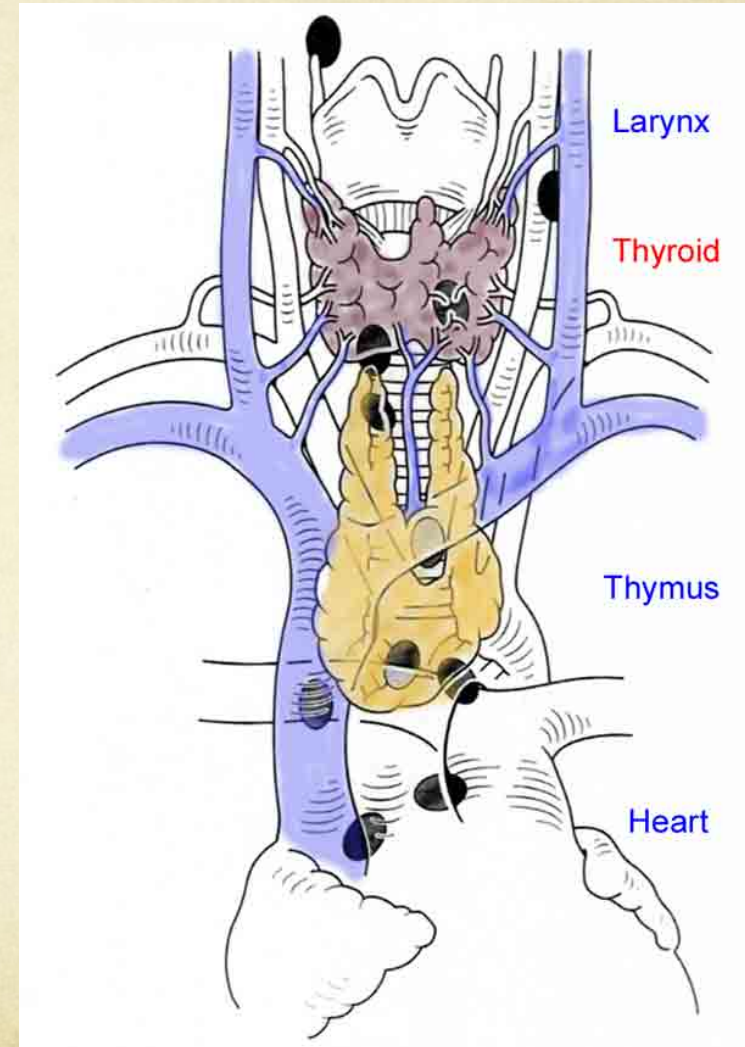


3 Patients
1 Pathology
3 Different Problems

Registrar Teaching
Gratian Punch
Oct 2013

Scope of Session

- Basic Sciences Recap
 - Ca^{2+} Physiology
 - Causes of Hypercalcaemia
 - Classification of Hyperparathyroidism
 - Parathyroid anatomy
- You're an Endocrine Surgeon in Rooms
- Your pre operative workup
- Planned Surgical Management
- Outcome and further decision making !!!

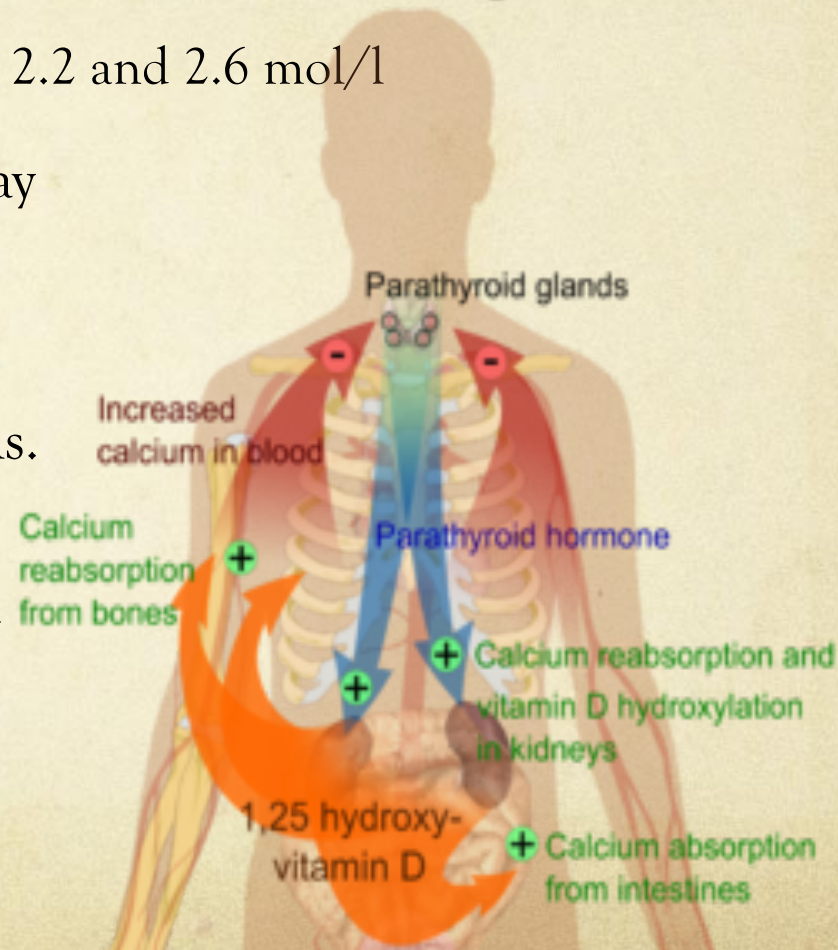


Basic Sciences – Ca^{2+} Physiology

- Calcium exists in extracellular plasma
 - Free ionized state (45%) - normal level of 4.5 to 5.0 mg/dL
 - bound to other molecules (55%) Note 80% to albumin.

Calcium regulation

- Normal plasma levels:
 - total (bound and unbound) calcium is 2.2 and 2.6 mol/l
- Calcium highly modulated by interplay
 - PTH,
 - calcitonin, and
 - vitamin D
- Chief cells secrete PTH when Ca^{2+} falls.
- PTH stimulates:
 - osteoclasts to increase bone resorption
 - kidney to \uparrow Ca^{2+} resorption
 - renal production of $1,25[\text{OH}]_2\text{D}_3$
 - intestine to \uparrow absorption Ca^{2+} PO_4^{3-}
- Negative feedback loop:
 - calcium-sensing receptors (CaSRs)



Causes of Hypercalcaemia

○ Parathyroid

Primary hyperparathyroidism:
Sporadic, Familial

○ Nonparathyroid Endocrine

Thyrotoxicosis
Pheochromocytoma
Acute adrenal insufficiency
Vasointestinal polypeptide
hormone-producing tumor
(VIPoma)

○ Malignancy

Solid tumors
Lytic bone metastases
Lymphoma and
leukemia
Parathyroid hormone-
related peptide
Excess production of
 $1,25(\text{OH})_2\text{D}_3$
Other factors
(cytokines, growth
factors)

○ Medications

Calcium
supplementation
Thiazide diuretics
Lithium
Estrogens,
antiestrogens,
testosterone in breast
cancer
Vitamin A or D
intoxication

○ Other

Benign familial
hypocalciuric
hypercalcemia
Milk-alkali syndrome
Immobilization
Paget's disease
Acute and chronic
renal insufficiency
Aluminum excess
Parenteral nutrition

What are the two most common causes of hypercalcaemia in the community?

a. *Primary hyperparathyroidism and malignancy*

Classification of Hyperparathyroidism

Elevated Ca^{2+} & Inappropriate PTH level (high or normal)

○ Primary

- Sporadic
- Familial
 - MEN 1
 - MEN 2A
 - Familial isolated HPT

○ Secondary

Uremic hyperphosphatemia leads to hypocalcemia.

Compensatory mechanism serving to maintain phosphate balance in uremia – as normalization of calcium and phosphate levels occur – PTH Levels rise.

Failing kidney is unable to hydroxylate vitamin D_2 to active vitamin D_3 .

○ Tertiary

2 settings:

- secondary HPT in whom the parathyroid glands become autonomous and hypercalcemia develops
- post renal transplant pts

Basic Sciences – Parathyroid Gland Anatomy

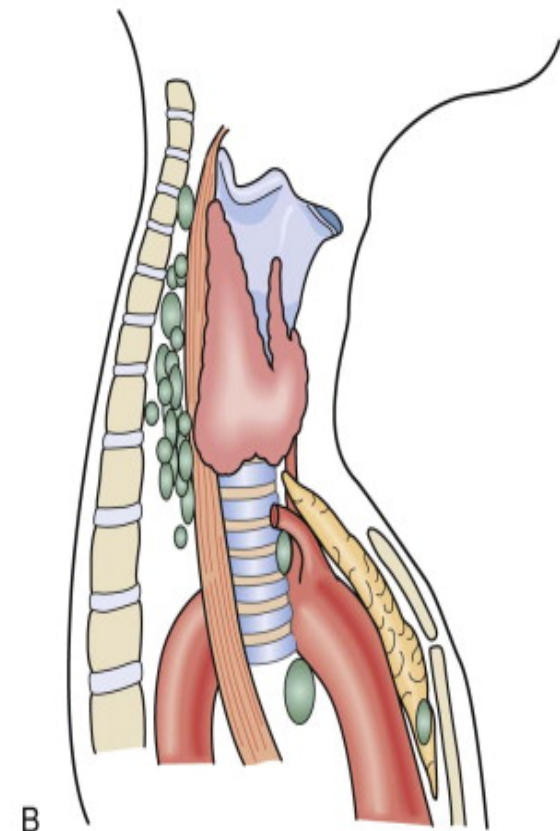
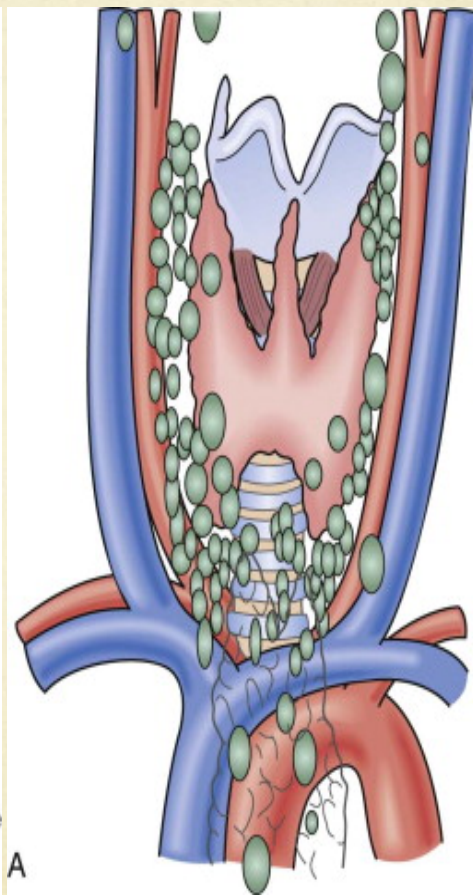
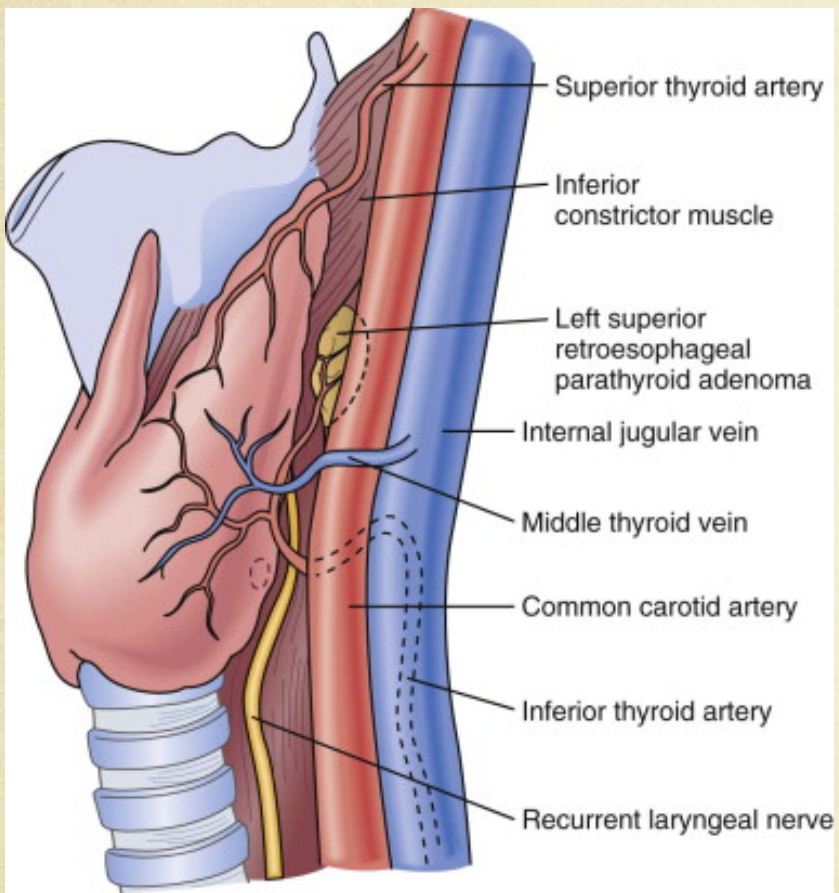
○ Superior gland:

- > 90% deep to mid portion of the superior pole thyroid near the cricothyroid junction.
- 4% seen more inferiorly, deep in relation to the mid pole of the thyroid lobes
- 3% located/above most superior aspect of the thyroid
- 1% retropharyngeal spaces
- 1% retroesophageal spaces
- 0.2% in the thyroid gland

○ Inferior parathyroid glands:

- 69% located inferior, posterior, or lateral to the lower thyroid pole
- 26% more inferiorly in the neck, in the thymic tongue, or in the cervical portion of the thymus
- 2% anterior mediastinum
- 0.2% inferior to the thymus gland in the mediastinum
- Very rarely can fail to descend with the thymus and may remain cephalad to the superior glands.

Basic Sciences – Parathyroid Gland Anatomy



You're the Endocrine Surgeon

○ Patient 1

- 39yo male
- Renal calculi
- Ca^{2+} 3.4mmol/L
- PTH 11pmol/L

○ Patient 2

- 44yo female
- Asymptomatic
- Ca^{2+} 2.91
- PTH 9.3pmol/L

○ Patient 3

- 62yo female
- Depression
- Ca^{2+} 3.1mmol/L
- PTH 13pmol/L

But all the GP letters just say:

“didn't have time to book anything else, please review and advise.”

So what now?

24Hr Urine and Imaging

Why do 24 hr urine?

Imaging:

○ Patient 1

- Urine high Ca^{2+}

- US Neck shows
single superior
adenoma right side

No SESTAMIBI

○ Patient 2

- Urine high Ca^{2+}

- US Neck shows
no identifiable
lesion

- SESTAMIBI
Neck shows non
localising
identifiable
lesion

○ Patient 3

- High Urine Ca^{2+}

- US Neck shows
single apparent
inferior lesion left
side

- SESTAMIBI Neck
shows localised to
inferior parathyroid
left side

- Concordance

Patient Consent and Recommendations to GP's on Operative Plans

- | | | |
|---------------------------|--|----------------------------|
| ○ <u>Patient 1</u> | ○ <u>Patient 2</u> | ○ <u>Patient 3</u> |
| - US localised | - Non localised | - Localised |
| - Bikie with TATS on neck | - Necklace model who is scarred of keloid scarring | - Concordance |
| | - Wants the endoscopic resection if you do it? | - Doesn't care about scars |

What is your recommendation to each patient on operative plan?

1. Endoscopic assisted resection
2. MIPS only (don't bother to consent for 4 gland)
3. MIPS +/- 4 Gland exploration (extend small cut if have too!)
4. Straight to 4 Gland Exploration (collar incision)

Surgery and Outcomes

- | | | |
|---------------------|---------------------------------|------------------------------|
| ○ <u>Patient 1</u> | ○ <u>Patient 2</u> | ○ <u>Patient 3</u> |
| - MIPS | - 4 Gland | - MIPS |
| - Easily found 2.3g | - 3 rd para enlarged | - 2.1g |
| - nodule with | - 1.8g | - frozen consistent |
| - frozen consistent | - frozen consistent | - with parathyroid |
| - with parathyroid | - with parathyroid | - adenoma |
| - adenoma | - adenoma | - Day 1 Post op |
| - Day 1 Post op | - Day 1 Post op | - Ca ²⁺ 3.0mmol/L |
| - PTH Normal and | - PTH Normal | - PTH 12pmol/L |
| - CMP normal | - and CMP | - MDT Meeting |
| | - normal | - review histopath |
| | | - says not certain |
| | | - about parathyroid |
| | | - adenoma |

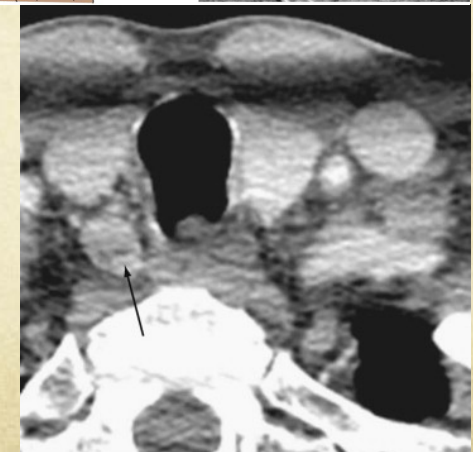
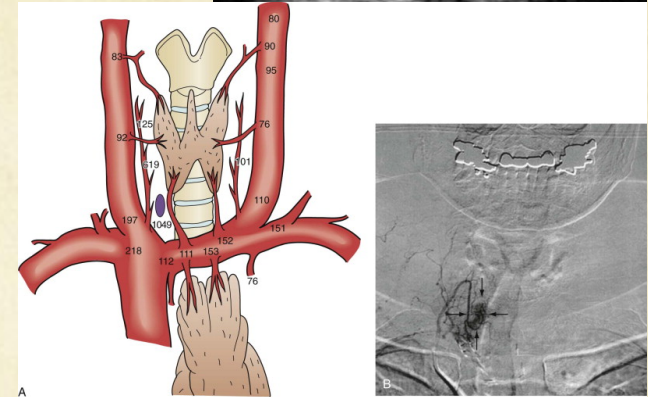
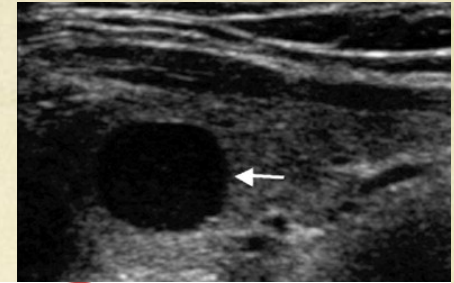
Who are you happy about?

How do you follow up each of these patients?

(eg. When do you see in rooms, take more blood, etc...)

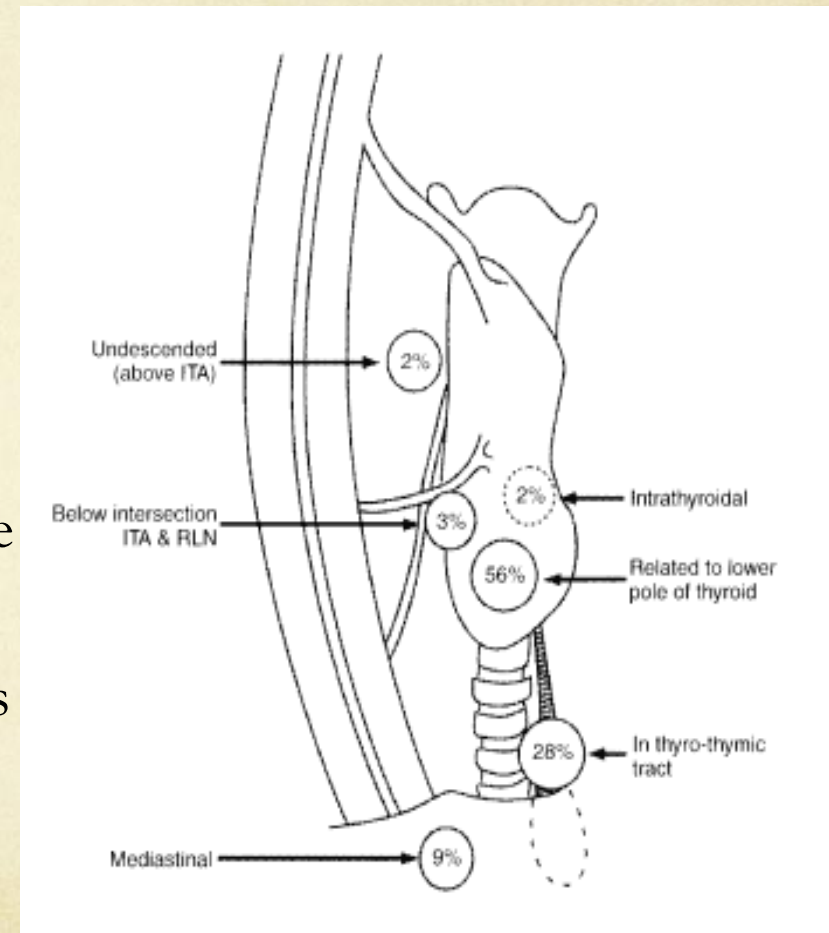
Not Happy with Pt 3 – What Now?

- Repeat
 - Bloods:
 - CMP + PTH
 - Imaging:
 - U/S Neck
 - SESTAMIBI SCAN NECK
 - 4D CT Scan neck + Chest
(imaged gated to motion/artefact of table and respiratory pattern)
 - MRI Neck
 - PET Scan neck
 - Interventional Studies: venous sampling
- Plan Surgical Intervention:
 - Repeat MIPS vs 4 Gland exploration
 - Intra-operative assistance with localisation:
 - Pre operative IV methylene blue infusion (5mg/kg)
 - Gamma probe assisted intraoperative localisation
 - Intraoperative US



Intra operative steps for a “missing” parathyroid gland

1. Look in the retroesophageal space
2. Perform a cervical thymectomy.
3. Open the carotid sheath.
4. Search for an undescended gland, occasionally found in undescended thymic tissue.
5. Perform intraoperative ultrasound of the thyroid gland.
6. Perform bilateral internal jugular venous sampling for PTH.
7. If the gland cannot be found, terminate the operation, leaving normal parathyroid gland intact.



5 Discussion and Question Slides

1. Criteria for surgery in Primary Hyperparathyroidism?
2. Accuracy of localisation for pre operative imaging?
3. How to check if you have been successful and what is cure?
4. Describe Difference between:
 1. Persistent Primary Hyperparathyroidism
 2. Recurrent Primary Hyperparathyroidism
5. Describe some of the anatomical characteristics of parathyroids that could results in persistent Hyperparathyroidism?

What are the Criteria for Surgery in Primary Hyperparathyroidism?

Symptomatic Patients

Symptoms: (stones, bones, abdominal groans and psychic moans)

1. muscle weakness,
2. fatigue,
3. volume depletion,
4. nausea and vomiting,
5. Pancreatitis
6. Neuropsychiatric manifestations:
 1. depression,
 2. Confusion
7. Severe cases, coma and death.

Asymptomatic Patients

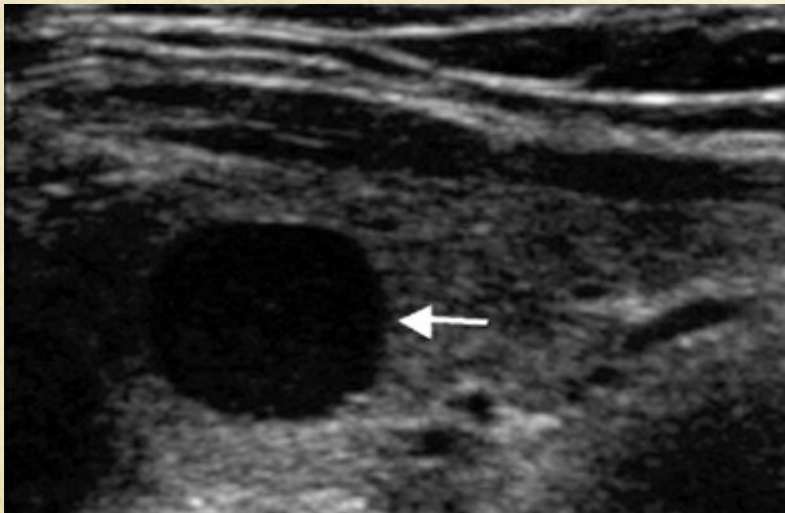
1. Total serum calcium greater than 1.0 mg/dL (0.25 mmol/L) above the upper limit of normal
2. Creatinine clearance less than 60 mL/min
3. Bone mineral density T score ≤ -2.5 at any site and/or previous fragility fracture
4. Age < 50 years
5. Inability or unwillingness to comply with biannual biochemical surveillance

Bilezikian JP, Khan AA, Potts JT Jr, et al: Guidelines for the management of asymptomatic primary hyperparathyroidism 2008, Summary statement from the Third International Workshop on Asymptomatic Primary Hyperparathyroidism, J Clin Endo Metab 94(2): 333-334, 2009.

Accuracy of Pre Op Imaging

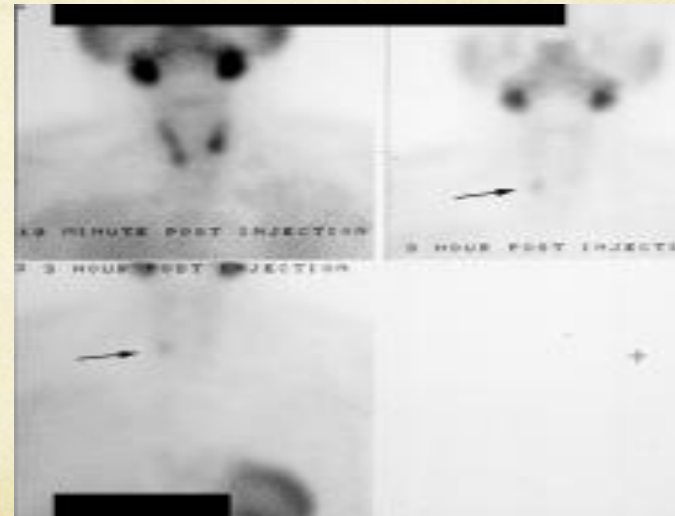
US Neck (High Freq 7.5- or 10-MHz)

1. Radiologist v Surgeon
2. Confounded by:
 1. Multinodular goiters
 1. Poor assessment of multi-gland
3. Identify 75% abnormal glands



SESTAMIBI Neck

1. Technetium-99m (99mTc) sestamibi radionuclide scan of the neck
2. Washout images show the adenoma
3. Sensitivity 60-90% for solitary adenoma
4. Sensitivity drops to 50% localisation of multiple adenoma



Concordance increases sensitivity for single adenomas to 90%

Success, Cure and Follow Up

- Operative Success (High volume centres should be >95%):
 - Frozen Section – consistent with parathyroid adenoma
 - Rapid PTH assay – reduction by 50% approx 10 min post excision
 - Formal Histopathology consistent with Parathyroid adenoma
- Cure:
 - Biochemical resolution for >6 month
- Follow up:
 - Routine post op appointment x 1
 - With GP for yearly CMP level

Persistent v Recurrent Hyperparathyroidism

- Persistent Hyperparathyroidism:
 - Continuation/redevelopment of HPT <6/12 after parathyroid exploration
 - Usually the result of inadequate resection, range 1-6%.
- Recurrent Hyperparathyroidism: (1-3% annual risk)
 - Development of HPT > 6 months after successful parathyroid surgery
 - Results from the development of hyperfunctioning parathyroid tissue.
 - Causes
 - Recurrent parathyroid adenoma,
 - Parathyroid hyperplasia,
 - Parathyroid carcinoma, and
 - Parathyromatosis - rare condition with seeding and subsequent growth of aberrant parathyroid cells occurs after contamination of the operative field during previous parathyroid surgery.
- Note: Recurrent HPT is less common than persistent disease; however, recurrence frequently occurs in the setting of familial HPT, a condition in which all residual parathyroid tissue is genetically abnormal.

Describe some of the anatomical characteristics of parathyroids that could results in persistent Hyperparathyroidism?

1. Dumbbell shaped parathyroid adenoma (inadequate resection eutopic tissue)
2. Multiple parathyroid adenomas
 1. 80% have 1 parathyroid adenoma
 2. 2 - 4% have 2 parathyroid adenomas
 3. Parathyroid hyperplasia = all 4 glands enlarged = approx 13% all pts
3. Ectopic parathyroid gland
 1. Inferiorly descended superior gland
 2. Mediastinal locations 1%
 3. Multiple other locations
4. Supernumerary parathyroid glands approx 15-20%
5. Parathyroid cancer = 1%

Shameless Plug

PLEASE HELP in the AUDIT OF LANGUAGE
INTERPRETATION FOR EMERGENCY
SURGERY during November !!!



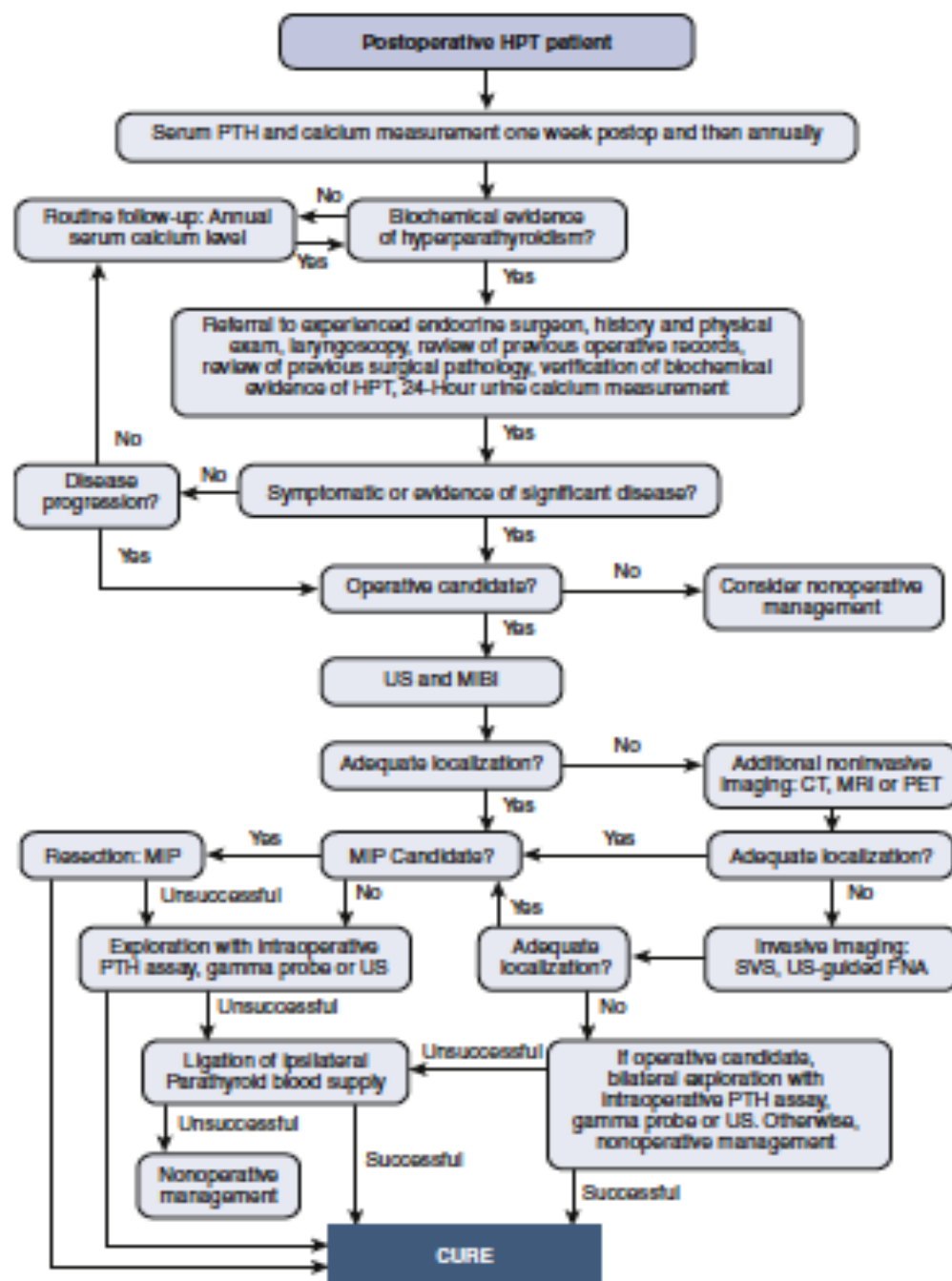


FIGURE 7 Algorithm for the diagnosis and management of recurrent and persistent HPT. (From Fracchetti JD, Udelsman R: Remedial operation for primary hyperparathyroidism, *World J Surg* 33[11]:2324–2334, 2009.)