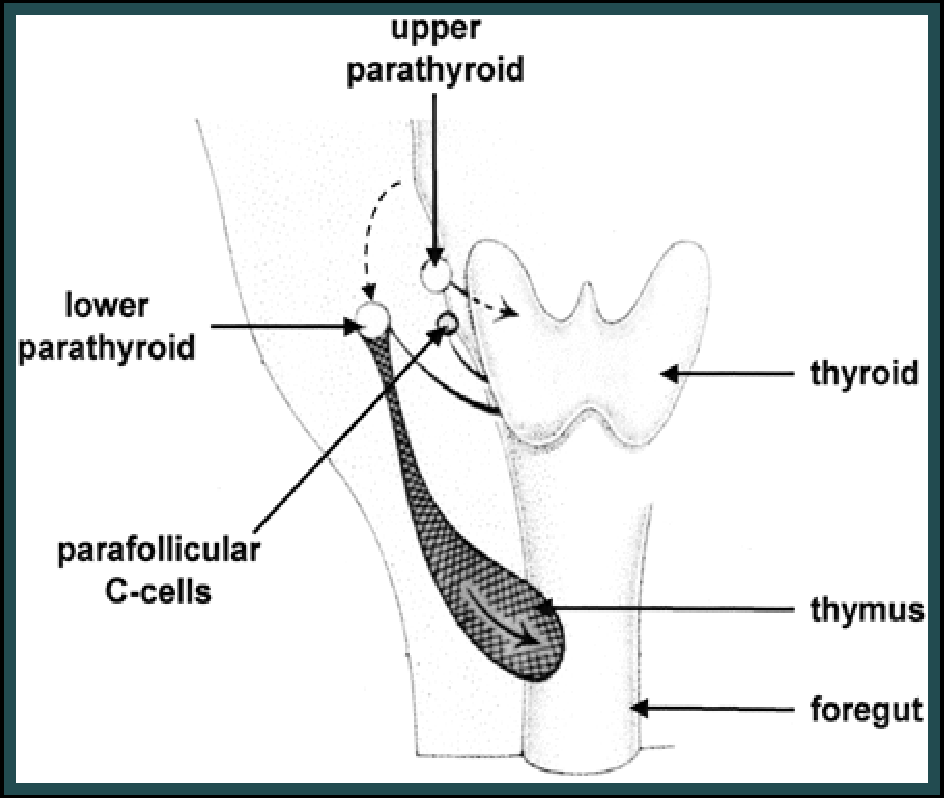
*Bolland MJ et al. Association between primary hyperparathyroidism and increased body weight: a metanalysis. 2004;90:1525.*

*Yeh MW et al. Incidence and primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab. 2013; 98: 1122-9.*

# Anatomy

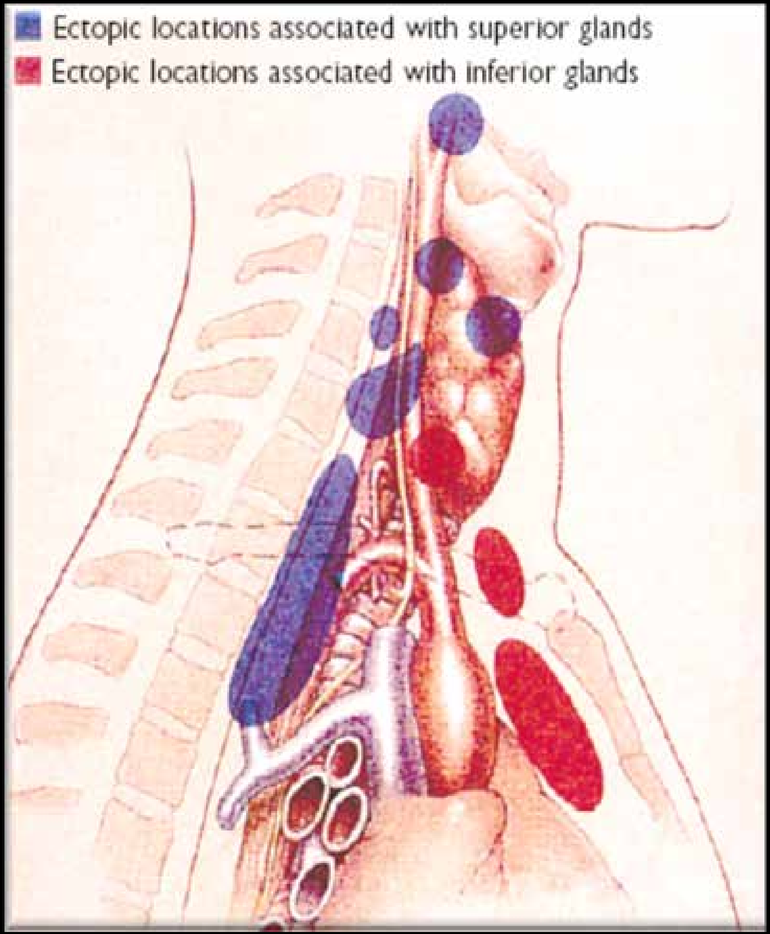
- Most have 2 upper & 2 lower




- Upper (superior):
  - 4th pharyngeal pouch
  - Posterolateral to upper thyroid lobes
  - Usually 1-2 cm superior to recurrent laryngeal nerve
- Lower (inferior):
  - 3rd 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

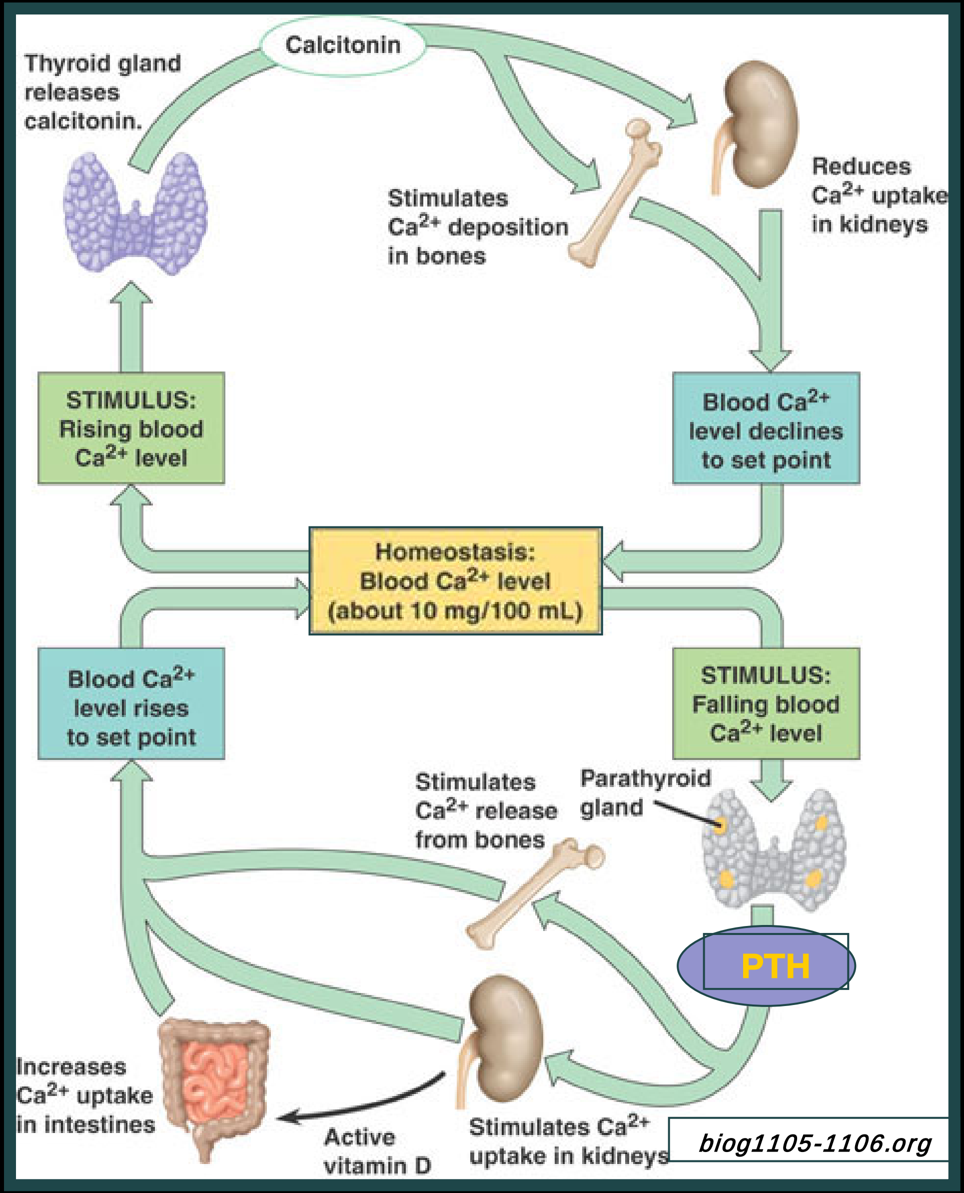



| | |
|---|---|
| Intra-Thymic & Intra-Thyroidal | 33-38% |
| Retroesophageal | 31% |

*Phitayakorn R et al. Incidence and location of ectopic abnormal parathyroid glands. Am J Surg. 2006;191:418-23.*

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

# Function




## *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"**

| | |
|---|---|
| GI | Dry mouth, thirst, polydipsia, anorexia, nausea, vomiting, constipation |
| GU | Polyuria/nocturia,renal stones, nephrocalcinosis, uremia |
| MS | Fatigue, muscle weakness, arthralgia, bone pain, osteoporosis |
| Neuro | Drowsiness, lethargy, stupor, confusion |

- **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 ↑PTH, ↑Ca, ↓phosphate

# Forms of Hyperparathyroidism

## *PRIMARY*

- Single adenoma in 80-90%
- Multiple in 10-19%
  - Hyperplasia
  - Multiple Endocrine Neoplasia
  - Multiple Adenomas (2-3%)
- Malignancy < 1%

# *Forms of Hyperparathyroidism*

## *SECONDARY*

- 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 ↑ PTH

# *Imaging*

- Ultrasound
- MRI
- Conventional CT
- 4DCT
- Interventional
- Scintigraphy

# *Imaging*

- **Many surgeons advocate for 2 concurrent imaging studies for localizing a parathyroid adenoma**

- **US and scintigraphy level II evidence as first-line imaging (US first, then scintigraphy confirmatory)**

*Phillips CD, Shatzkes DR. Imaging of the parathyroid glands. Semin US CT MR. 2012; 33:123-9.*

# *Imaging Performance*

| | US | MIBI scan | combined | CDUS |
|---|---|---|---|---|
| Sensitivity | 88% | 70% | 87% | 97% |
| Specificity | 94% | 100% | 100% | 100% |
| Accurracy | 91% | 85% | 98.6% | 98.6% |

N = 56

*Mohammadi A et al. Preoperative localization of parathyroid lesion: diagnostic usefulness of color doppler ultrasonography. Int J Clin Exp Med. 2012;5:80-6.*

| | Sensitivity | Specificity |
|---|---|---|
| **MIBI (planar)** | **88%** | **82%** |
| **MIBI (SPECT)** | **100%** | **85%** |
| **MRI** | **94%** | **95%** |

*Denham et al. J Am Coll Surg 1998;186:293-304* *Meta-analysis of 50 studies*

**4DCT - 92% sensitivity, 93% specificity**

*Chazen JL et al. AJNR. 2012;33:429-33* N = 35

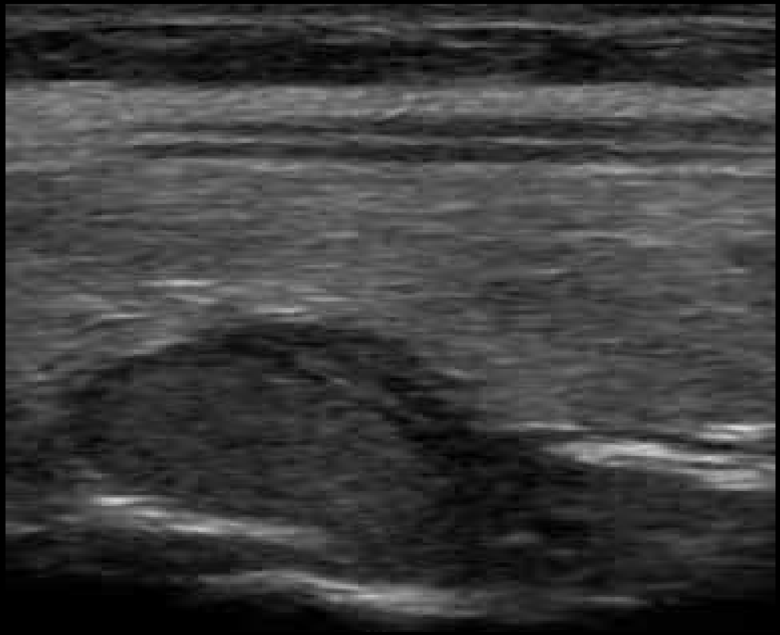
**CEUS - Did not improve from US or MIBI**

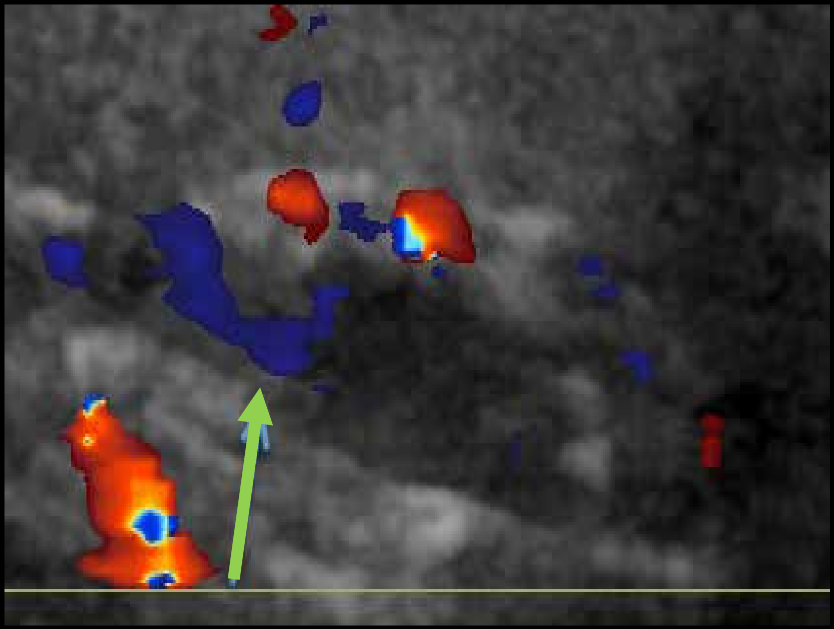
*Karakas E et al. J Clin Imaging Sci. 2012;2:64* N = 25

# *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*

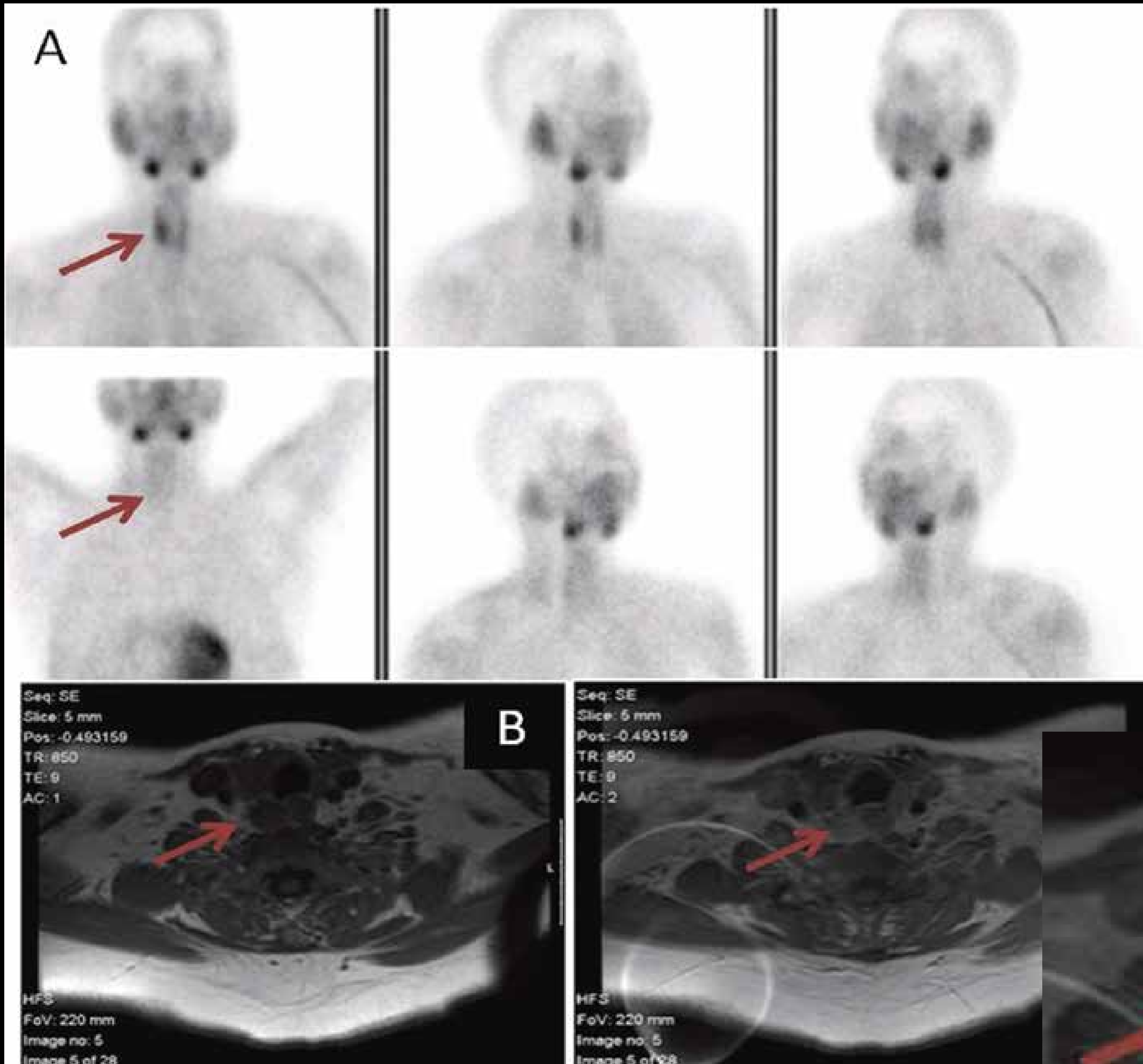
- Not typically first line
- Surface neck and chest coils for mediastinum
- Hyoid bone to lung apices; 3 mm thickness
- T1 hypointense, T2/STIR hyperintense, avid enhancement (but 30% without this typical pattern)
- Sensitivity 64 – 78%; Specificity 88 – 95%
- Useful for detecting ectopic mediastinal glands (sensitivity > 80%)

*Medscape*

*Dijkstra B, Healy C, Kelly LM et al. Parathyroid localization – current practice. J R Coll Edinb. 2002; 47:599-607.*

# *MRI*

- 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*
*Dijkstra B, Healy C, Kelly LM et al. Parathyroid localization – current practice. J R Coll Edinb. 2002; 47:599-607.*

# *4DCT*

- 4$^{th}$ 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)

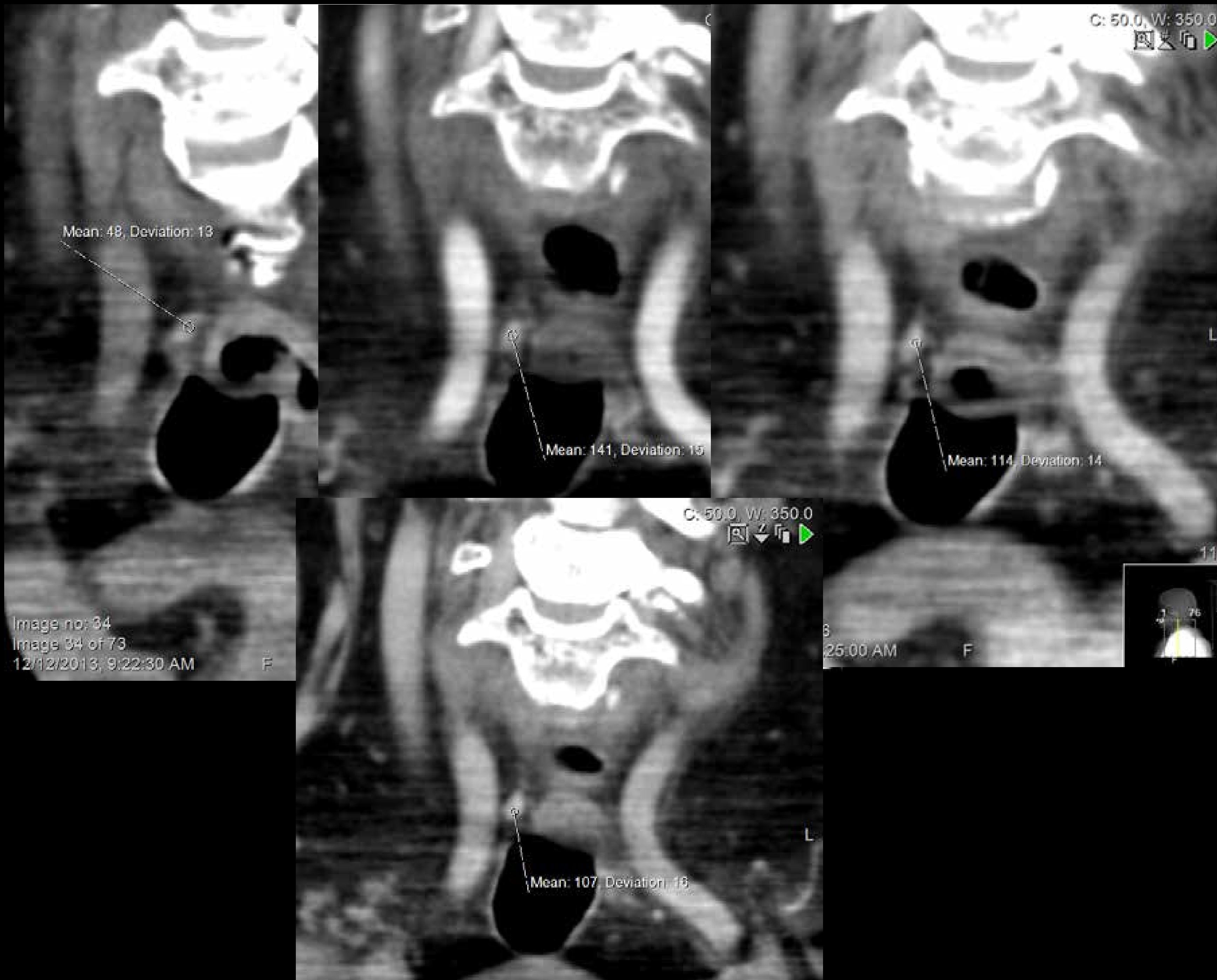

Mean: 48, Deviation: 13
Mean: 141, Deviation: 15
Mean: 114, Deviation: 14
Mean: 107, Deviation: 16
C: 50.0, W: 350.0
C: 50.0, W: 350.0
L
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Image 34 of 73
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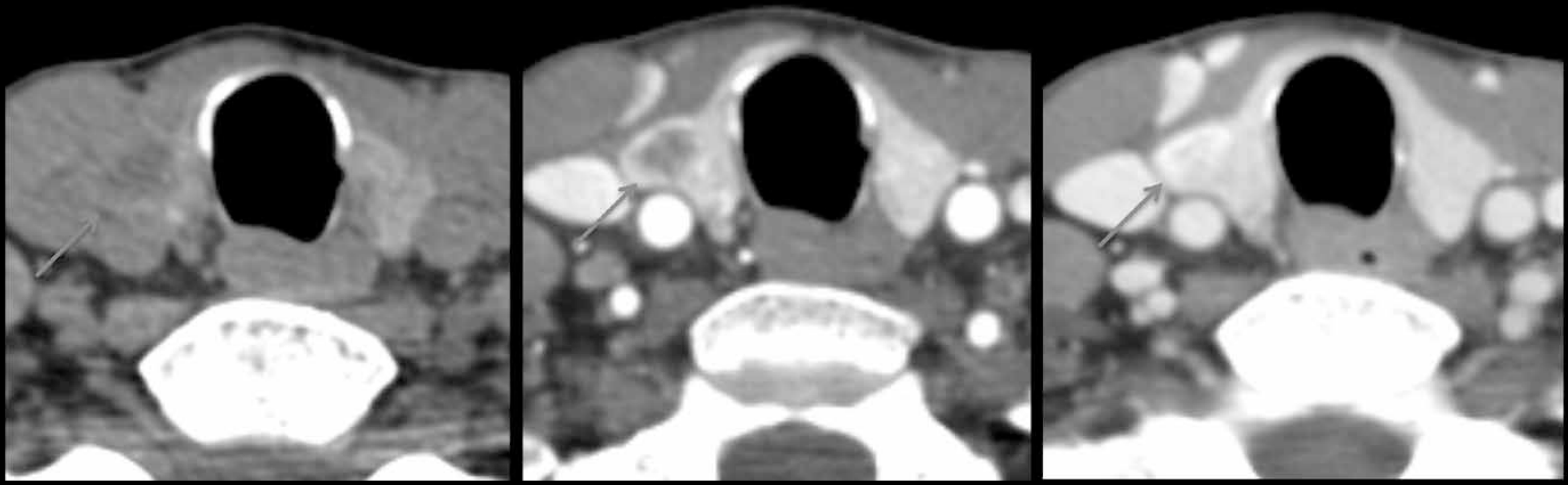
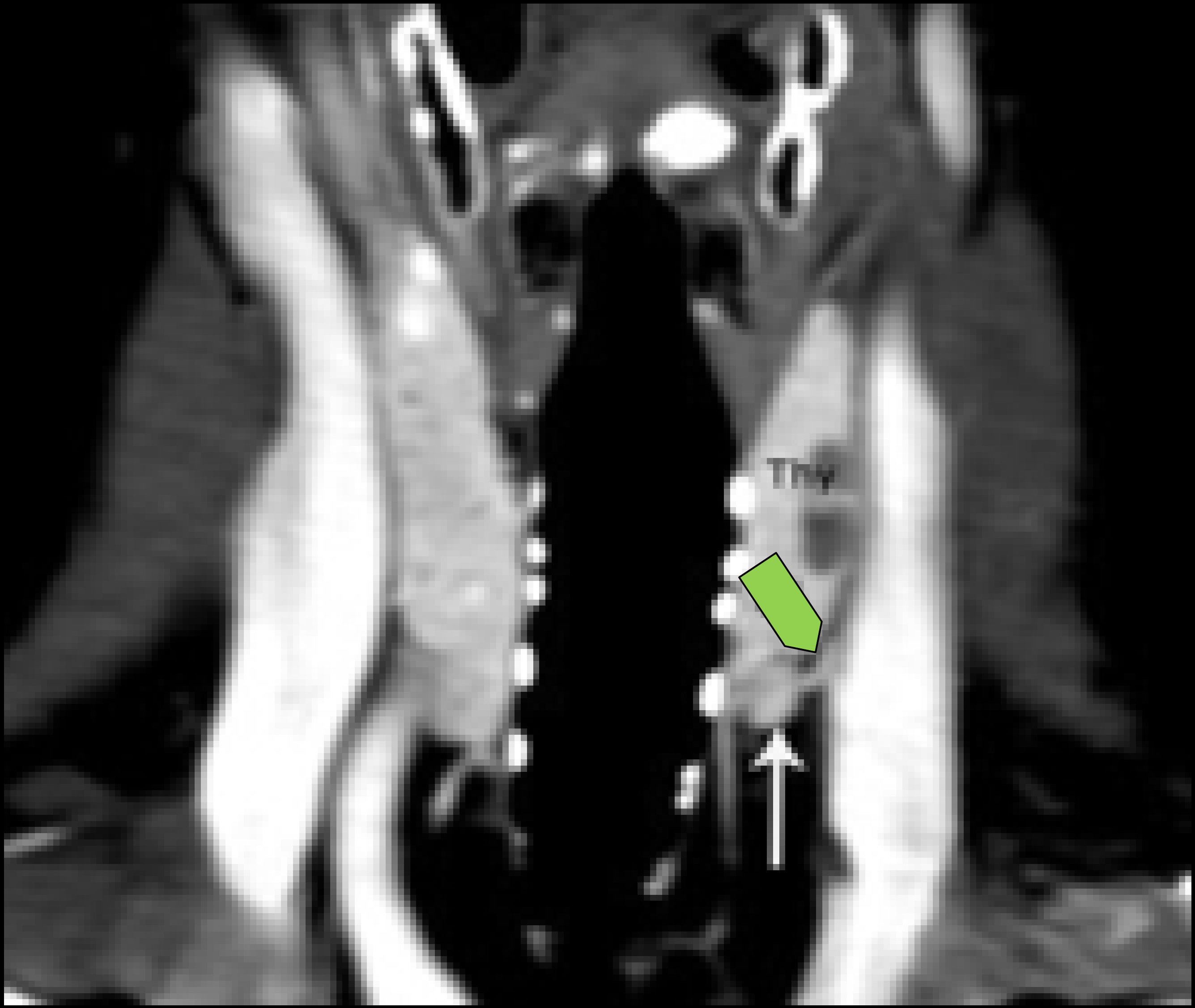


Axial CT images in noncontrast (A) early post-contrast (B) and delayed post-contrast (C) phases demonstrate an intrathyroidal lesion with subtle hypodensity on precontrast imaging and delayed enhancement. This enhancement pattern is seen less commonly than early enhancement and washout.




# Polar Vessel Sign

*Bahl M et al. Prevalence of polar vessel sign in parathyroid adenomas on the arterial phase of 4DCT. AJNR. 2014;35:578-81.*

# *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

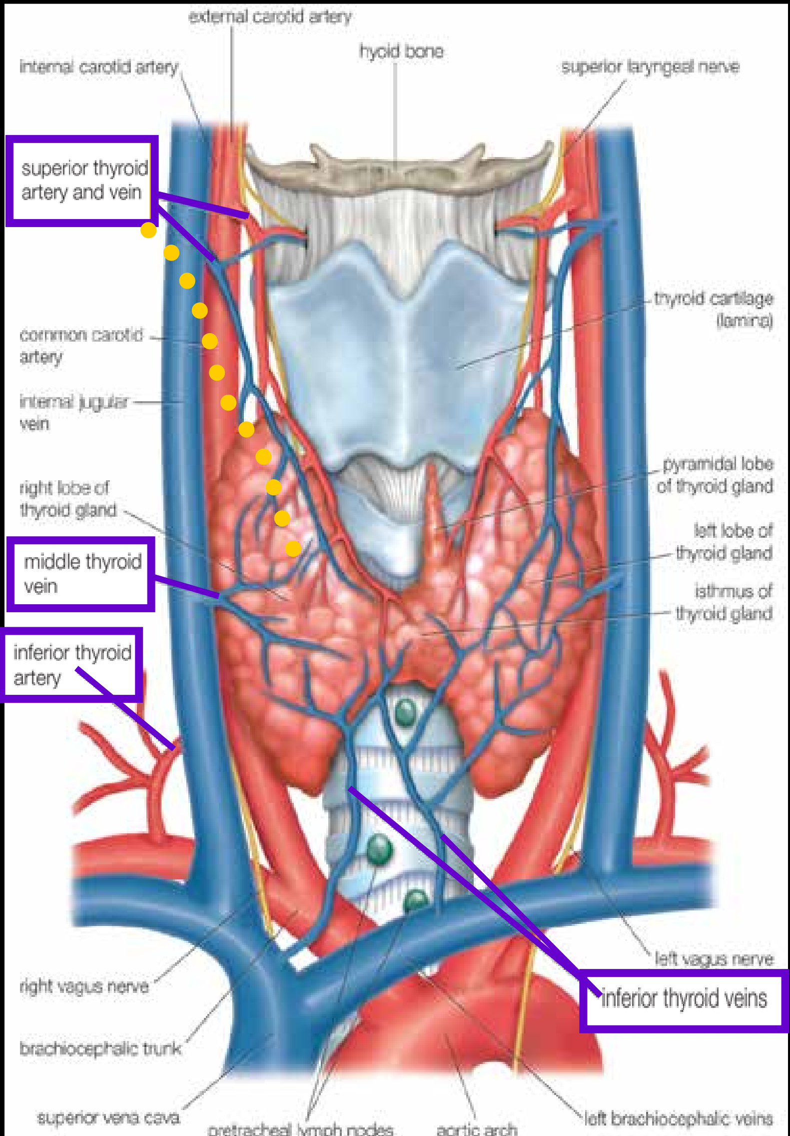
If equivocal, perform digital arteriography or venous sampling with rapid PTH

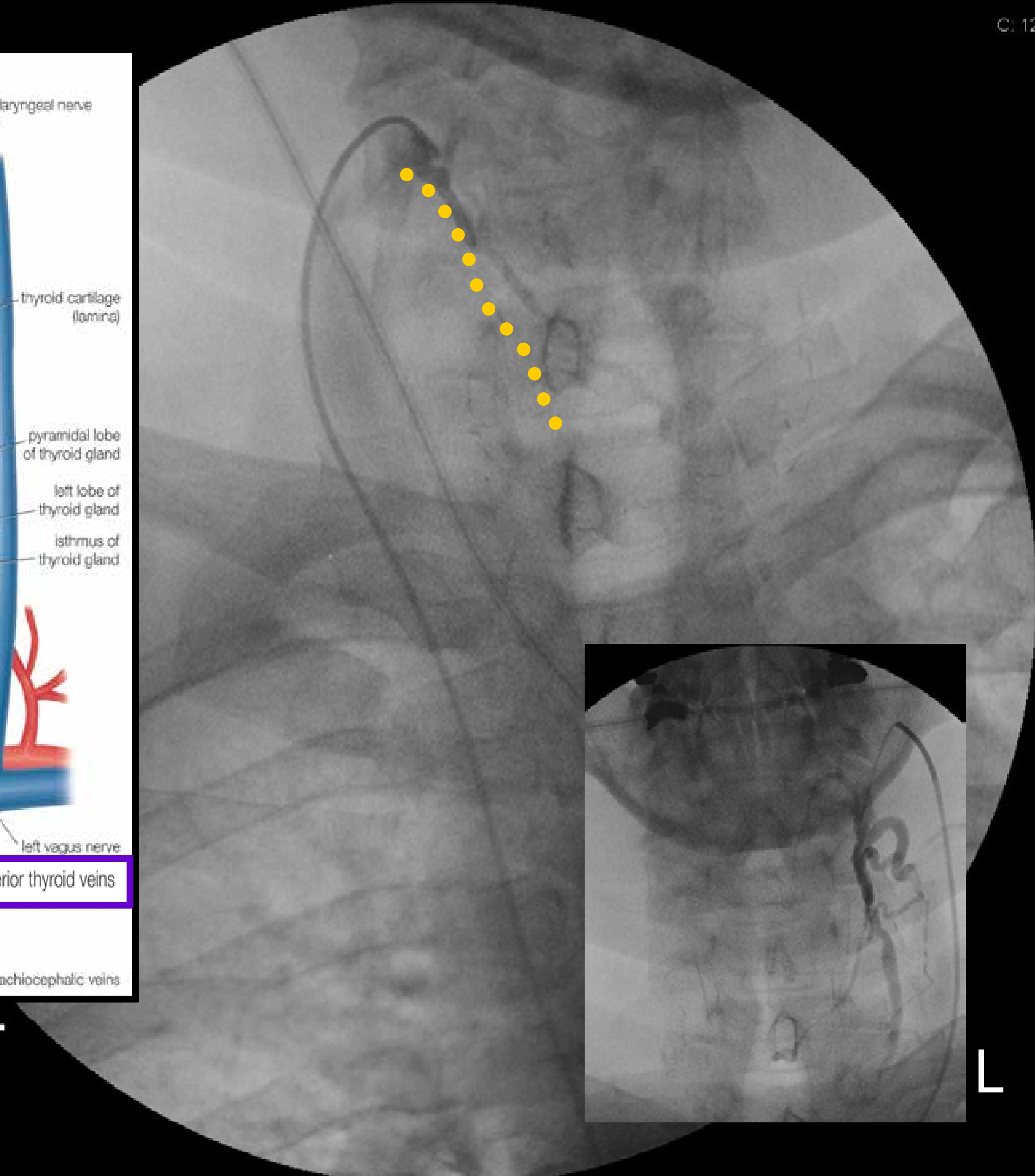
*Savader SJ et al. Venous interventional radiology with clinical perspectives. 2nd Ed. 2000. Thieme.*

- **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

| Site# | Location | Assay result |
|---|---|---|
| 1. | Left Internal Jugular v.—superiorly | 143 |
| 2. | Left Middle thyroidal v. | 102 |
| 3. | Left I. J. vein – Inferiorly | 165 |
| 4. | Left Subclavian v. | 97 |
| 5. | Left Innominate v. | 289 |
| 6. | Hemiazygos v. | 1374 |
| 7. | Right Internal Jugular v.—superiorly | 128 |
| 8. | Right Superior thyroidal v. | 190 |
| 9. | Right I. J. vein – Inferiorly | 99 |
| 10. | Right Subclavian v. | 146 |
| 11. | Right Innominate v. | 130 |
| 12. | Superior Vena Cava | 235 |
| 13. | Azygos v. | 153 |
| 14. | Right atrium | 109 |
| 15. | Common hepatic v. | 87 |
| 16. | Inferior Vena Cava – suprarenal | 136 |


external carotid artery
hyoid bone
internal carotid artery
superior laryngeal nerve
superior thyroid artery and vein
thyroid cartilage (lamina)
common carotid artery
internal jugular vein
pyramidal lobe of thyroid gland
right lobe of thyroid gland
left lobe of thyroid gland
middle thyroid vein
isthmus of thyroid gland
inferior thyroid artery
left vagus nerve
right vagus nerve
inferior thyroid veins
brachiocephalic trunk
superior vena cava
pretracheal lymph nodes
aortic arch
left brachiocephalic veins


RT
L

Adenoma appears as rounded, densely staining blush

Bakal CW, Silberzweig JE et al. Vascular and Interventional Radiology Principles and Practice. 2002. Thieme.

**FIGURE 34-3.** Parathyroid adenoma supplied by the left internal mammary artery. A single vessel from the thymic branch (*long arrow*) of the internal mammary artery supplies an oval, smooth-margined area of intense, homogeneous blush (*wide arrow*), which is typical of a parathyroid adenoma. (From Miller DL. Endocrine angiography and venous sampling. *Radiol Clin North Am* 1993;31:1051–1067, with permission.)

# *Scintigraphy*

## *C-11 methionine (MET-PET)*

**Meta-analysis:**

**9 studies with 258 patients**

**Sensitivity - 81%**

**Detection Rate - 70%**

**Not recommended as first line**

*Caldarella et al. Diagnostic performance of positron emission tomography using C-11-methionine in patients with suspected parathyroid adenoma: a meta-analysis.*

# *Scintigraphy*

## *FDG-PET vs DPMIBI SPECT*

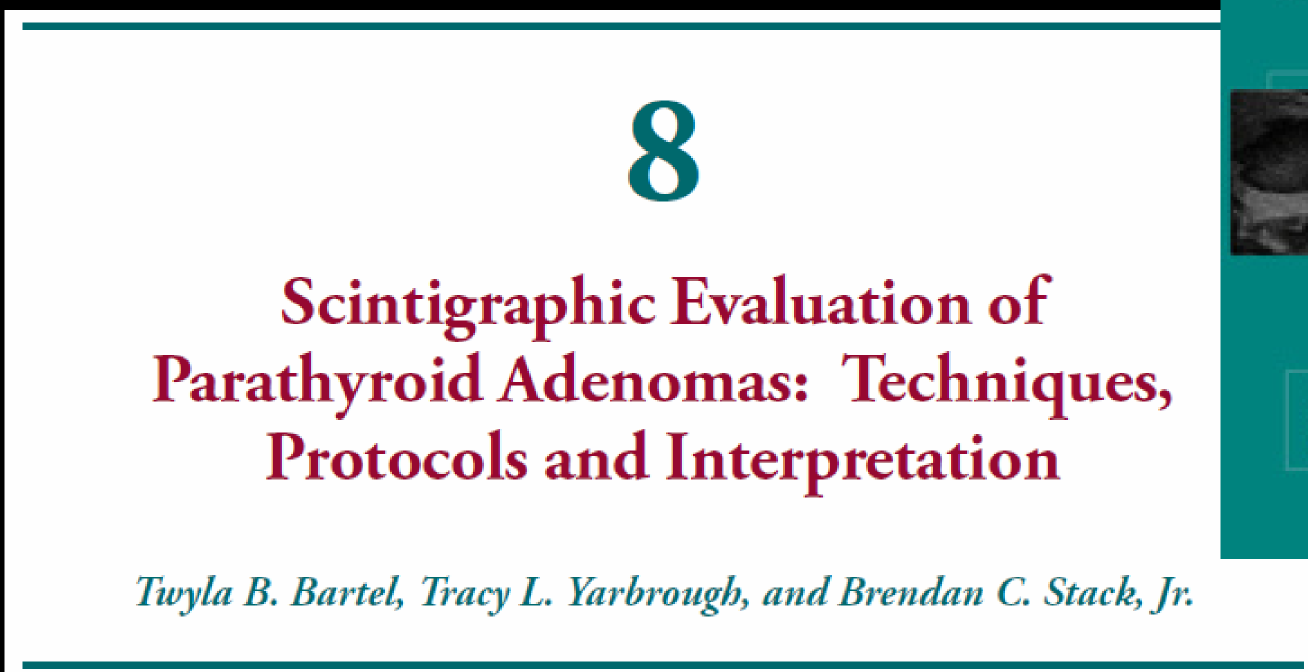
**FDG-PET (N=21):**

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

*Neumann et al. J Nucl Med 1996;37(11):1809-15*

# *Scintigraphy*

Parathyroid Surgery – Fundamental and Advanced Concepts. Plural Publishing. 2014.



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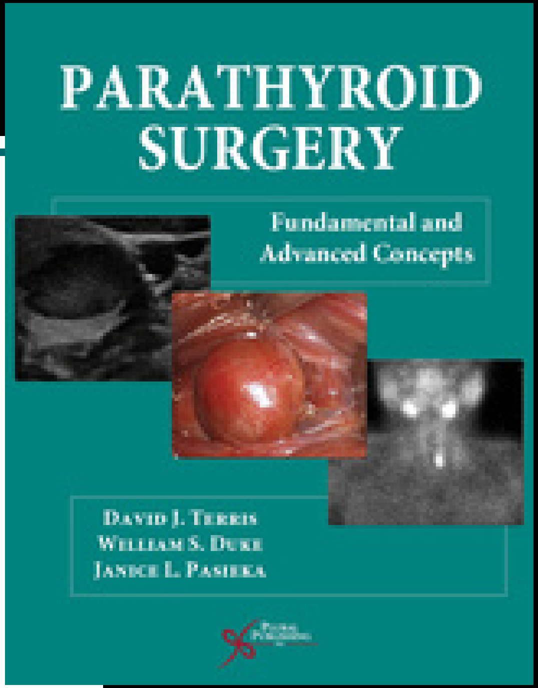
Scintigraphic Evaluation of Parathyroid Adenomas: Techniques, Protocols and Interpretation

*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 (MIBI)** – 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 MIBI; 140 keV, T½ = 6 hrs

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

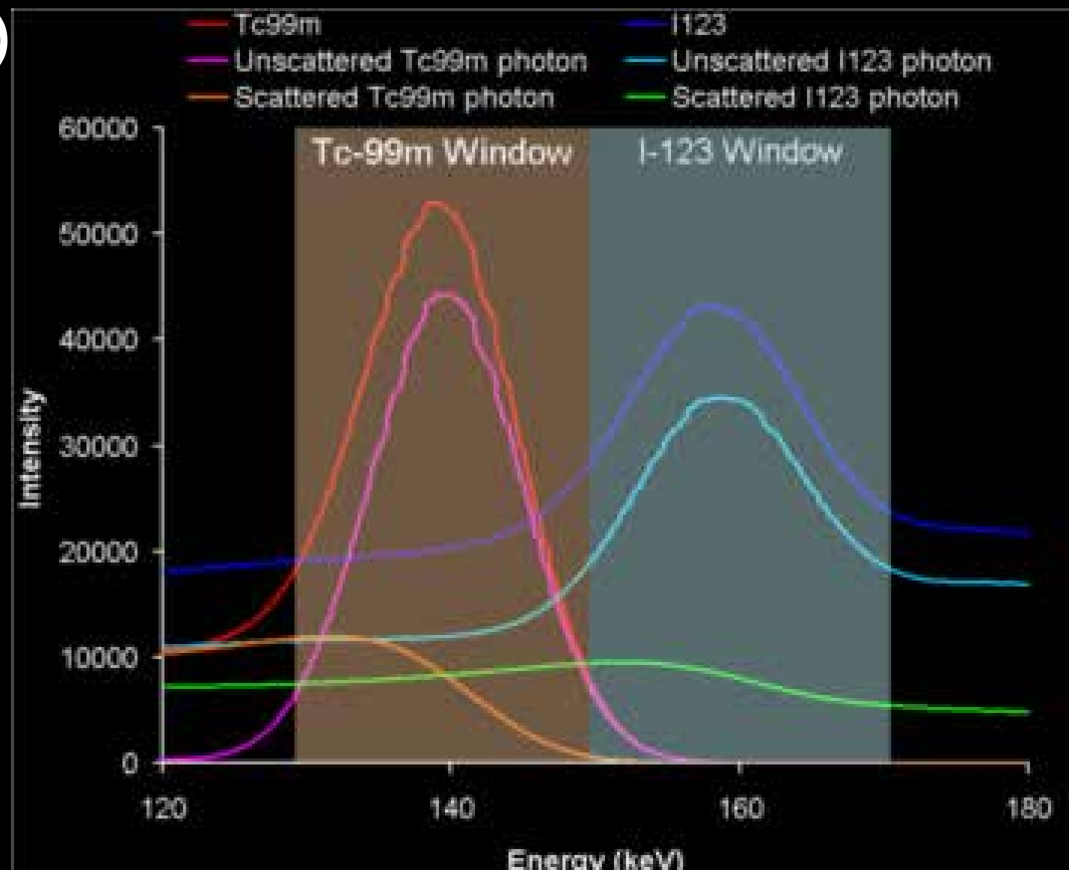
- In-111-pentetrotide (Octreoscan) - some parathyroid glands have somatostatin receptors; 173 & 247 keV, T½ = 67 hrs

- 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: *$^{99m}$Tc-sestamibi/$^{123}$I*

- MIBI uptake by thyroid & parathyroid
- $^{123}$I uptake by thyroid only
- Administer MIBI, then I-123
- Final image = (I-123 – MIBI)

# Tc-99m sestamibi

- 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

  *O'Doherty et al. J Nucl Med 1992;33:313-8*

- Preferred parathyroid imaging agent worldwide
- T1/2 = 6 hours, 140 keV

# *Tc-99m sestamibi*

- 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

# *Tc-99m sestamibi*

*False Positives*:

- Thyroid adenomas
- Cervical lymph nodes
- Malignancy

*False Negatives*:

- Small adenomas
- Displaced/obscured by goiter
- Ectopic adenoma
- Low mitochondrial activity

# *Tc-99m sestamibi*

**Advantages over other radiotracers:**

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

# Tc-99m Sestamibi Dual-Phase Imaging


*Early* *Delayed*

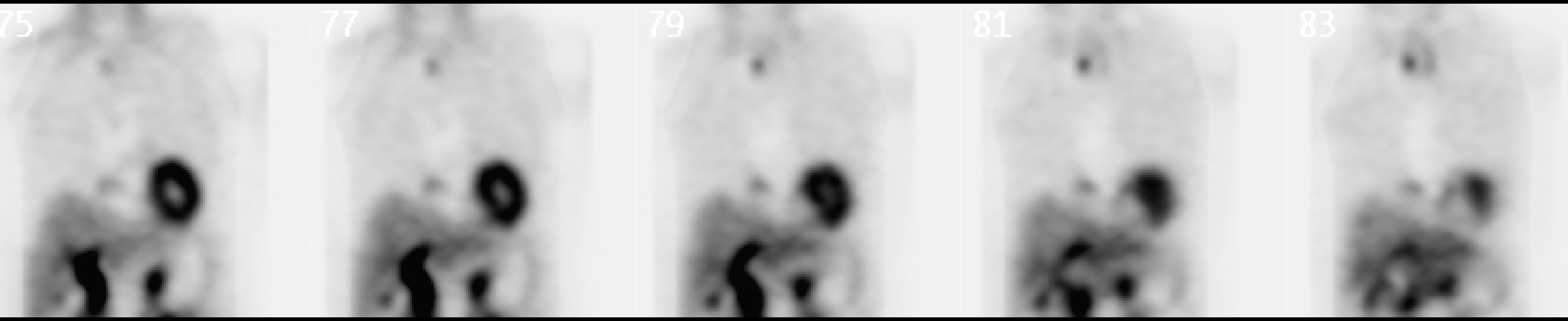
- Uptake by thyroid & parathyroid
- Delayed imaging w/ greater washout from thyroid compared to parathyroid adenoma (persistent focal uptake on delayed images)

# *Single Isotope Dual-Phase SPECT Imaging*

- **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**

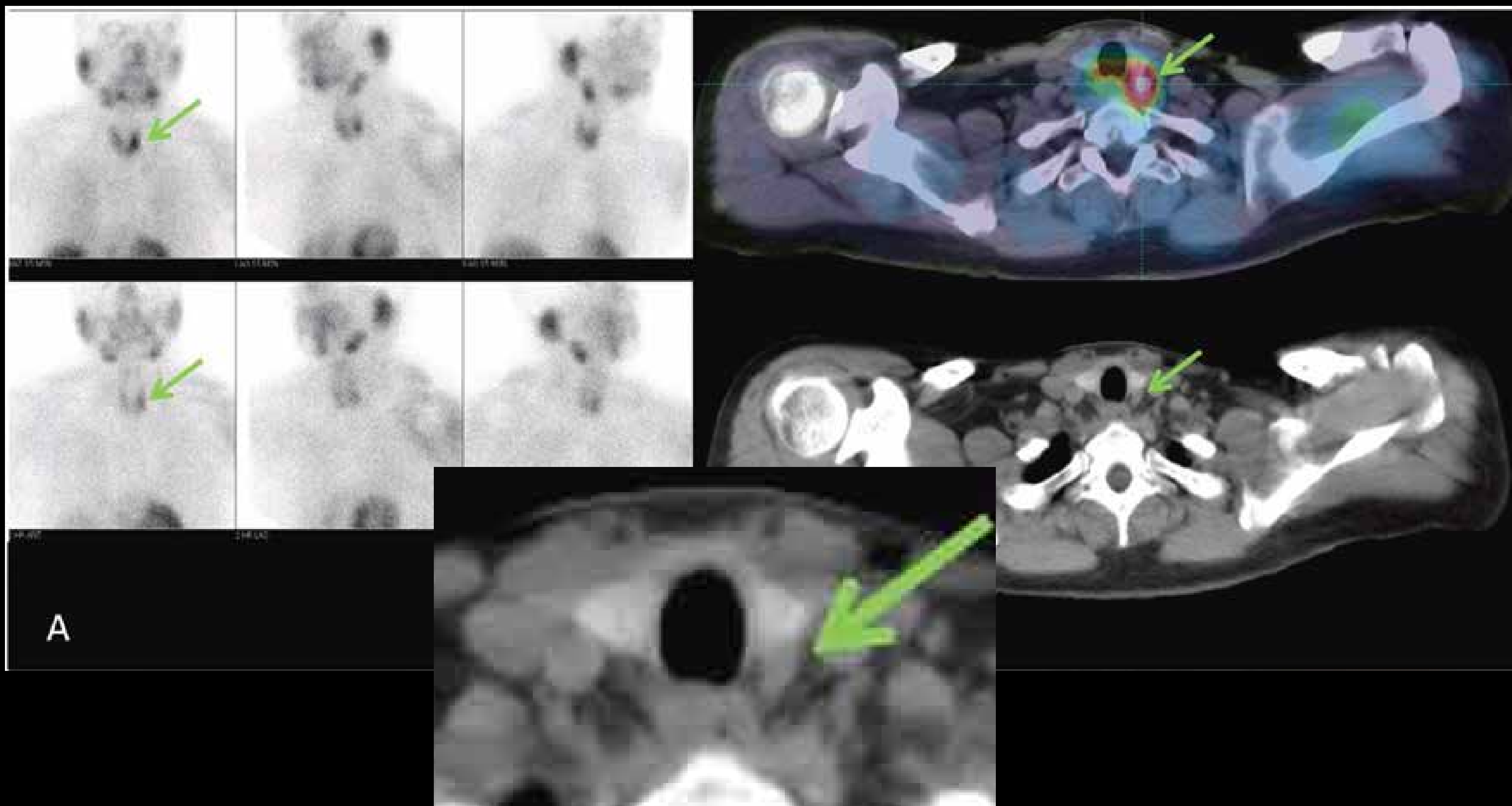
# *Tc-99m Sestamibi Dual-Phase SPECT Imaging*


*Early Images*



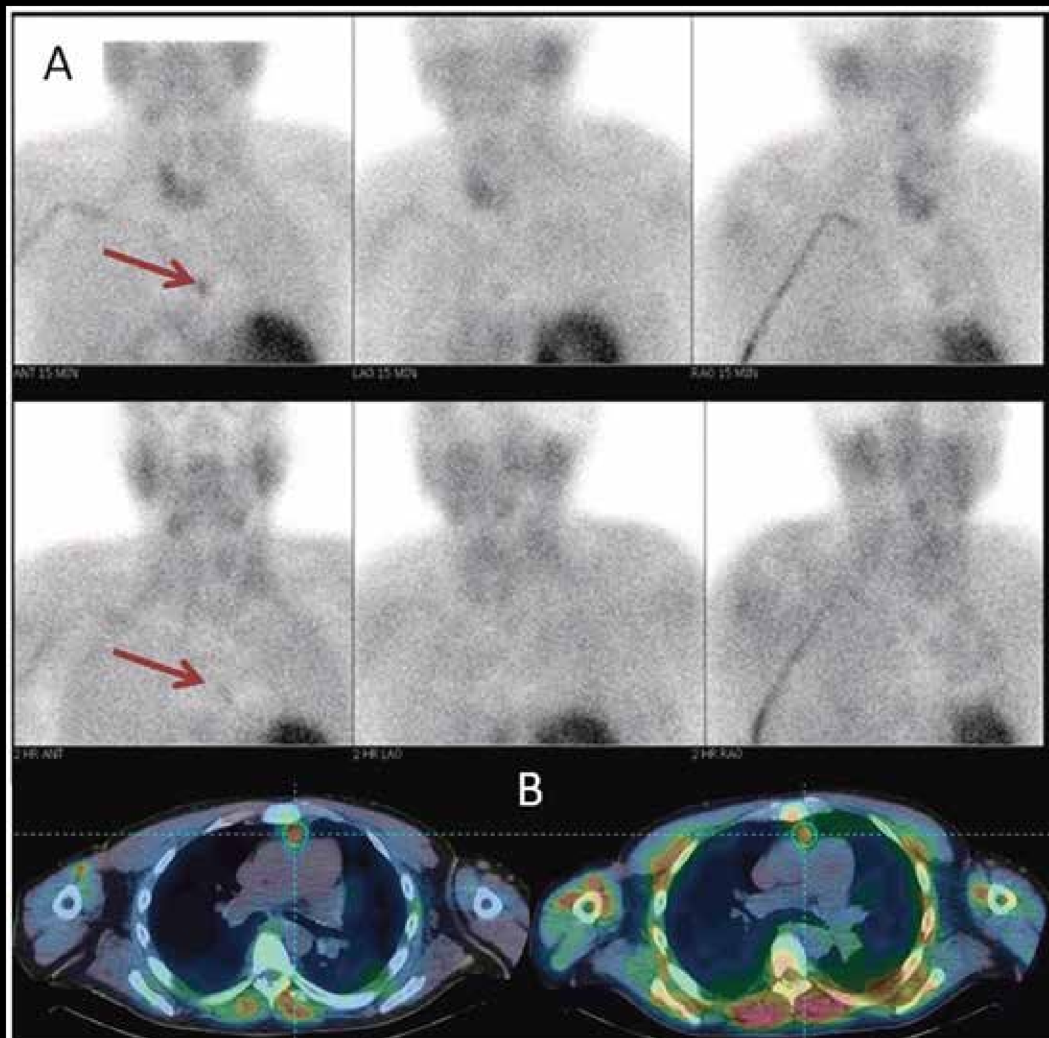

*Delayed Images*

# *SPECT/CT*



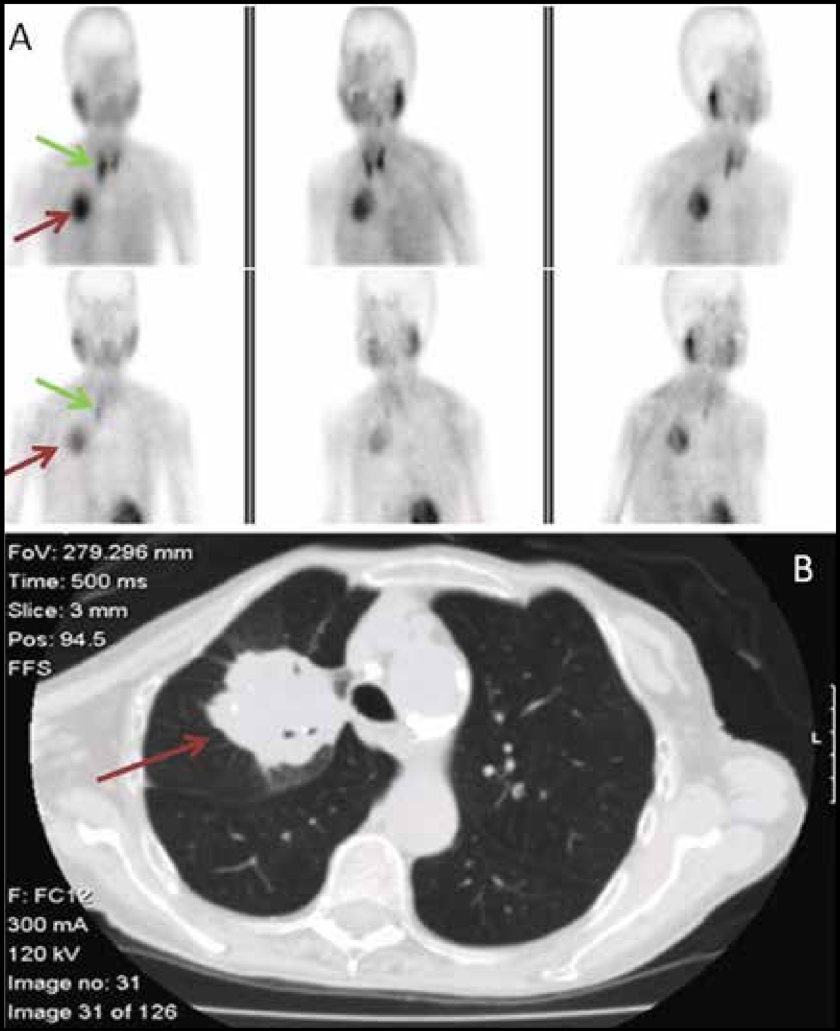

*From Terris Parathyroid Book Chapter* – SPECT/CT localized to left inferior-posterior parathyroid gland

# *SPECT/CT*




*From Terris Parathyroid Book Chapter* – ectopic parathyroid adenoma

# *SPECT/CT*




*From Terris Parathyroid Book Chapter* – right inferior parathyroid adenoma & lung cancer

# *Operative Procedures*

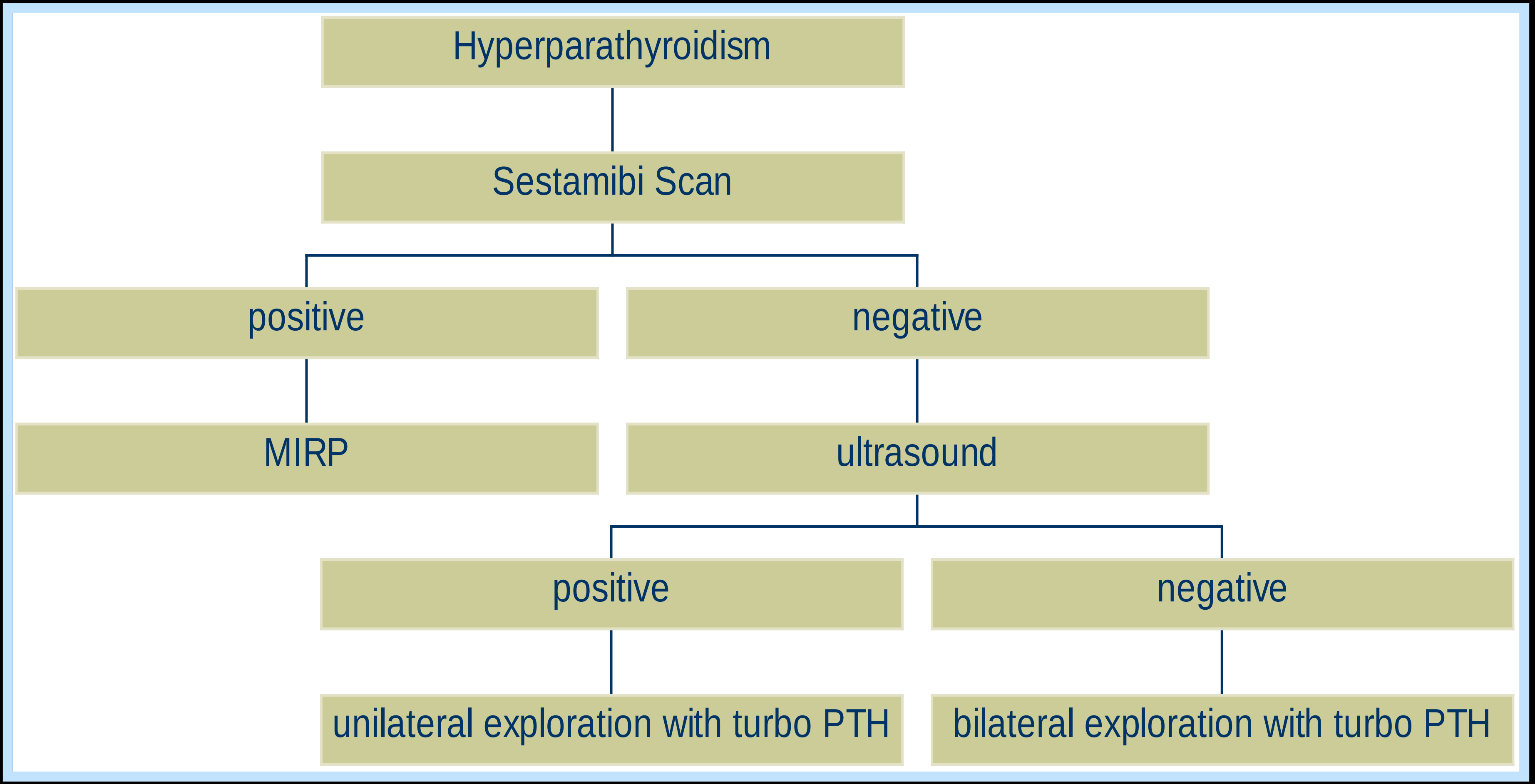
- Bilateral Exploration
- Unilateral Exploration
- Radioguided Parathyroidectomy
- Minimally-Invasive Radioguided Parathyroidectomy (MIRP)
- Autologous Transplantation

# Radioguided Parathyroidectomy

**Intraoperative gamma probe localization**

*Courtesy, Brendan Stack, MD*

# Our Protocol




*Courtesy, Brendan Stack, MD*

# *MIRP*

**Advantages:**

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

*Costello D, Norman J. Surg Oncol Clin No Amer. 1999; 3:555-64*

# *Intraoperative PTH*

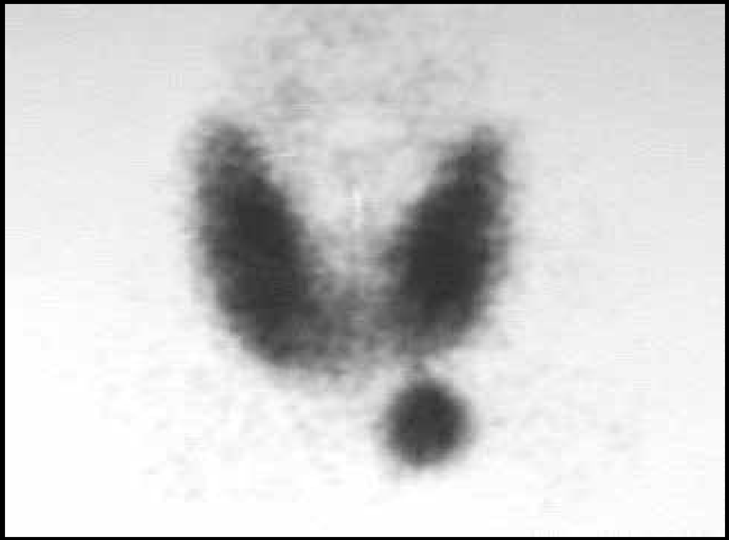
- **Eliminates need for intraoperative frozen-section analysis**
- **Measure PTH drop during "safety window" (time between adenoma excision & when other glands start producing PTH)**
- **Venous blood (usually anterior jugular) sample before gland removal & 10 min after excision**
- **> 50% decline in PTH @ 10 minutes from baseline indicates successful removal of adenoma (relying on drop only has 22.4% failure rate)**

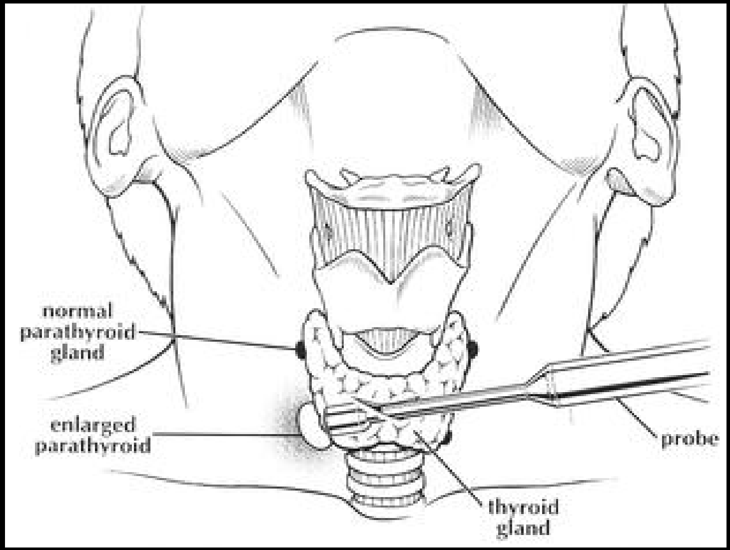
***Immulite***

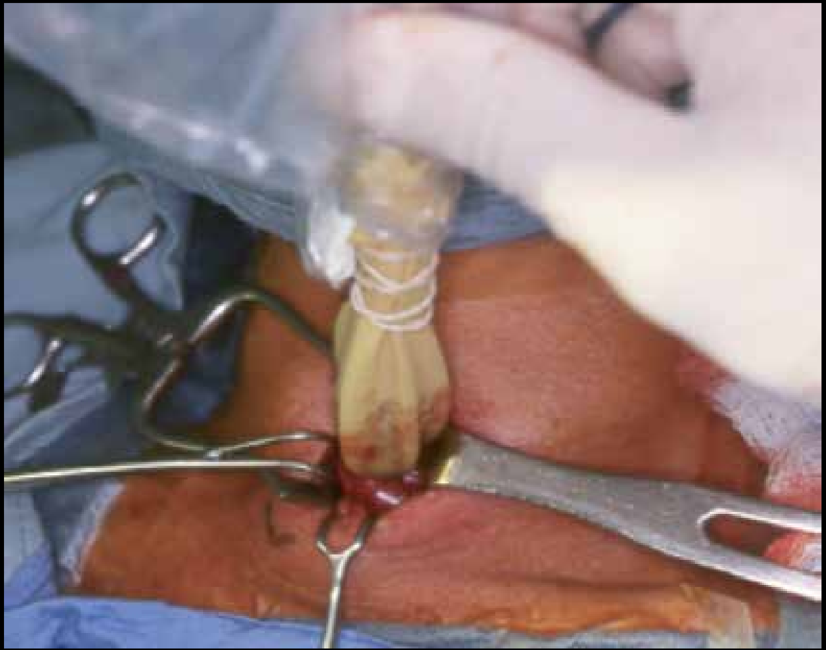
***Elecsys 1010***

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

*Richards ML, Thompson GB, Farley DR et al. Arch Surg. 2011; 146:280-5.*
*Murphy et al. Surgery 1999;126:1023-9*



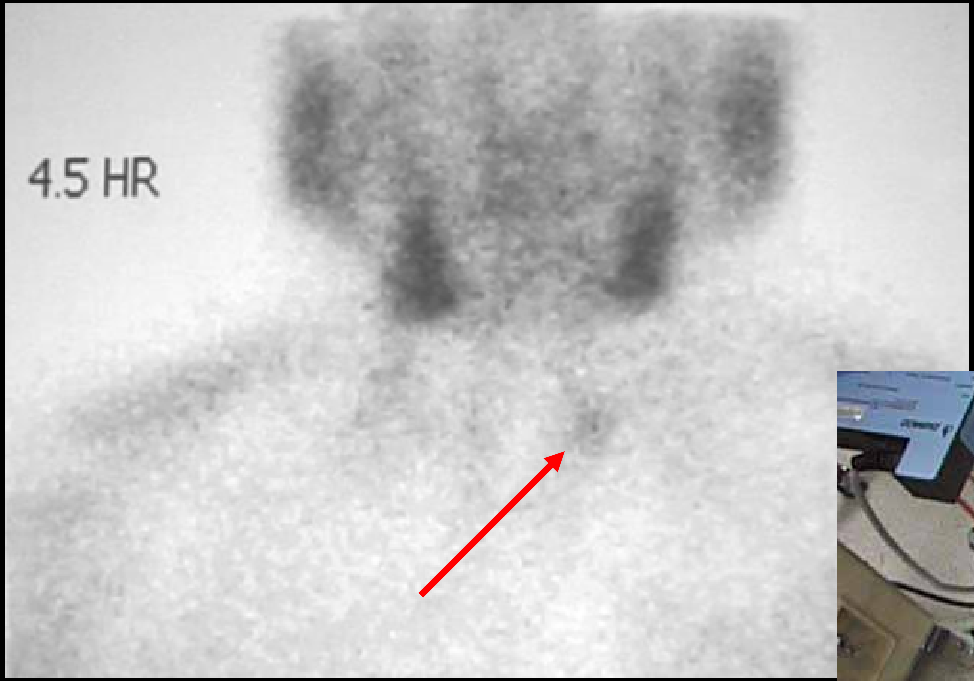

normal
parathyroid
gland
enlarged
parathyroid
probe
thyroid
gland



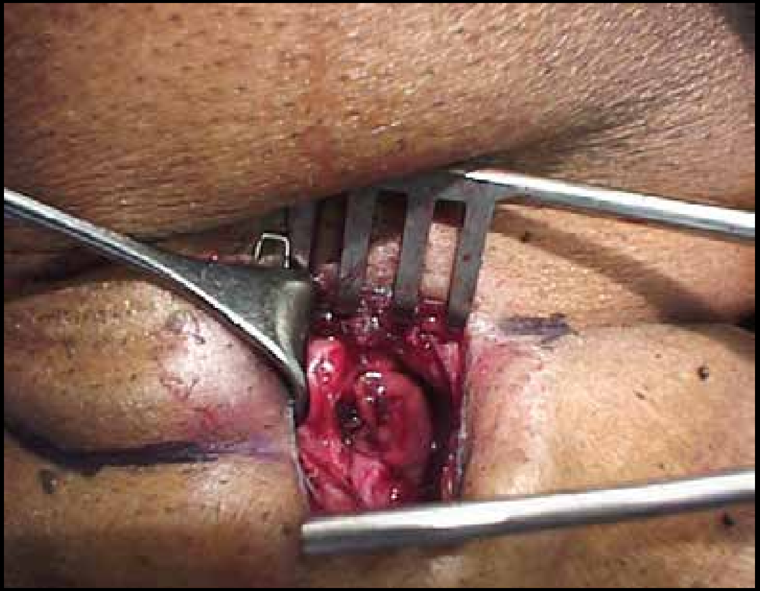
## *MIRP Case Example*

- African American female with an incidental finding of hypercalcemia
- Co-morbidities of hypertension and diabetes
- No history of stones, neuromusc. SXs, or GI complaints
- Post-menopausal

*Courtesy, Brendan Stack, MD*

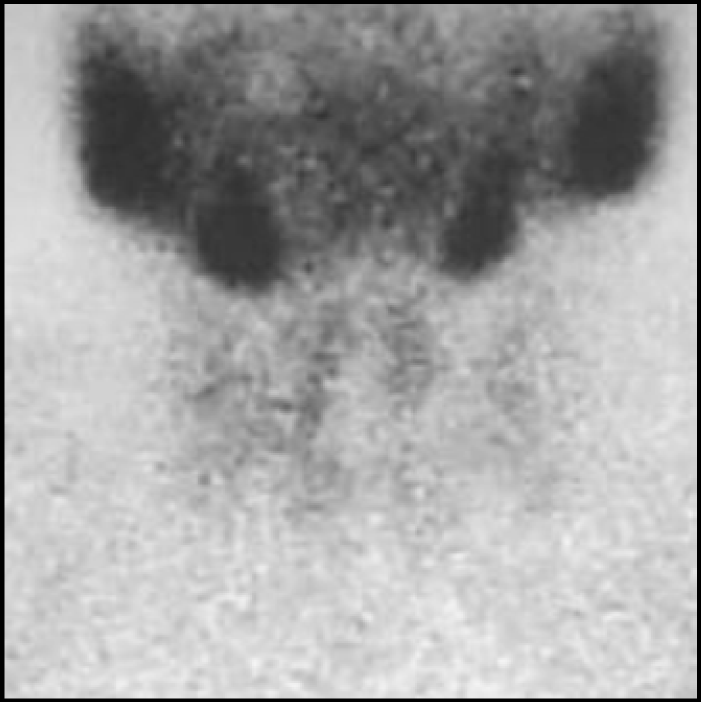



**Gamma probe guided external marking**



**Minimal access incision**

*Pre-op*



*Post-op*

# *Cost/Benefit Analysis*

- 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)

Lubitz CC et al. Preoperative localization strategies for primary hyperparathyroidism: an economic analysis. 2012;19:4202-9

# Radiation

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

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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.

| | Tc-99m-MIBI (mCi) | | | EFFECTIVE DOSE (mSv) | | | |
|---|---|---|---|---|---|---|---|
| | | Scintigraphy Only | SP SPECT/CT | DP SPECT/CT | 4DCT | SP SPECT/CT & 4DCT | DP SPECT/CT & 4DCT |
| Pt 1 | 28.0 | 9.3 | 14.1 | 18.9 | 30.0 | 44.1 | 48.9 |
| Pt 2 | 24.9 | 8.3 | 13.1 | 17.9 | 8.9 | 22.0 | 26.8 |
| Pt 3 | 28.1 | 9.4 | 14.2 | 19.0 | 10.0 | 24.2 | 29.0 |
| Pt 4 | 28.1 | 9.4 | 14.2 | 19.0 | 10.0 | 24.2 | 29.0 |
| Pt 5 | 27.0 | 9.0 | 13.8 | 18.6 | 18.0 | 31.8 | 36.6 |
| | **More pts to be accumulated prior to presentation** | | | | | | |
| | SP = Early **OR** Late SPECT/CT<br>DP = Early **AND** Late SPECT/CT | | | | | | |

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.

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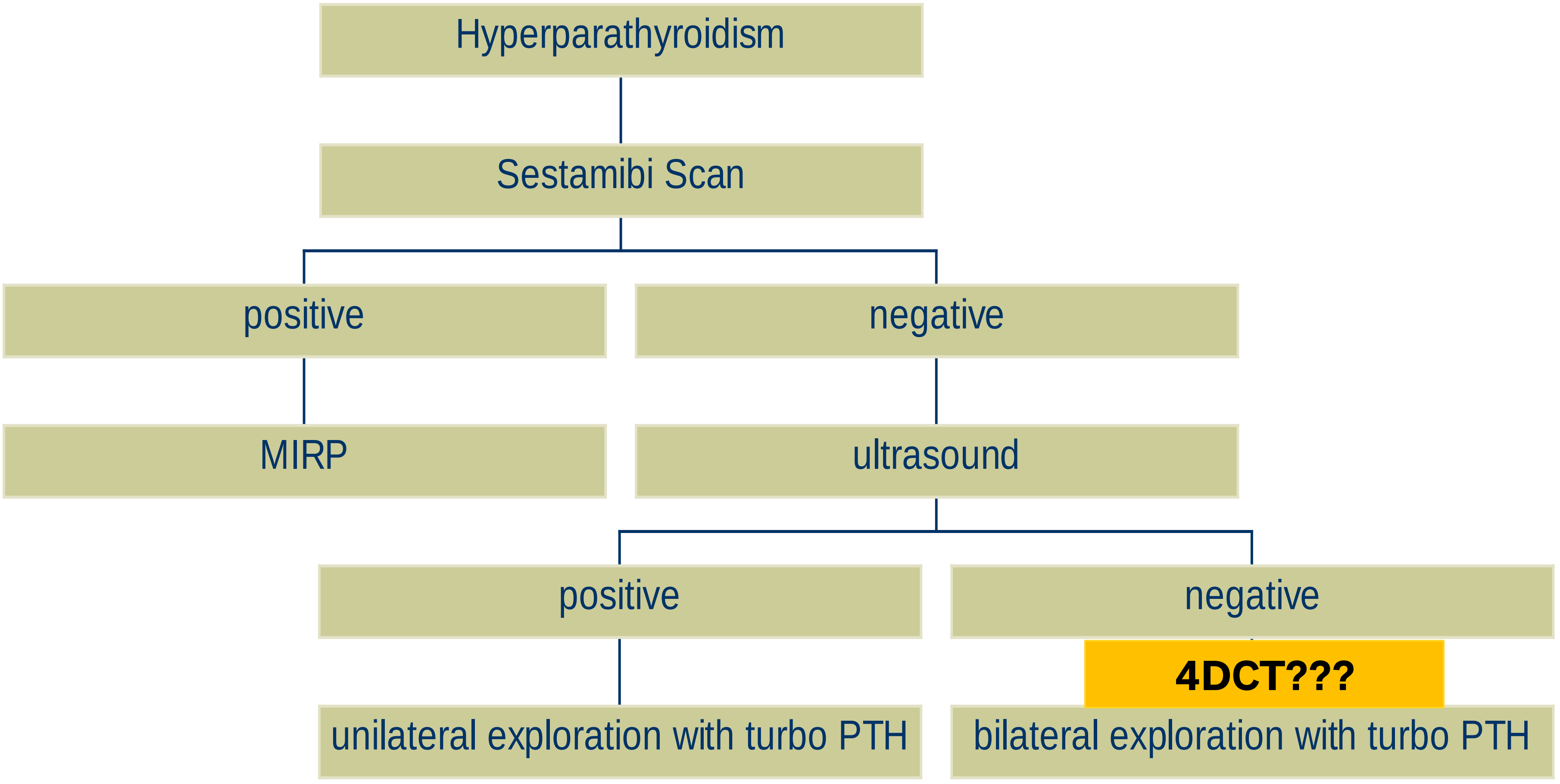
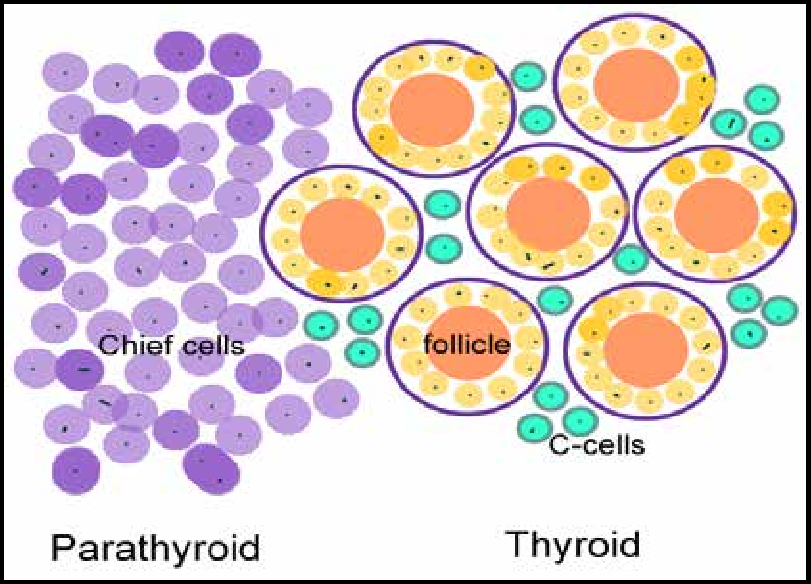



*Courtesy, Brendan Stack, MD*

# *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!!

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