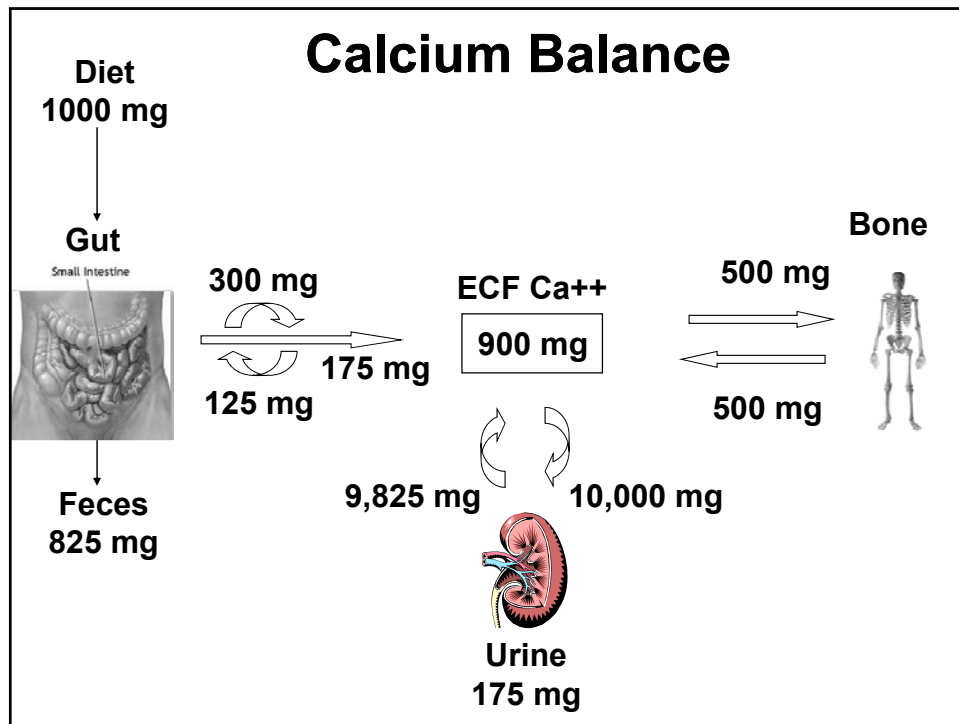


Review of Parathyroid Disease

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Objectives

- **Review the normal physiology of pathways influencing parathyroid hormone response**
- **Distinguish between the clinical scenario and causes of primary vs. secondary hyperparathyroidism**
- **Discuss indications for both conservative management and parathyroid surgery**
- **Develop an algorithm for maximizing the success of parathyroid surgery**

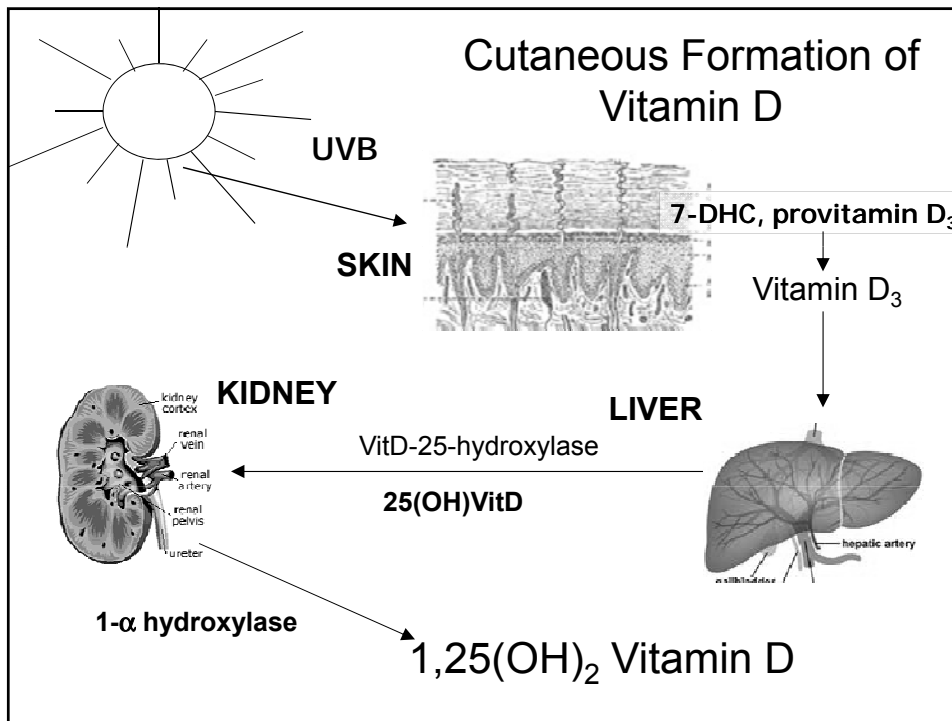
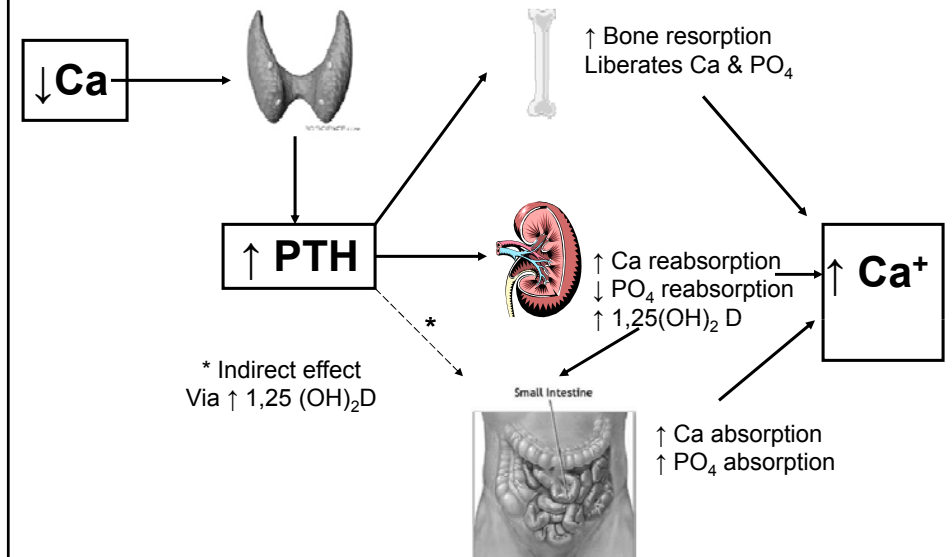


Parathyroid Hormone

- Maintains normal extracellular serum calcium
- Peptide hormone:
 - Stored and secreted as PTH 1-84 (intact PTH)
 - Plasma half life 10 min (bioactive)
- Cleaved in liver and kidney to:
 - N-terminal PTH (short-lived, active)
 - COOH-terminal PTH (long-lived, inactive)
- C-terminal PTH cleared by kidney
 - Increased with renal dysfunction

The diagram shows the human neck with the thyroid gland and the four parathyroid glands, which are small spots on the thyroid gland.

PTH Actions



Monday morning, 8:15

- 58yo WF presents with worsening bone loss
- She has lost 2" of height from her youth, but denies a history of fractures
- She does not smoke, does not require chronic steroid therapy, and she has no strong family history of hip fracture
- She has a long-standing history of intermittent diarrhea, nausea, constipation and has been told that she has "irritable bowel syndrome"

DXA Results:

LS T-score -2.8, -6.2% since 2012

TH T-score -1.8, -5.5%

FN T-score -2.1

Labs reveal:

Calcium 9.2 (8.6 – 10.4)

Albumin 4.0 (3.5 – 5.0)

Phos 2.2 (2.3 – 4.7)

Vitamin D 11.1 (30-50)

PTH 89 (10 – 72)

Diagnosis?

Vitamin D Deficiency State

- Malabsorption is leading cause of ↓stores
- Lack of proper metabolism of 25(OH)D to 1,25(OH)₂D in renal disease
 - This includes the elderly, with low efficiency
- Phenobarbital ↑ 25(OH)D degradation
- Dilantin antagonizes at gut
- ↓Ca, ↓PO₄ and ↑PTH

Vitamin D Deficiency Prevalence

- Hospitalized patients: Thomas et al found 25(OH)vitD <25 in 57% of 290 pts on a medical service
- Holick et al studied 1536 community dwelling women, mean age 71: 52% with 25(OH)vitD <30
- 79% of 80+yo women living in retirement homes in Netherlands

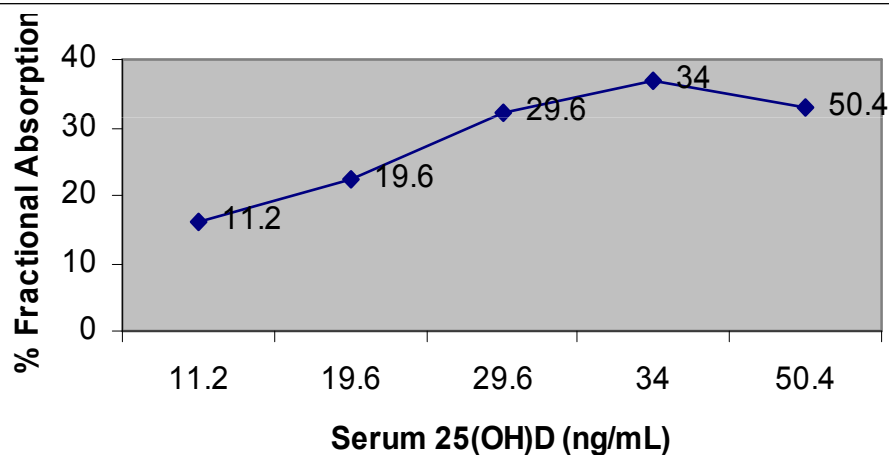
Not everyone needs to have their vitamin D levels checked. Consider in:

- Elderly (age >65-70yo)
- Institutionalized/NH
- Dark skinned individuals
- Obese individual
- Hospitalized on general medicine service
- Patients with osteoporosis
- Fragility fractures
- Meds that increase vitamin D metabolism
- Pregnant women
- Malabsorption
- s/p bariatric surgery

How much Vitamin D is enough?

- Physiologic response to vitamin D: PTH
 - Expected inverse relationship between serum 25(OH)vitamin D and PTH
 - **PTH reaches suppressed plateau at vitamin D concentrations of 28-44 ng/mL**
 - Elevated PTH associated with high bone remodeling rate and osteoporotic bone fragility

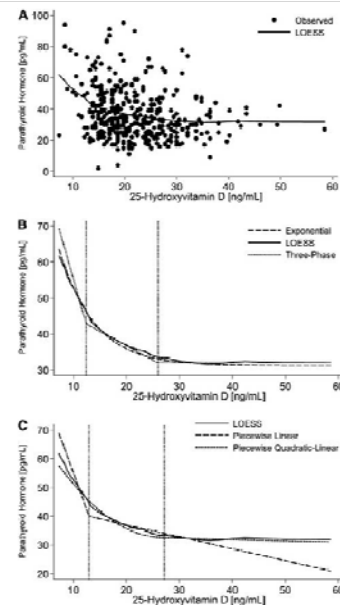
Intestinal Calcium Absorption



Compiled from Bischoff et al, Heaney et al, Barger-Lux et al

Optimal serum level of 25(OH)vitamin D remains debated:

- 445 healthy volunteers
- Age > 65yo
- Normal kidney/hepatic function
- National Institute on Ageing
- STOP/IT trial



Durazo-Arvizu R A et al. J. Nutr. 2010;140:595-599

Secondary Hyperparathyroidism

- **Vitamin D deficiency**
 - Malabsorption
 - Gastric bypass patients
 - Inadequate sunlight
 - Elderly
 - Ethnicity
- **Calcium deficiency**
 - Poor intake, malabsorption
- **Hypercalciuria**
 - Idiopathic
 - Bartter syndrome
 - High sodium diet
- **Renal disease**
 - Poor 1- α hydroxylase
 - Phosphorous and magnesium abnormalities
- **Loop diuretics**
 - Also causes hypercalciuria
- **Anti-epileptics**

Tuesday morning, 9am

- 65yo AAM presents for routine physical exam
- Labs reveal essentially normal chemistries, except for:
- Calcium 10.9mg/dL (normal range 8.5 – 10.5mg/dL)
- You have him return for further discussion
 - Never had a kidney stone
 - Does not smoke
 - Has never had a fracture or height loss
 - Generally feels well – good cognition, good energy

Repeat labs:

Calcium: 10.6

Phos: 3.2

Vitamin D: 22

PTH: 126 pg/mL (normal 10-72)

creatinine 0.92

Etiology of Hypercalcemia

- **Primary hyperparathyroidism and Malignancy explain >90% of all cases**
- **Primary hyperparathyroidism explains 90% of outpatient referrals**
- **Malignancy may cause 50% of ill or hospitalized patients**
- **Patients with known malignancy may also have primary hyperparathyroidism**

Other Causes

- Vitamin D intoxication
- Milk-alkali syndrome
- Thyrotoxicosis
- Immobilization
- Familial hypocalciuric hypercalcemia
- Thiazides & lithium
- Granulomatous disease
- Paget's
- Rhabdo
- Pheochromocytoma

Hypercalcemia Usually Asymptomatic

- Neurologic symptoms predominate
 - Depression
 - Mental sluggishness
 - Confusion
 - Coma
 - Muscle Weakness
- Gastrointestinal
 - Constipation
 - Anorexia
 - Nausea/vomiting
 - PUD, pancreatitis

Hypercalcemia Sx

■ Renal

- Polyuria – interferes with action of ADH on distal tubule – nephrogenic DI
- Nephrolithiasis
- Nephrocalcinosis

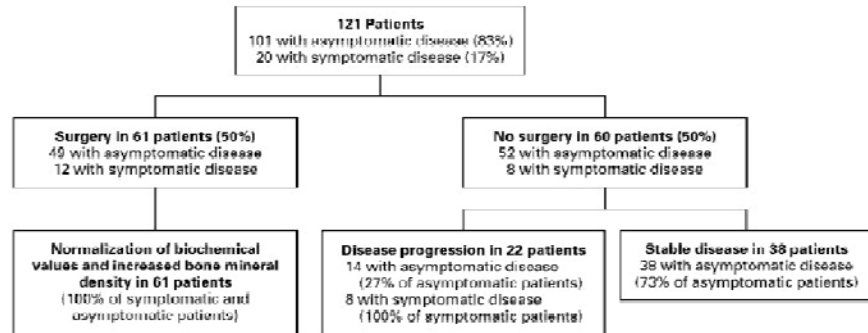
■ Cardiovascular

- Hypertension
- Shortened QT
- Bradycardia
- 1st Degree AV block
- Severe: ST seg depression and sinus arrest

Primary Hyperparathyroidism

- 80% Unifocal adenoma; 20% 2-4 gland adenomas or hyperplasia; <1% carcinoma
- Cause – unclear
 - Increased “setpoint” of serum calcium
 - Increased # of functional PTH cells
- Genetic predisposition is rare – can be seen in cases of MEN, especially MEN1
- Risk factors – possibly prior radiation to the neck

Natural History of Primary Hyperparathyroidism

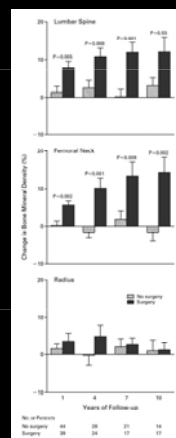


Silverberg SJ et al. N Engl J Med 1999;341:1249-1255.



Improvement in BMD after Parathyroidectomy

Mean (\pm SE) Change in Bone Mineral Density at Three Sites in Patients with Primary Hyperparathyroidism, According to Treatment.



Silverberg SJ et al. N Engl J Med 1999;341:1249-1255.



Parathyroidectomy Criteria

- **Serum calcium > 1 mg/dL over upper limit of normal or > 12 mg/dL**
- **Nephrocalcinosis, nephrolithiasis or decreased creatinine clearance (from any cause)**
- **Reduced cortical bone density or fragility fracture**
 - Look at forearms and femoral neck BMD
- **Age < 50 yo**
- **Symptoms**
 - Especially mental sluggishness, vague abdominal complaints

Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third intl workshop.

Bilezikian JP, Khan AA, et al. J Clin Endocrinol Metab. 2009;94(2)335.

Diagnosis: Biochemical/Labwork

- **Hypercalcemia + inappropriately suppressed PTH**
- **Best localization tool:**
 - “Localize your best parathyroid surgeon!”
- **80-85% are single adenomas**
- **2-5% are double adenomata**
- **10-15% are diffuse, 4-gland adenomata or hyperplasia**
- **Four-gland parathyroid exploration has traditionally been the gold standard**
- **Localizing studies can reduce the surgical extent and complications of surgery, but continue to be poorly sensitive and specific**

Imaging for Primary Hyperparathyroidism

- **Sestamibi scanning**
 - **Technitium-99m-methoxyisobutylisonitrile**
- **Combined with SPECT has highest PPV**
- **Negative sestamibi occurs in 12-25% of patients with disease**
- **Often unrevealing in 4-gland hyperplasia and in those with coexisting thyroid disease**
- **SPECT successfully detects 96% single adenomas, but only 45% of multiglandular disease**

Ultrasound of Normal left thyroid bed



Small adenoma in right Inferior thyroid bed



Ultrasound for localization

- **Noninvasive, inexpensive, reproducible in the OR**
- **Particularly helpful in re-operative cases**
- **Can help identify thyroid pathology to facilitate operative planning**
- **Moderate sensitivity for single-gland adenoma (70-82%)**
- **Operator dependent**

Current Approach

- Diagnosis: Labs
- Sestamibi +/- SPECT
- Along with ultrasound
- If a concordant adenoma, then a unilateral approach
- Use intra-operative PTH
- Evaluate the ipsilateral gland – if normal, then stop; if abnormal, consider 4-gland exploration
- If imaging studies are not clearly concordant, then 4-gland exploration

Large but faint adenoma
In right posterior lobe



Surgical Management of Hyperparathyroidism

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Outline

- **Anatomy**
- **Localization studies**
- **Surgical options**
- **Recurrent laryngeal nerve monitoring**
- **complications**

Goals

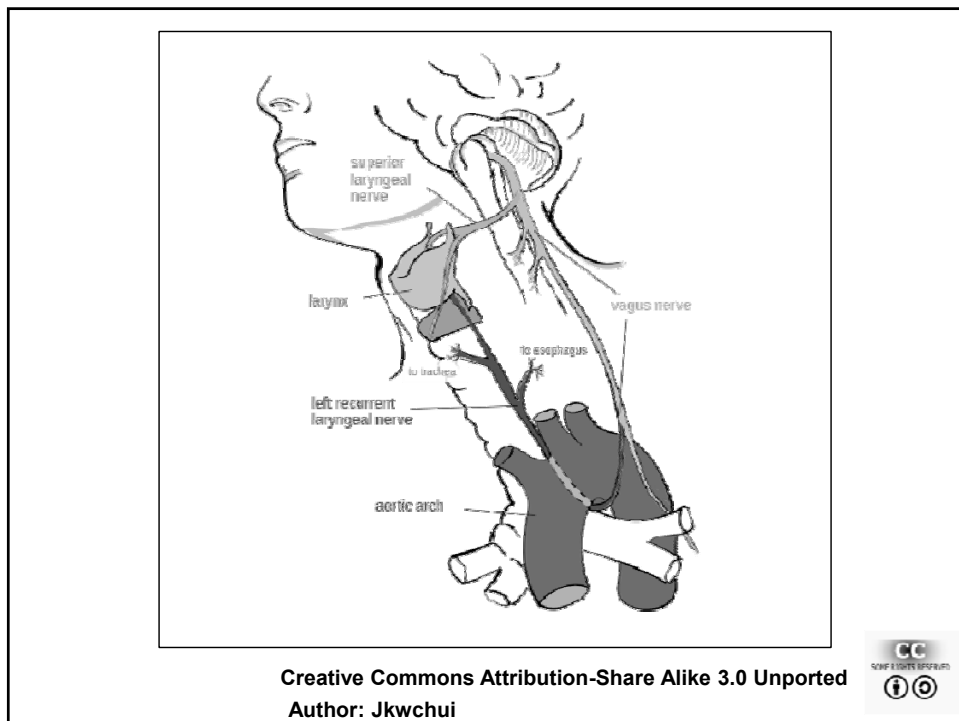
- 1. Find and treat ALL abnormal parathyroids**
- 2. Minimize dissection**
- 3. Attain durable cure**

History

- **1925 – Mandl, first successful parathyroidectomy**
- **1963 – Berson et al., measured human PTH**
- **1988 – Nussbaum et al., reported use of rapid PTH**
- **1990s – Irvin, IOPTH**

Anatomy and Embryology

- **Usually 4 glands**
 - **Designated by location right/left, superior/inferior**
- **Inferior parathyroid gland**
 - **3rd pharyngeal pouch (cephalad to superior glands)**
 - **Migrate with thymus**
- **Superior parathyroid gland**
 - **4th pharyngeal pouch**
 - **More consistent**



Hyperparathyroidism

- **Primary**
 - Unregulated overproduction of parathyroid hormone (PTH)
- **Secondary**
 - Overproduction of PTH secondary to a chronic abnormal stimulus for its production
 - Chronic kidney disease, overproduction of PTH occurs in response to hyperphosphatemia, hypocalcemia, and Vitamin D deficiency
- **Tertiary**
 - Excessive secretion PTH after longstanding secondary hyperparathyroidism and resulting in hypercalcemia.

Primary Hyperparathyroidism

- **Diagnosis**
 - Elevated serum calcium
 - Elevated PTH
- **Etiology**
 - Solitary Adenoma (80-85%)
 - Double Adenomas (2-4%)
 - Multiple Gland Hyperplasia (10-30%)
 - Parathyroid Carcinoma (0.5%)
 - MEN syndromes

Clinical Presentation

"Bones, stones, abdominal groans, and psychic moans."

- **Physical exam**
 - Usually non contributory
 - Laryngeal
- **Laboratory analysis**
- **Imaging studies**

Surgical Indications

- **Surgery is advised in patients with overt manifestation of primary hyperparathyroidism or inability to comply with annual surveillance.**

National Institutes of Health (NIH) consensus panel for surgery in asymptomatic primary hyperparathyroidism

Serum calcium (above normal)	1.0mg/dL
Creatinine Clearance	<60 cc/min
Bone mineral density	T-score <-2.5 at any site and/or previous fracture fragility
Age	<50

Bilezikian JP, et al. Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Third International Workshop. J Clin Endocrinol Metab. Feb 2009; 94(2): 335–339

Observation

- **For those who do not undergo surgery**
 - **Calcium every 6 months**
 - **Annual serum creatinine**
 - **Annual bone density (lumbar spine, hip, distal third of radius)**

Localization Studies

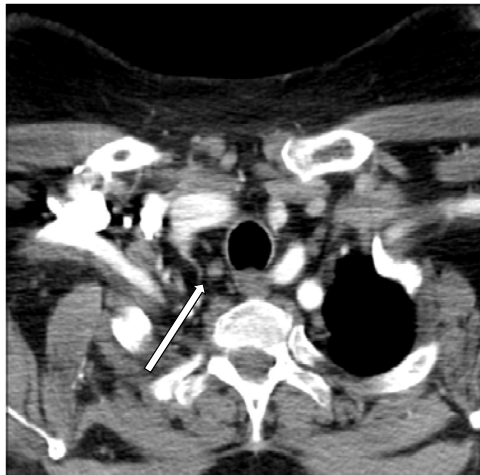
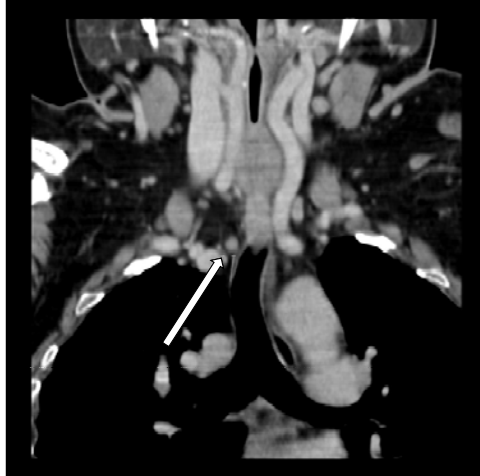
- **Localization of diseased parathyroid is the major limitation of a minimally invasive approach (MIP)**
- **Preoperative vs operative techniques**

Preoperative imaging studies

- **Ultrasound**
 - **Most frequently used**
 - **Low cost, no ionizing radiation**
 - **User dependent, NO mediastinal visualization**

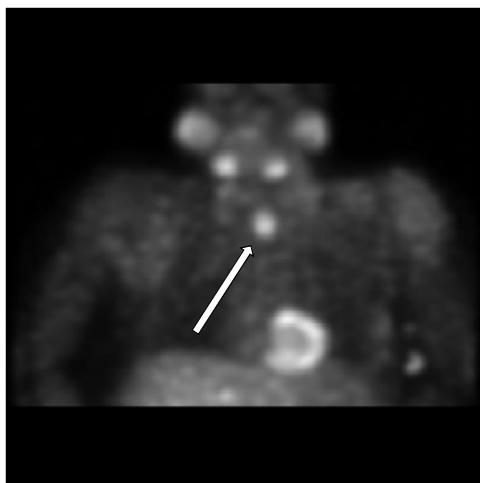
Preoperative imaging studies

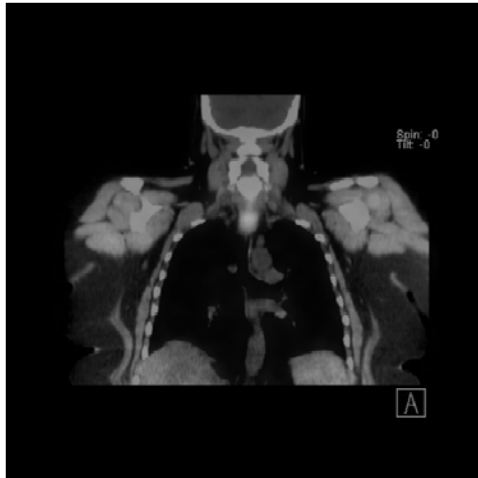
- **Computed tomography (CT)**
 - **May be effective as an adjunct to first line imaging techniques**
 - **4D-CT**
 - **3D imaging + contrast perfusion over time**
 - **Newer modality, appears to be effective in localizing hyper-functioning glands**
- **Magnetic resonance imaging (MRI)**



Preoperative imaging studies

- **Sestamibi scan**
 - Relies on differential washout times (thyroid vs abnormal parathyroid)
 - Thyroid pathology can result in false positives
 - Frequently used in conjunction with other anatomic imaging modality
- **Single photon emission computed tomography (SPECT)**
 - Superposition of the two radiomarkers results in more accurate localization





Intraoperative Adjuncts

- Radioguided
- Methylene blue
- Rapid IOPTH



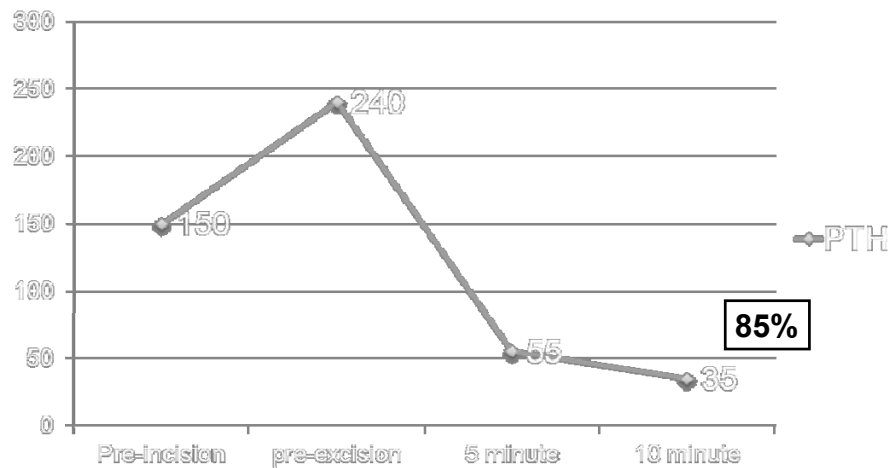
Intraoperative PTH

- **Extensively described in patients with primary HPT**
 - **Confirms complete excision of hyperfunctioning gland prior to leaving the OR**
 - **Alerts surgeon to additional hypersecreting glands**

Intraoperative PTH

- **When peripheral PTH drop >50% from their highest (either preincision or preexcision) value in 10 minutes after removal of abnormal parathyroid then postoperative normal or low calcium levels are predicted with excellent accuracy**

Intraoperative PTH



Surgical Technique

- **Bilateral parathyroid exploration**
- **Minimally invasive parathyroidectomy (MIP)**

Bilateral Neck Exploration

- **Traditional / comprehensive approach**
 - **Less dependent on localization studies**
- **Examination of all parathyroid glands with appropriate resection of diseased glands**
- **Caution for multigland disease**
 - **First gland is mildly enlarged (75-200mg)**
 - **Despite IOPTH drop and/or imaging**

Bilateral Neck Exploration

- **When do you explore?**
 - **Known secondary / tertiary HPT**
 - **IOPTH fails to drop**
 - **Negative or discordant imaging studies**
- **What is the downside?**
 - **Larger incision**
 - **Hospitalization**
 - **Increased risk to RLN**



Parathyroidectomy Options

- Single gland excision → BNE or MIP (unilateral vs focused exploration)
- Subtotal (3.5 gland excision)
- Total (4 gland excision) with autotransplantation

BNE

Minimally Invasive Parathyroidectomy

- **Depends upon preoperative ability to localize adenoma**
- **US and sestamibi**
 - **Both positive and concordant = focused exploration**
 - **1 positive, 1 negative = focused exploration + IOPTH or unilateral exploration (2 gland)**
 - **Discordant = bilateral exploration + IOPTH**
 - **Both negative = bilateral exploration + IOPTH**

What makes a parathyroid operation minimally-invasive?

- **Size of the scar**
- **Type of anesthesia**
- **Number of sides explored**
- **Number of glands explored**

Minimally Invasive Parathyroidectomy

Various approaches

- **Small incision parathyroidectomy**
 - **Outpatient**
 - **Local anesthesia**
- **Endoscopic / video assisted parathyroidectomy**

Minimally Invasive Parathyroidectomy

- **Advantages**
 - **Less pain**
 - **Smaller incision**
 - **Lower morbidity**
 - **Decreased length of hospital stay**

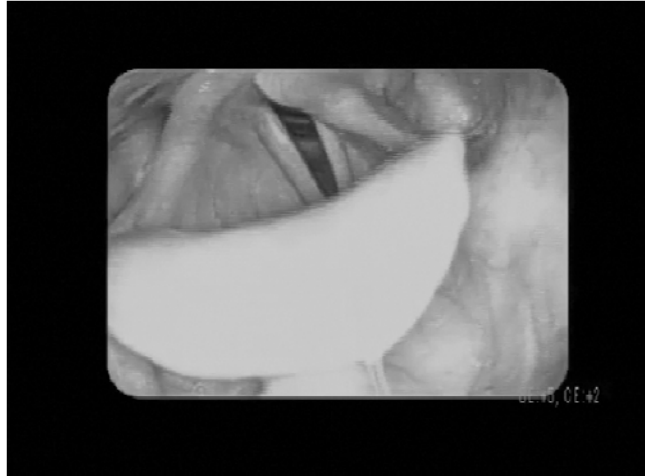
Complications

- **Recurrent laryngeal nerve injury**
- **Failure to localize parathyroid gland**
- **Persistent hyperparathyroidism**
- **Hypocalcemia**
- **Bleeding**
- **Scar formation**
- **infection**

Laryngeal exam

- **Note vocal quality**
 - Michel et al., 1988
 - 26% with voice change → 3% VCP
- **Preoperative endoscopic exam**
 - 3.5% with VCP
 - 2-3% related to benign disease

Shin JJ, et al. The Surgical Management of Goiter: Part I. Preoperative Evaluation. *Laryngoscope*. 2011; 121:60-67

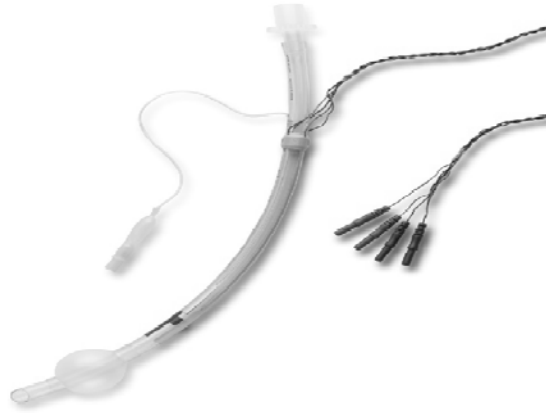


Nerve Monitoring

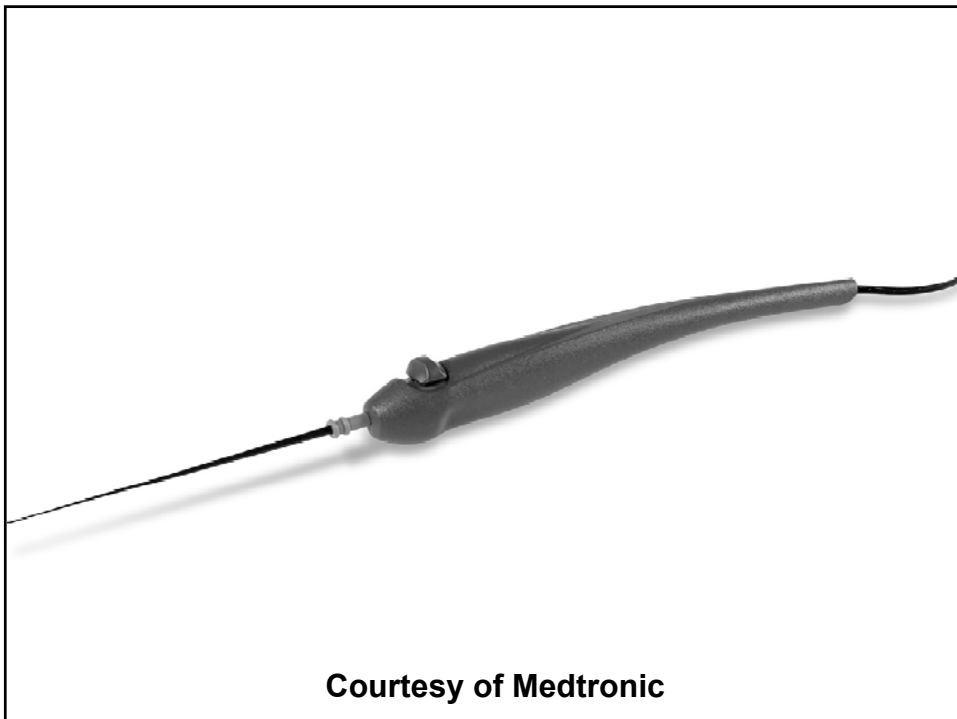
“Garbage in, garbage out...”

Set up

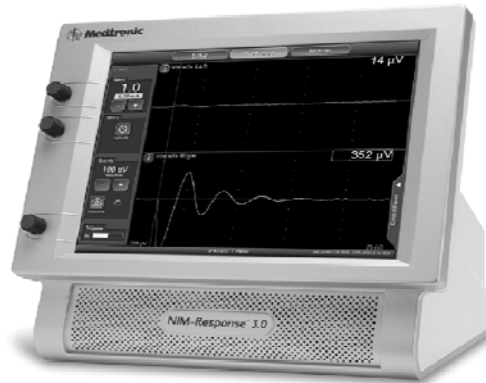
- **Flexible nasolaryngoscopy (in clinic)**
- **ETT position / patient position**
- **Neural mapping for identification**
- **Monitoring**
- **Flexible nasolaryngoscopy (in clinic)**



Courtesy of Medtronic



Courtesy of Medtronic



Courtesy of Medtronic

Clinical Benefits

- Reduction in RLN injury
- Intra-operative diagnosis of RLN injury
- Aiding identification / dissection
- Alternative approaches

Dionigi G, et al. Why monitor the recurrent laryngeal nerve in thyroid surgery? *J Endocrinol Invest.* 2010, 33: 819-822.

Nerve Injury

- **Infrequent but detrimental complication**
 - **Unilateral versus bilateral**
 - **Temporary (9.8%) versus permanent (2.3%)**
 - **Genther DJ, et al., 2014**
- **Direct visualization of nerve has been shown to be safer than neural avoidance**
- **Use of the nerve monitor can be prognostic**

Treatment Failure

- **Persistence**
 - **< 6 months**
 - **Elevated calcium**
 - **Avoidable versus unavoidable**
 - **Suspect multi-gland disease**
- **Recurrence**
 - **> 6 months**
 - **Elevated calcium/PTH**

Conclusion

- **Important to develop a working relationship with an endocrinologist**
- **Gold standard remains BNE**
- **MIP / focused exploration are approaching cure rates for BNE in most series**