

Parathyroid Surgery

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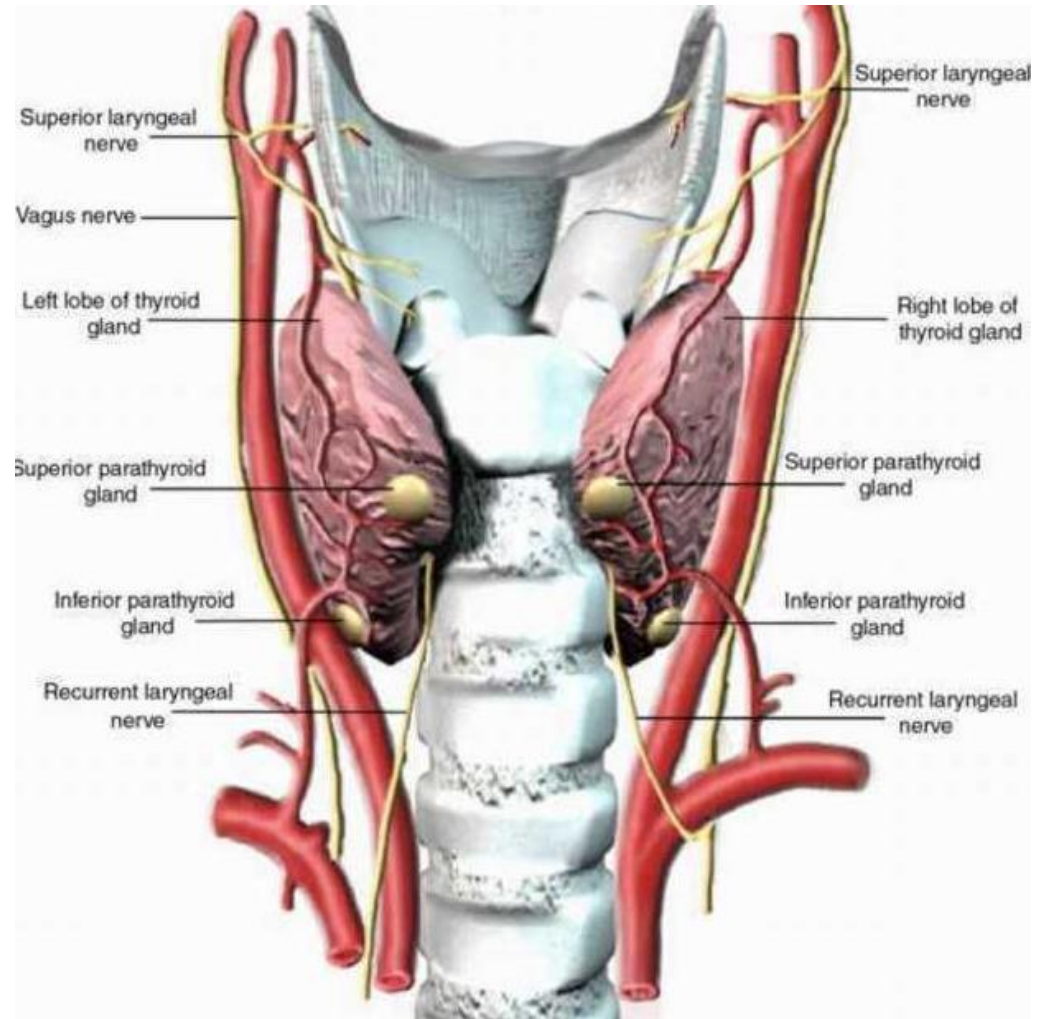
Objectives

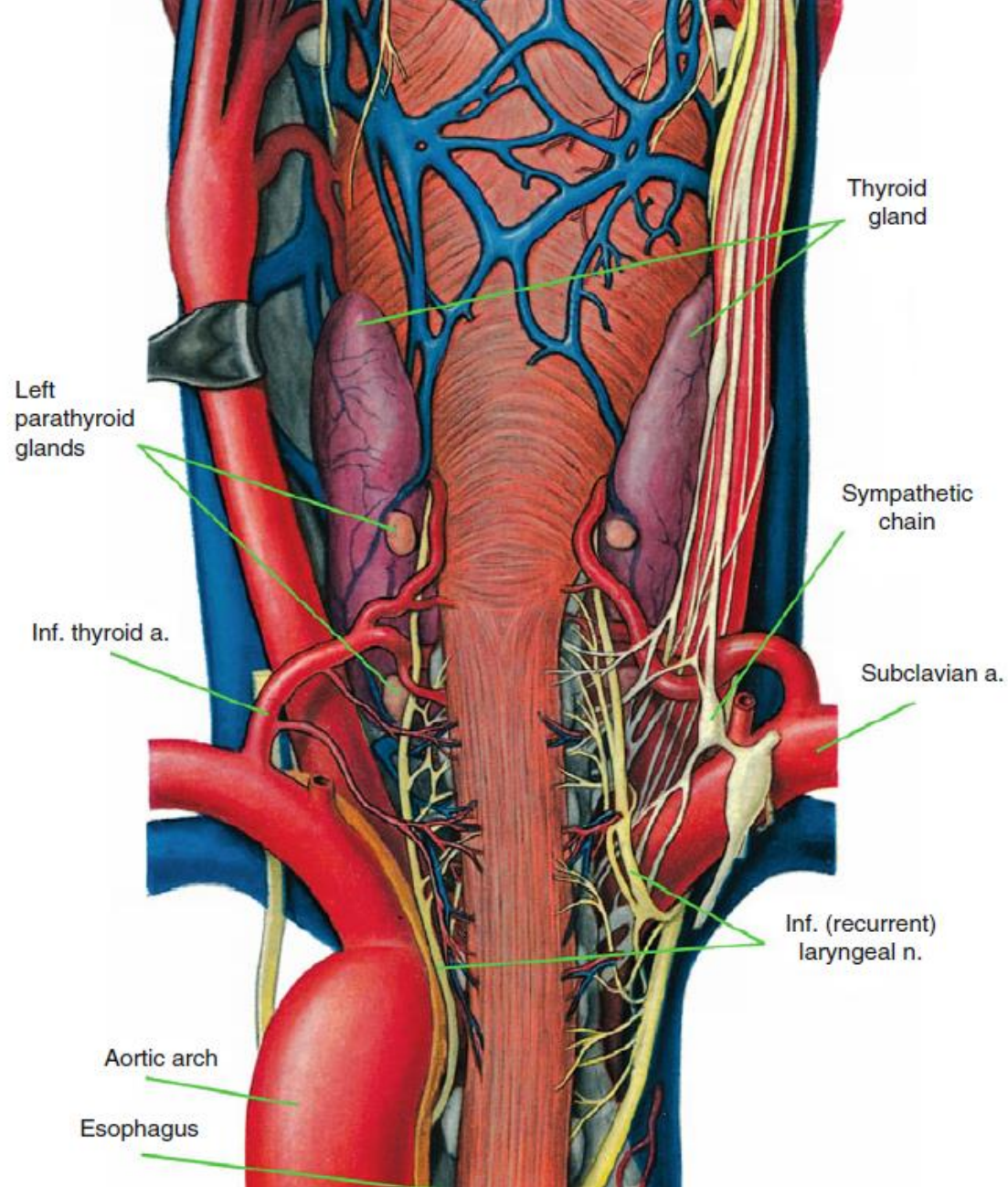
- ❖ Embryology, anatomy, and function of the parathyroid gland
- ❖ Location of parathyroid including ectopic locations
- ❖ Physiology of parathyroid gland
- ❖ Etiology, differential diagnosis, and management of hypocalcemia
- ❖ Etiology, differential diagnosis, and management of hypercalcemia
- ❖ Diagnosis, etiology, and pathology of hyperparathyroidism
- ❖ Diagnostic tests of parathyroid function
- ❖ Diagnosis and management of parathyroid carcinoma
- ❖ Etiology, diagnostic imaging, pathology, and management of hyperparathyroidism
- ❖ Surgical management of hyperthyroidism
- ❖ Diagnosis, investigation, and management of persistent and recurrent hyperparathyroidism
- ❖ Pathogenesis and clinical features of MEN syndrome

Anatomy

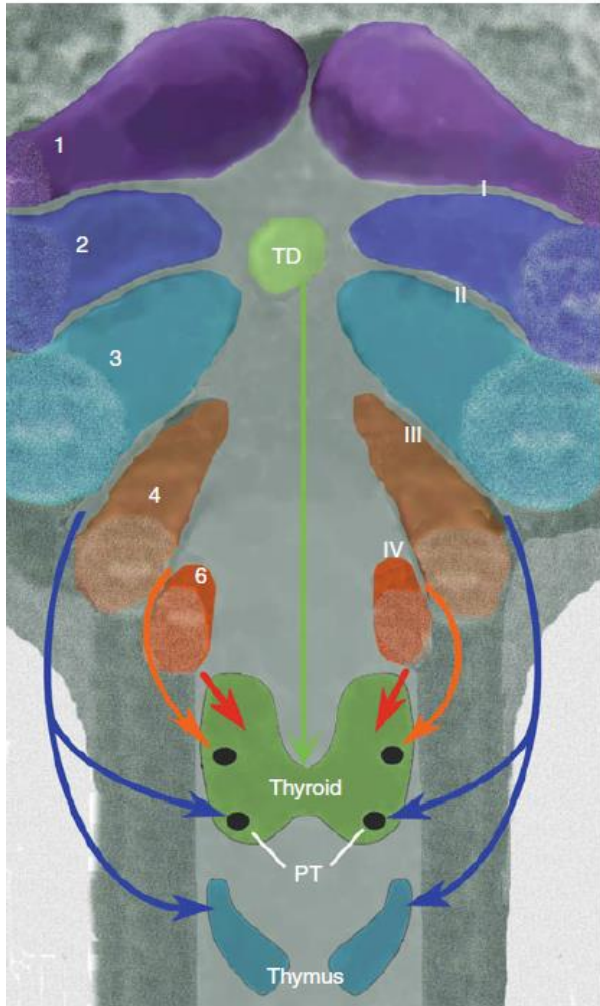
- Usually 4 glands
- Superior glands typically on posteromedial aspect of thyroid near tracheoesophageal groove
- Inferior glands more widely distributed
- Normal wt 35-40 mg

- Superior glands usually found in the middle third of the thyroid
- Inferior glands in the lower third
- All four glands supplied by inferior thyroid artery, superior glands may receive some contribution from the superior thyroid arteries
- Usually a single end-artery supplies each gland





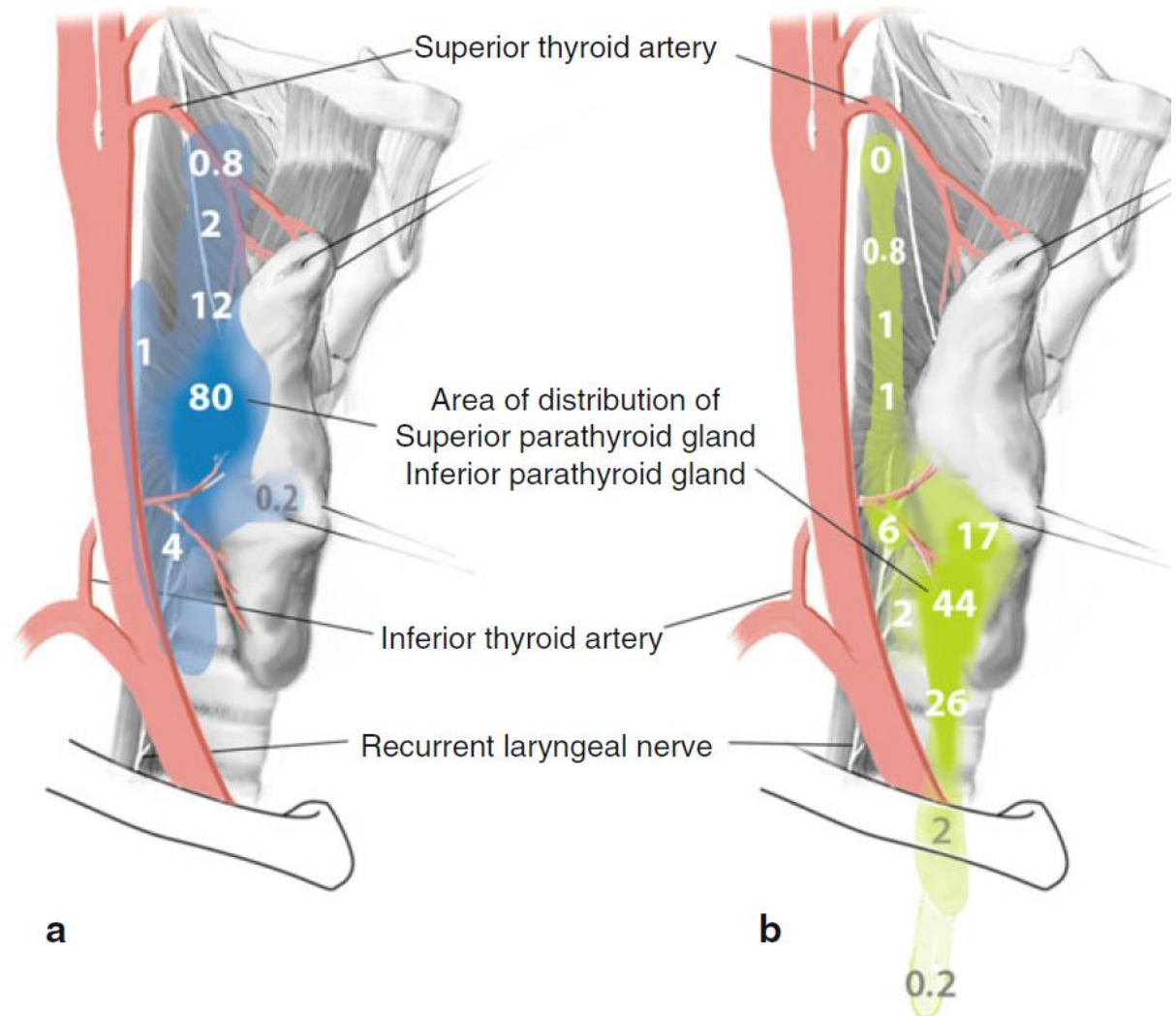
Embryology



- Develop from pharyngeal pouches
- 3rd pouch forms inferior glands and thymus
- 4th pouch forms superior glands

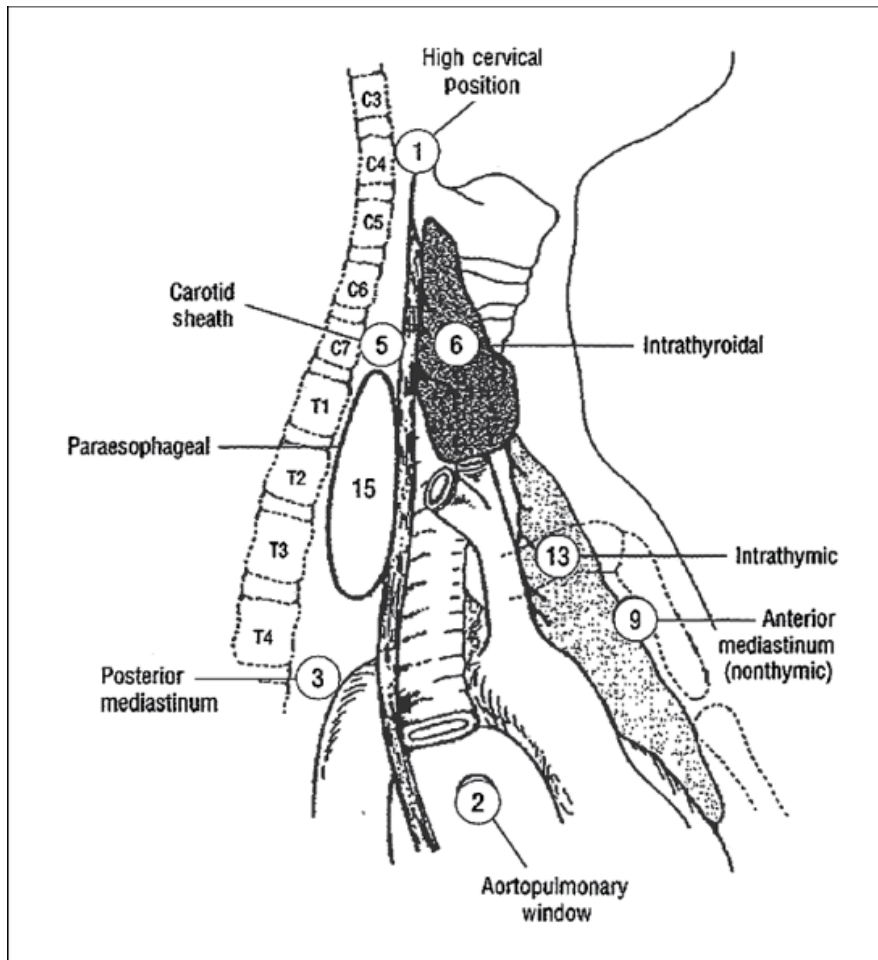
Normal locations of PTGs

Fig. 39.1 Normal location of superior (a) and inferior (b) parathyroid glands. Numbers represent the percentages of glands at different locations (also indicated by the *darker shading*) (From [16], with permission)



- Of the following, the most common location for an ectopic parathyroid gland is:
 1. Carotid Sheath
 2. Intra-thyroidal
 3. Thymus
 4. Posterior mediastinum

Ectopic parathyroid glands



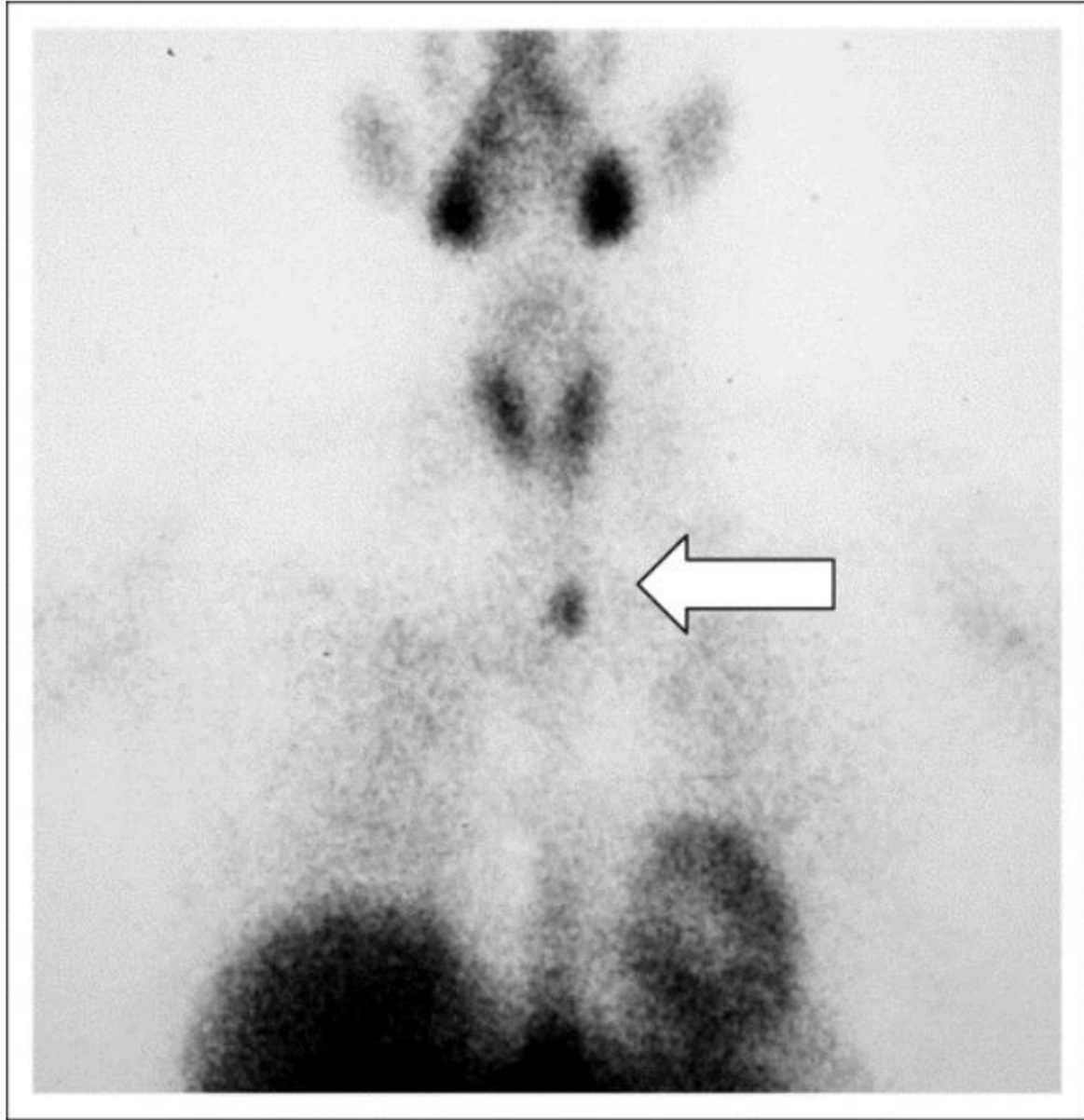
Location	Number
High cervical	1
Aortopulmonary window	2
Posterior mediastinum	3
Carotid sheath	5
Intrathyroid	6
Anterior mediastinum (nonthymic)	9
Intrathymic	13
Paraesophageal (neck)	15

Shen W, Duren M, Shen W et al (1996) Reoperation for persistent or recurrent primary hyperparathyroidism. Arch Surg 131:861–867; discussion 867–869

- 2.5-22% of individuals have supernumerary glands

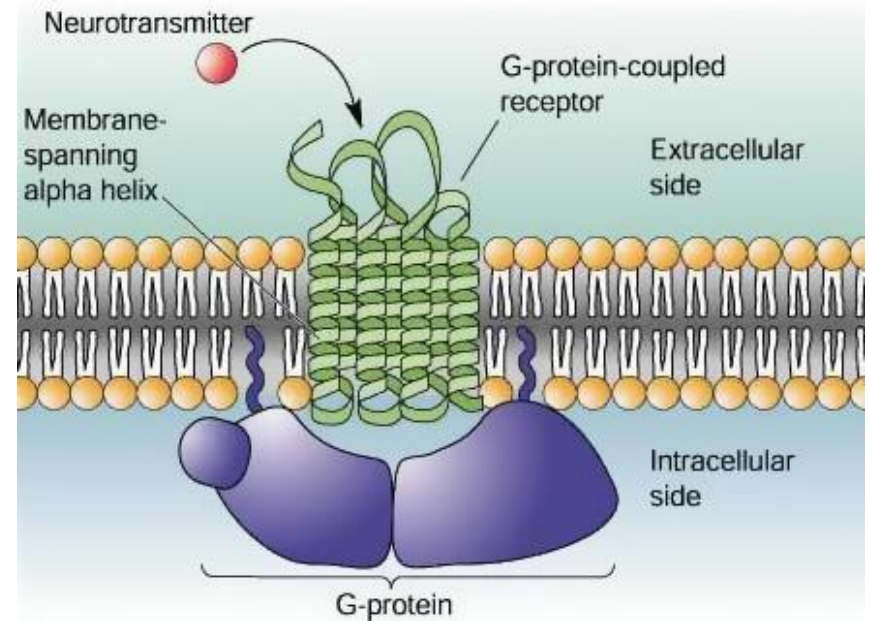
Source: Morita SY, Dackiw APB, Zeiger MA: *McGraw-Hill Manual: Endocrine Surgery*: <http://www.accesssurgery.com>

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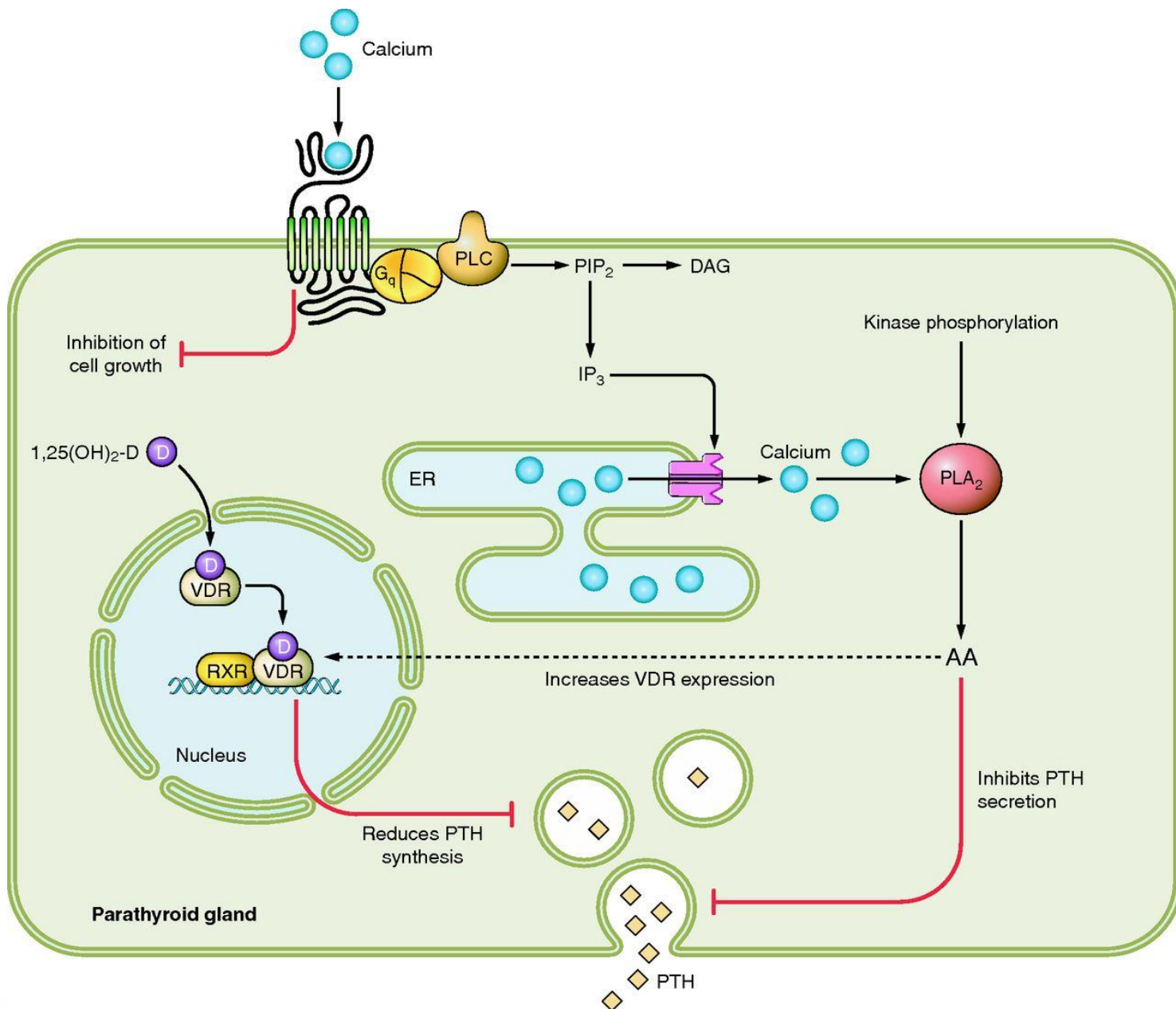


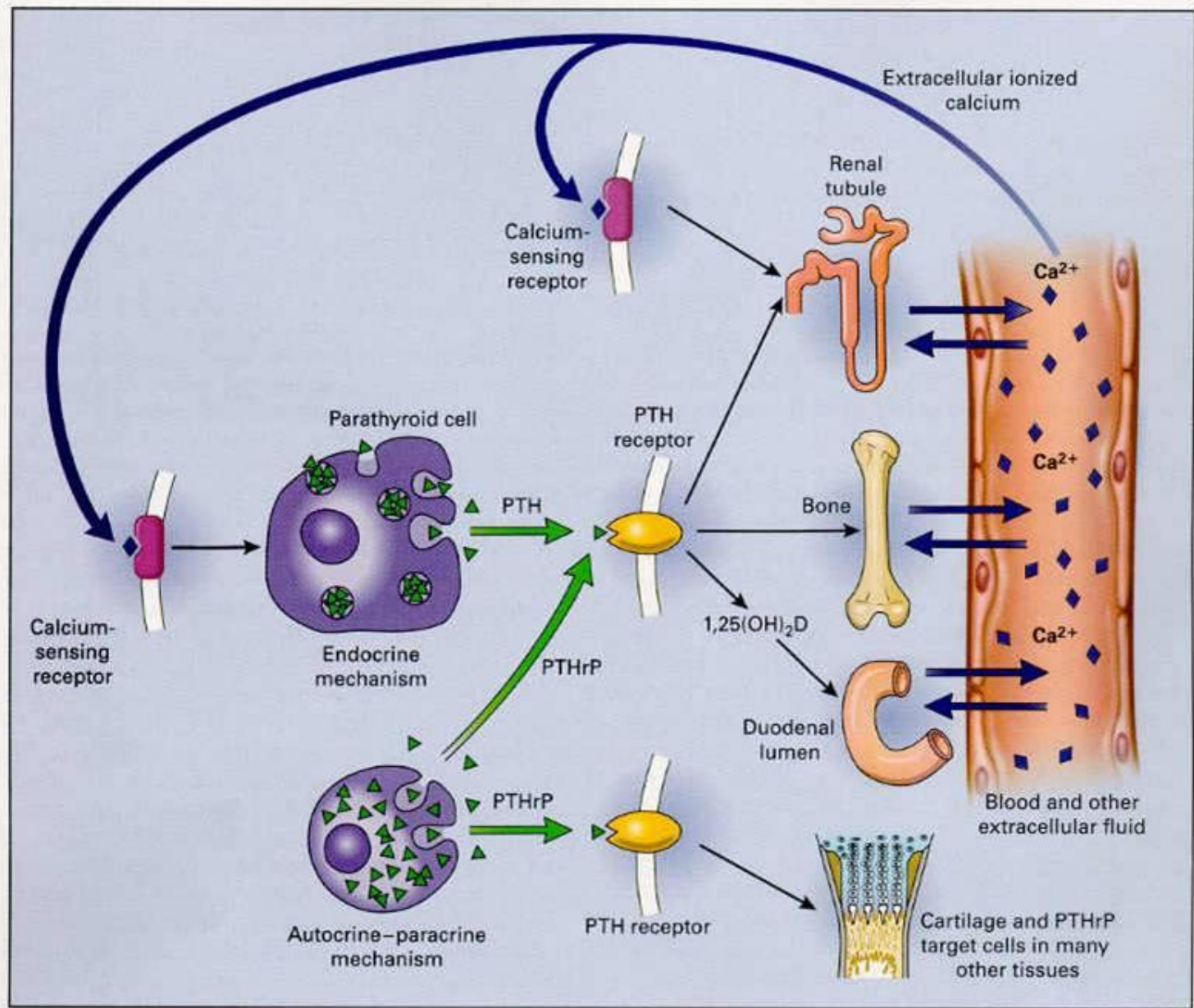
Physiology

- PTGs sense 1-2% changes in Ca level
- Calcium sensing receptor (CaSR) receptor



- If Ca is not normalized
 - Sustained elevation in PTH results in increased renal synthesis of the active metabolite of Vit D resulting in increased intestinal Ca absorption, renal absorption and bone Ca release
 - Decreased intracellular degradation of PTH, increased levels of PTH mRNA, and increased parathyroid cell proliferation up to 10-100x normal mass (secondary hyperparathyroidism)





Pathophysiology

Hypoparathyroidism

- Hypocalcemia and hyperphosphatemia
- Most common cause is iatrogenic

Table 29.1 Causes of hypoparathyroidism

1. Transient hypoparathyroidism
 - (a) Transient neonatal hypoparathyroidism
 - (b) Hypo- or hypermagnesemia
 - (c) Transient postsurgical hypoparathyroidism
2. Permanent hypoparathyroidism
 - (a) Genetic
 - (i) Abnormal parathyroid development
 - (ii) Defects in PTH gene
 - (iii) Activating mutations of CaSR
 - (b) Acquired
 - (i) Postsurgical hypoparathyroidism
 - (ii) Autoimmune/idiopathic hypoparathyroidism
 - (iii) Radiation-induced hypoparathyroidism
 - (iv) Metastatic infiltration of the parathyroids
 - (v) Deposition of heavy metals in parathyroid
3. Pseudohypoparathyroidism (types 1a, 1b, and 2)

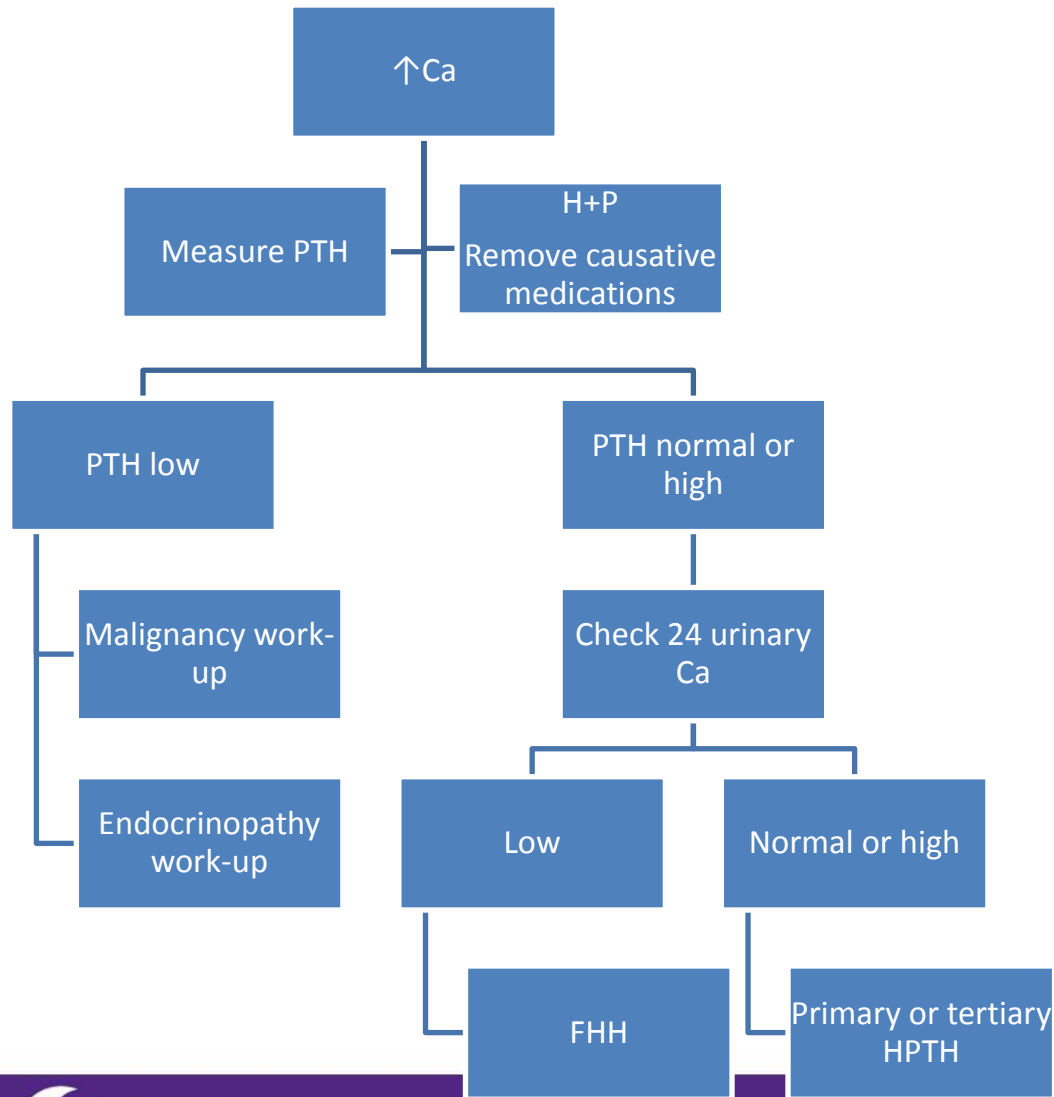
Hypocalcemia

- Symptoms
 - Neuromuscular irritability
 - Peri-oral numbness, paresthesias, cramps, tetany, laryngospasm, Chvostek, Trousseau
 - Fatigue/lethargy
 - Irritability
 - Prolonged QT

Hypocalcemia

- Management
 - Calcium administration
 - Oral or IV preparations
 - Replace Mg
 - Vitamin D
 - Thiazide diuretics
 - ↓ urinary secretion

Hypercalcemia



BOX 39-1 Differential Diagnosis of Hypercalcemia*

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)

Granulomatous Diseases

Sarcoidosis

Tuberculosis

Histoplasmosis

Coccidiomycosis

Leprosy

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

Hypercalcemia

- Classic symptoms
 - Painful bones, kidney stones, abdominal groans, psychic moans, fatigue overtones
- Most patients diagnosed biochemically prior to symptom appearance
 - Less than 20% of primary HPT patients have renal symptoms and less than 5% have evidence of osteitis fibrosis cystica

Hypercalcemia

- Hypercalcemic crisis
 - Marked elevated of serum Ca with acute signs/symptoms
 - Management
 - Aggressive rehydration
 - Subcutaneous injection of calcitonin or bispohsphonates
 - Glucocorticoids
 - Dialysis

Primary hyperthyroidism

- Causes:

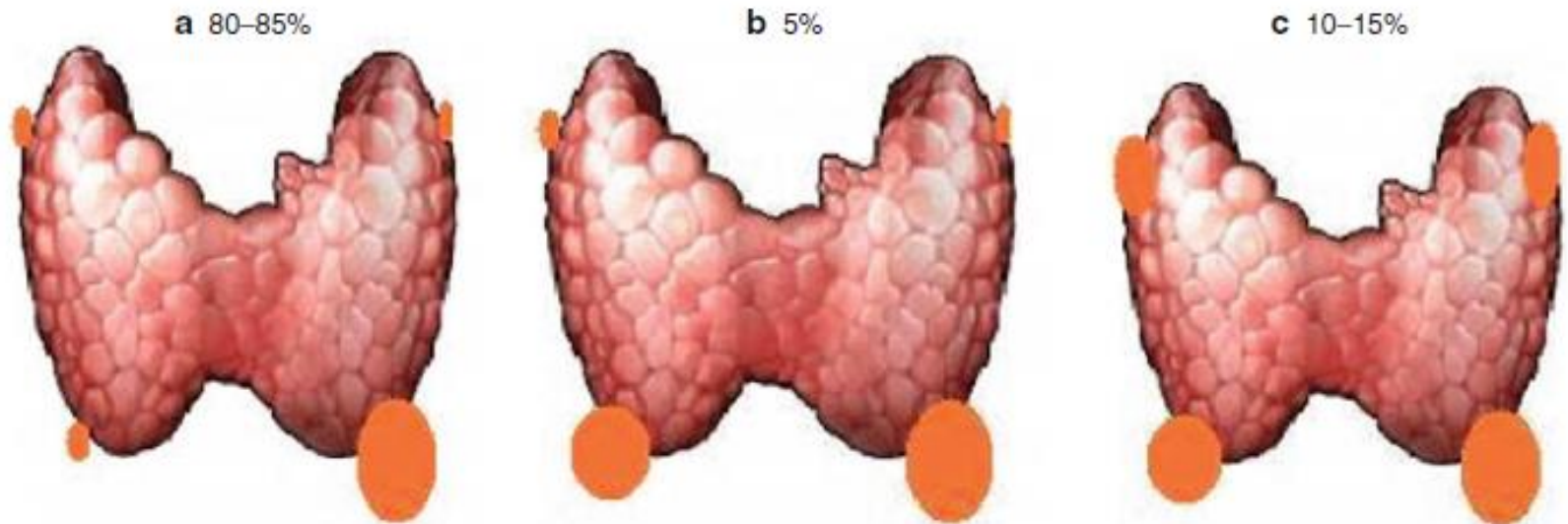


Fig. 32.1 Parathyroid gland enlargement in primary hyperparathyroidism (a) single adenoma, (b) double adenoma, (c) multigland hyperplasia. (a) 80–85%, (b) 5%, (c) 10–15%

Primary hyperparathyroidism

- The most common form of hyperparathyroidism
- Third most common endocrine disorder
- The most frequent explanation for hypercalcemia in the outpatient setting
- Incidence = 25 per 100,000 with peak in 5th and 6th decades of life
- Female to male ratio of 3:1

Work-up

- H&P
 - » Symptoms of hypercalcemia
 - » Evidence of other conditions associated with \uparrow Ca
 - » Associated endocrine disorders
 - » Explore family history
- Laboratory testing
 - » Serum Ca corrected for albumin, or ionized Ca
 - » Serum PTH
 - » Serum PO₄, lytes, BUN, Cr, 24-hr urine
 - » Exclude familial hypocalciuric hypercalcemia (renal Ca:Cr clearance <0.01)

Indications for surgery

- Symptomatic patients
 - Severe bone disease
 - Nephrolithiasis
 - Pancreatitis
 - Peptic ulcer disease

Indications for surgery

Table 32.1 Comparison of the NIH and the Third International Workshop guidelines for parathyroidectomy in patients with asymptomatic primary HPTH^a

Evaluation	2002	2008
Serum calcium (>upper limit of normal)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
24-h urine for calcium	>400 mg/day (>10 mmol/day)	Not indicated
Creatinine clearance (calculated)	Reduced by 30%	Reduced to <60 mL/min
BMD	T-score <-2.5 at any site	T-score <-2.5 at any site and/or previous fragility fracture
Age (year)	<50	<50

Adapted and modified from Bilezikian et al. [21].

^aSurgery is indicated in patients for whom medical surveillance is not desirable

- In patients with hyperparathyroidism, decreased bone mineral density can be diagnosed in which of the following regions?
 1. Skull
 2. Forearm
 3. Cervical spine
 4. Knee
 5. Ankle

Indications for surgery

- Patients who do not fulfill criteria may still benefit from parathyroidectomy
 - Improvements in mood, anxiety, cognitive impairments, and working memory
 - Decreased risk of bone fracture and improved BMD
 - Long-term cost-effectiveness versus observation, especially for younger patients

Pre-operative imaging

- Not appropriate for diagnosis of HPTH
- Pre-operative localisation is essential in order to avoid full neck exploration
- Sestimibi is best modality, especially when 3D images are obtained with SPECT (↑96% sensitivity compared with 80% for planar imaging)

Pre-operative imaging

- 99m Tc MIBI imaging
 - Uptake is observed in mitochondria rich tissues
 - Parathyroid is rich in mitochondria, but so is other metabolically active tissue
- 1.To localize hyperfunctioning parathyroid glands prior to the first operation
 - 2.To localize abnormal glands in recurrent or persistent HPTH

Pre-operative imaging

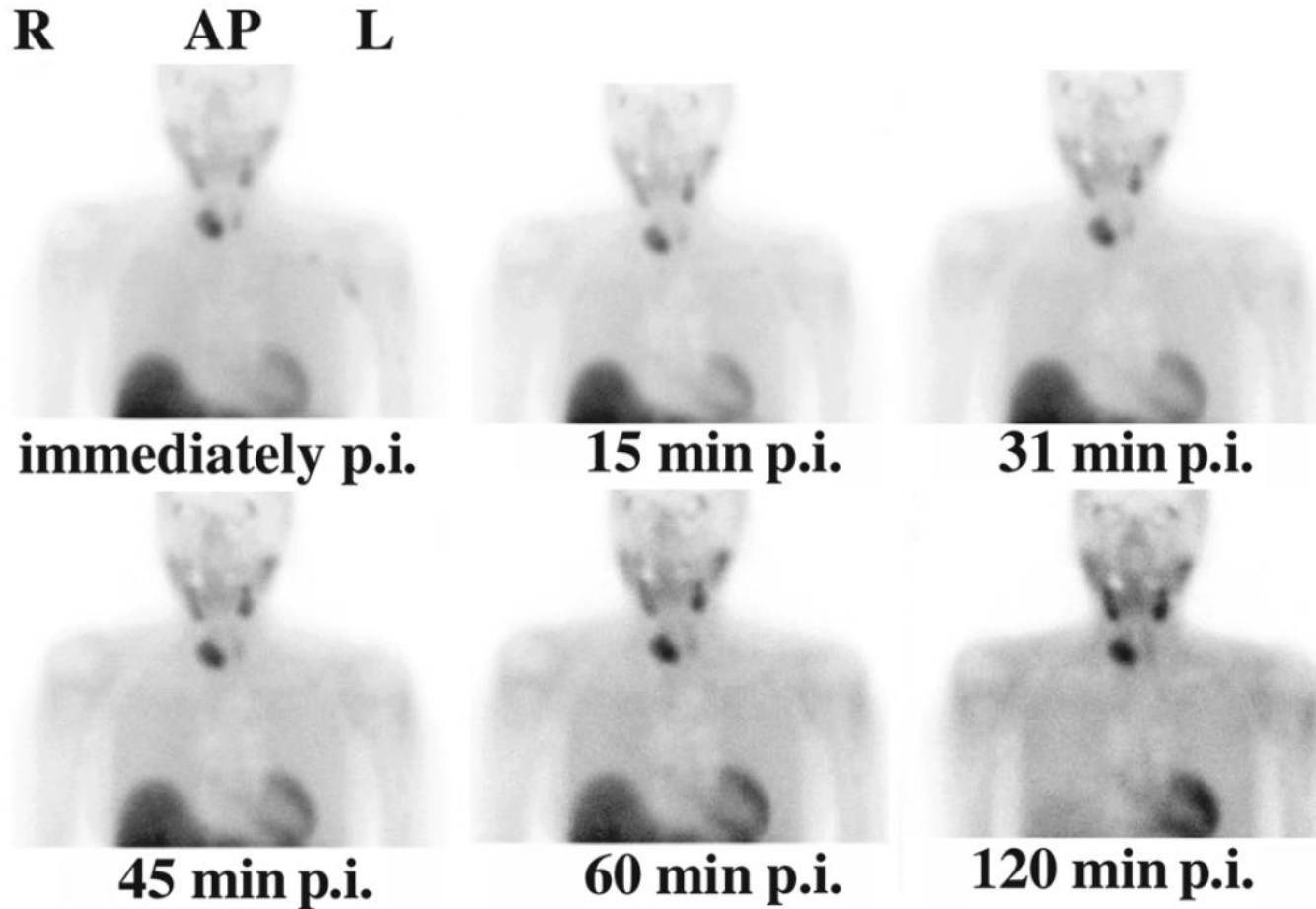


Fig. 31.2 Serial planar images of the neck region obtained immediately p.i., subsequently followed by images obtained at 15, 30, 45, 60 and 120 min p.i. Although the potential PA in the right lower position is depicted in the early images already, the lesion contrast is rising over time as shown by the subsequently

obtained delayed images. Having this information available, preoperative labelling of the potential PA can be timely optimized, if the patient is suited for minimally invasive parathyroid surgery and gamma probe navigation is also improved by better timing. *R* right, *L* left, *A* anterior, *P* posterior

Pre-operative imaging

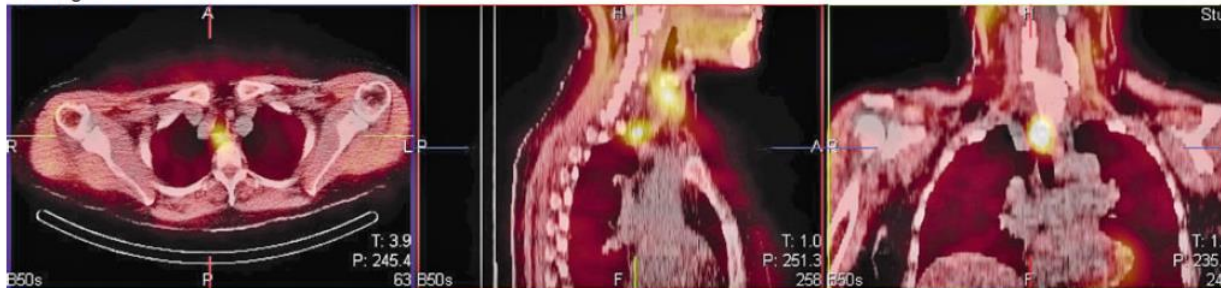
a CT



b SPECT



c Integrated SPECT/CT



R

L

D

V

R

L

Transaxial

Sagittal

Coronal

Ultrasonography

- Provides more detailed anatomic information compared to nuclear medicine imaging
- Assess for thyroid disease
- Less sensitive than nuclear imaging
- Normal parathyroid glands are too small to be seen, and ectopic glands are rarely visualised

Invasive localization

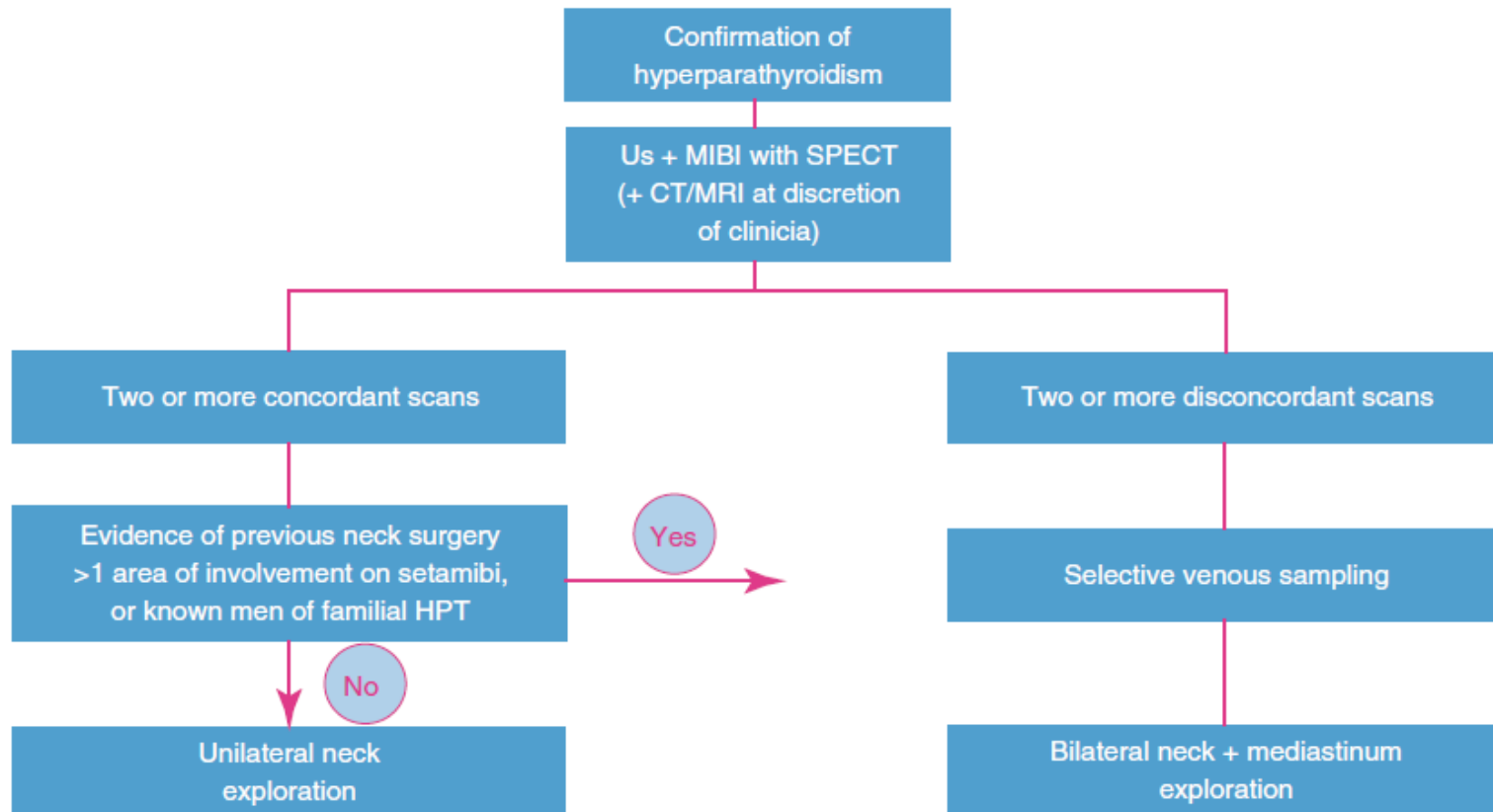
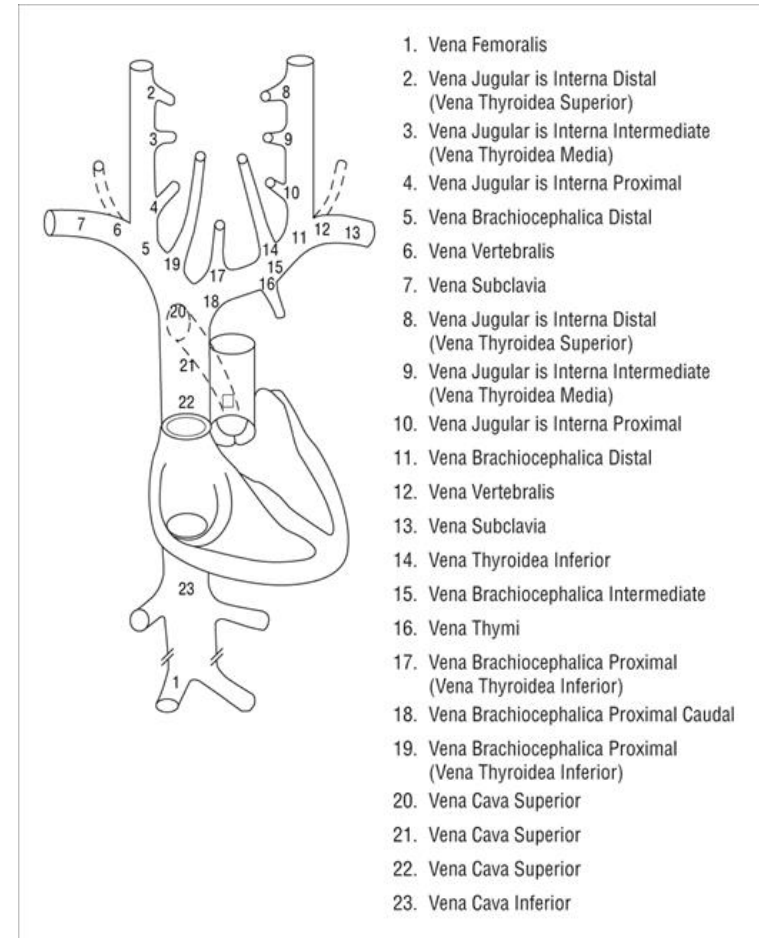


Fig. 31.17 Algorithm for the utilization of SVS in reoperative parathyroid surgery

Pre-operative imaging

- Invasive localization
 - Selective venous sampling
 - Selective arteriography



Selective venous sampling

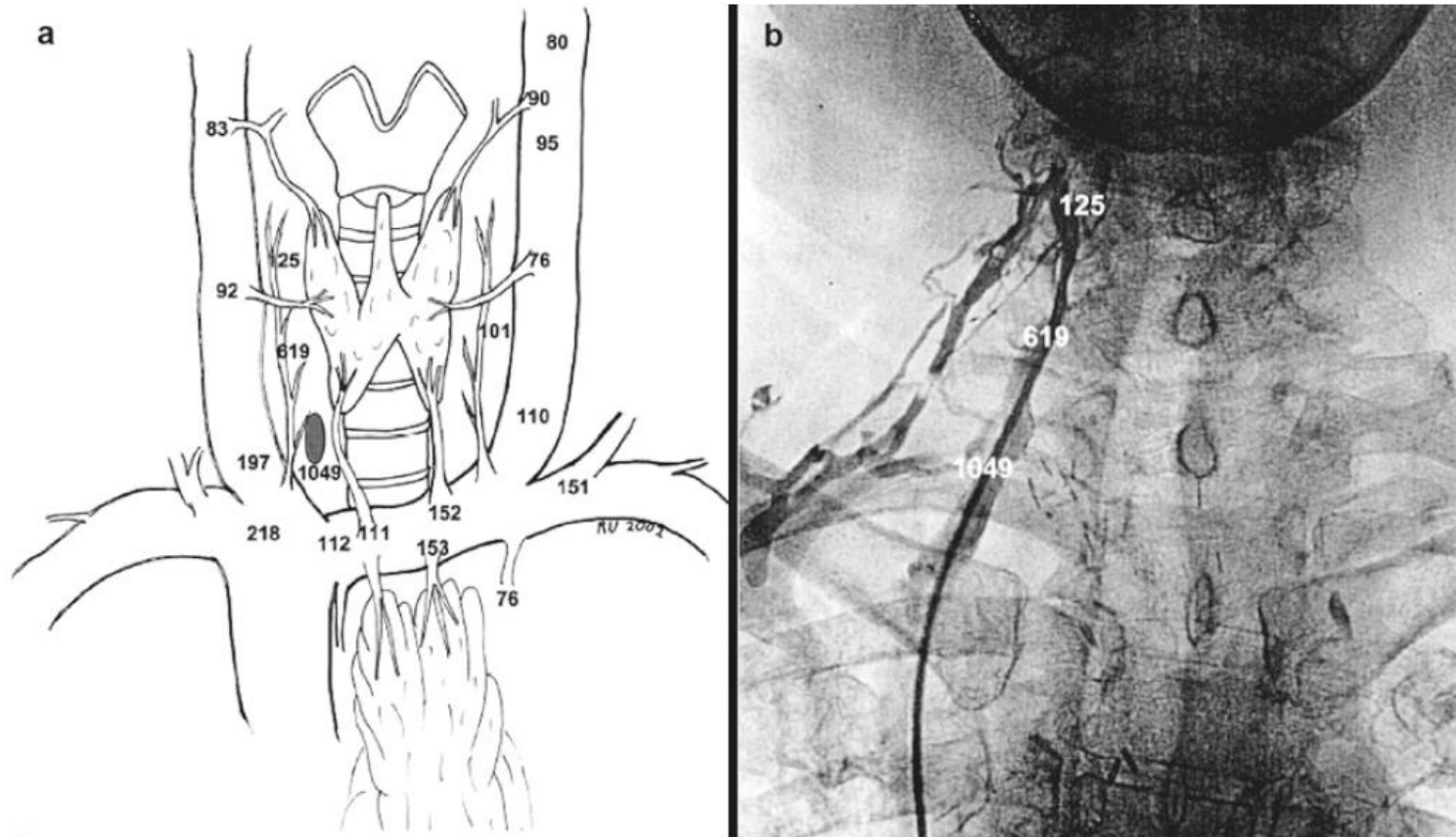


Fig. 31.19 (a) Venous PTH levels (pg/mL) obtained in the interventional suite in a patient with persistent hyperparathyroidism. A gradient was demonstrated in the right vertebral vein.

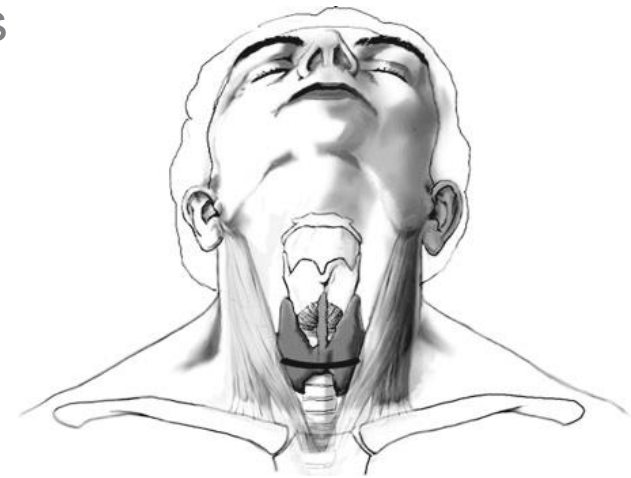
(b) Highly selective catheterization of this vein and the superimposed PTH values (pg/mL)

- The most common cause of hypercalcemia in patients with negative or discordant localization studies is which of the following?
 1. Four gland hyperplasia
 2. Multiple parathyroid adenomas
 3. Parathyroid carcinoma
 4. Single adenoma
 5. No identifiable parathyroid abnormality

Operative approaches

Operative considerations

- Semi-fowler position with neck extended
- Bolster beneath the shoulders
- Symmetric incision, preferentially in skin crease 3-4cm cranially to suprasternal notch
- Incision not to extend beyond SCM muscles
- Develop subplatysmal flaps
- Vertical incision divides strap muscles

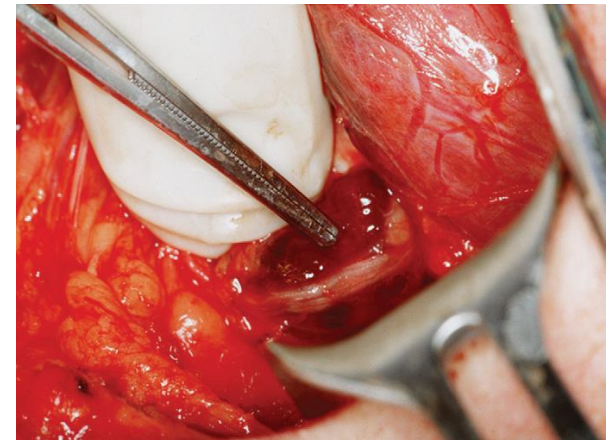


Operative considerations

- Strap muscles separated from underlying thyroid and thymus
- Complete exposure of the lateral aspects of the thyroid. Middle thyroid vein may be ligated for mobilization
- Fascial sheaths covering the thyroid should be removed to expose subcapsular parathyroid glands
- Dissection should be kept close to the thyroid to protect the RLN
- Operative field should be kept bloodless to prevent discoloration of the parathyroid glands

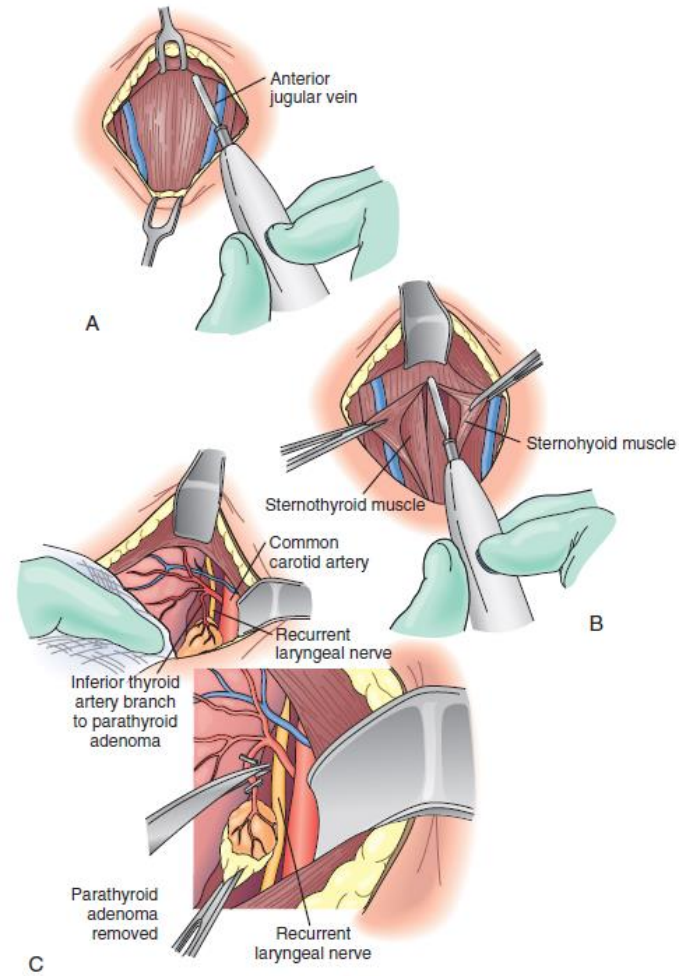
Gland identification

- Parathyroids have a light brown color, compared to the yellow hue of surrounding fat
- They are mobile in relation to the thyroid gland
- Less firm than lymph nodes
- Frozen section out of favor
 - Unreliable for hyperplasia vs adenoma
 - Can differentiate PT vs non-PT tissue, but increases incidence of transient post-operative hypocalcemia



Resection of PT tissue

- Vascular stalk of tumor should be ligated
- Capsule of gland should not be opened to prevent seeding of tissue
- Subtotal parathyroidectomy for multigland disease vs total parathyroidectomy with autotransplantation



Missing glands

1. Identify whether superior or inferior gland is missing
2. If superior gland is missing, explore retroesophageal space and above the thyroid cartilage
3. If inferior gland is missing, expose the thymus, open the carotid sheath, incise the inferior and posterior thyroid capsule, consider thyroid lobectomy
4. If 4 glands have been found, a supranumerary thymic gland must be considered and bilateral thymectomy is indicated

Bilateral neck exploration

- Conventional strategy
- Identifies all normal and abnormal parathyroid glands
- Distinguishes single-gland from multi-gland disease
- Preferred in multiple endocrine neoplasia and lithium-associated HPTH
- > 95% cure rate

Minimally Invasive Parathyroidectomy

- Local or regional block anesthesia may be used vs. general anesthesia
- Abbreviated incision (2-3cm) is made followed by creation of limited flaps
- Success is guided by intraoperative PTH assays

Fig. 33.3 (a) An abbreviated Kocher incision is made, the platysma is divided, and (b) the strap muscles are separated

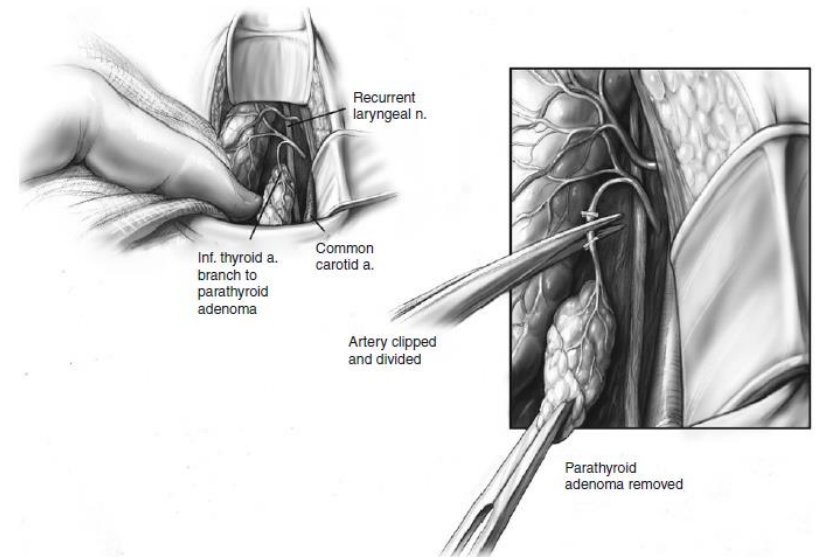
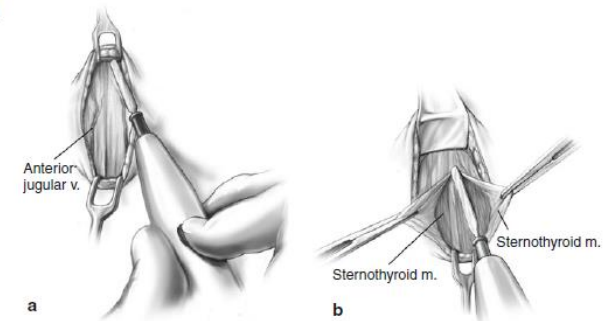


Fig. 33.4 The parathyroid adenoma is identified, its end-arterial blood supply is ligated, the recurrent laryngeal nerve is protected, and the adenoma is removed

Intraoperative localization

- Radio guided parathyroidectomy
- IV ^{99m}Tc injected 2-4 hours pre-operatively
- Gamma counter used to identify adenoma which usually emits radioactivity 20-50% higher than the post excision background

Minimally Invasive Parathyroidectomy

- Cure and complication rates similar to bilateral neck exploration
- 50% reduction in operating time
- Reduction in length of hospital stay
- Risk of permanent hypoparathyroidism is absent if a single gland is explored and removed

Minimally Invasive Parathyroidectomy

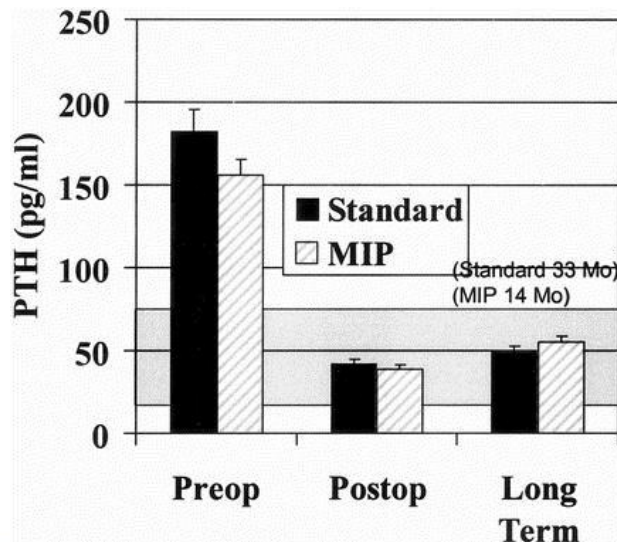
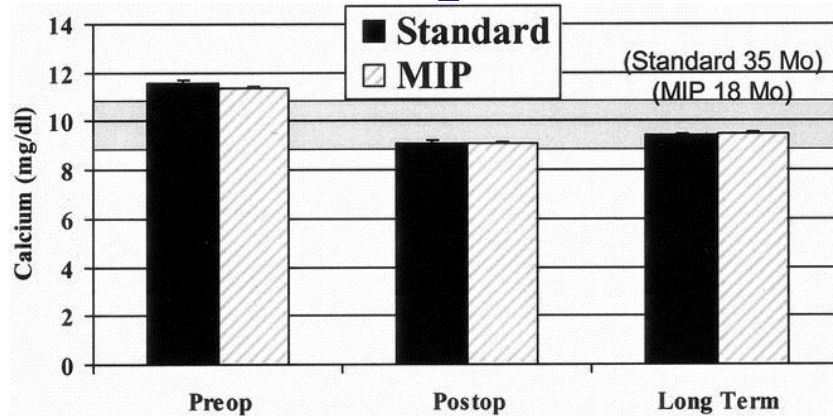


Table 2. COMPLICATIONS

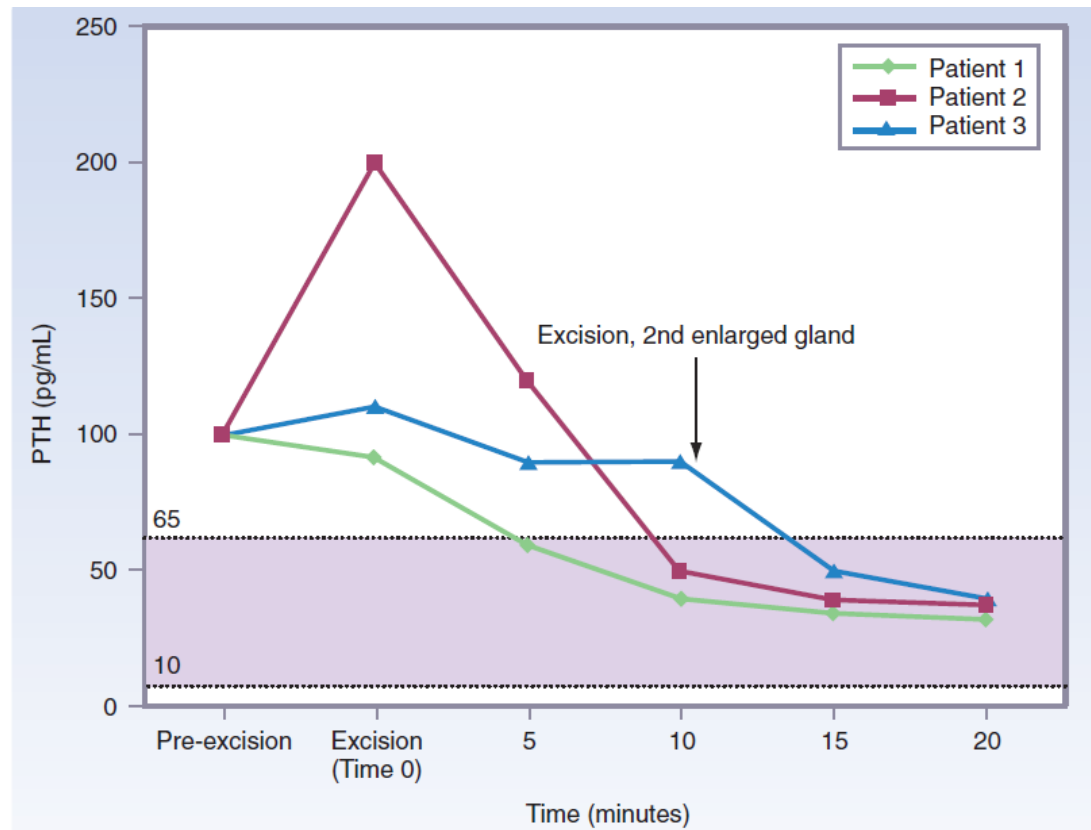
	n	Percent
Entire series	15/656	2.3
Standard	12/401	3.0
Ipsilateral recurrent nerve	3	0.7
Hypocalcemia	2	0.5
Atrial fibrillation	1	0.2
Deep venous thrombosis	1	0.2
Urinary retention	1	0.2
Neck hematoma	1	0.2
Neck edema	1	0.2
Cerebrovascular accident	1	0.2
Aspiration	1	0.2
MIP	3/255	1.2
Hematoma (coumadin)	1	0.8
Seizure	1	0.8
Ipsilateral recurrent nerve	1	0.8

MIP, minimally invasive parathyroidectomy. Two complications (1 recurrent nerve injury, 1 cerebrovascular accident) in the standard group occurred in redo cases. One of the complications (recurrent nerve injury) in the MIP group occurred in the redo setting. A postoperative neck hematoma occurred in an MIP patient who had been the recipient of a liver transplant and required chronic anticoagulation (coumadin).

- The intraoperative maneuver that is most associated with cure of hyperparathyroidism is which of the following?
 1. Confirmation of a 50% reduction in circulating levels of PTH 10-15 minutes after removal of the suspicious gland
 2. Selective venous sampling for PTH
 3. Identification of all 4 parathyroid glands
 4. Performance of transcervical thymectomy
 5. Removal of the thyroid lobe on the side of the suspicious gland

Biochemical cure

- Half-life of PTH is 3.5-4 minutes
- 50% reduction in PTH is predictive of cure in 96% of cases



Biochemical cure

- Multiple published criteria exist:

Table 28.1 Criteria for biochemical cure of PHPT with IOPTH

Miami	'...greater than or equal to 50% decay from the highest (pre-incision or pre-excision) value within 10 min after removing the hyperfunctioning gland(s)...'
Vienna	'...A decay of greater than or equal to 50% from baseline (pre-incision) within 10 min of resection is used to predict complete resection of hyper-secreting parathyroid tissue...'
Halle	'...decay into the low normal range ($\text{PTH} \leq 35 \text{ pg/mL}$) within 15 min of extirpation of the hyperfunctioning parathyroid tissue...'
Rotterdam	' t 10 qPTH levels between 100 and 200 ng/L combined with a decline of more than 70% or t 10 levels of more than 200 ng/L combined with a drop of 80% of qPTH to be interpreted as a measure for adequate surgery'
Rome	'...less than 50% drop from the highest pre-excision level and/or a T20 concentration higher than reference range and/or $>7.5 \text{ ng/L}$ higher than the T10...predicts MGD...'
Ann Arbor	'...a 50% drop from baseline (<i>pre-incision or manipulation</i>) and a return of the PTH level into the normal range (12–75 pg/mL)... at 5 or 10 min
Aarhus	'...PTH values at T5 below 20% of T0 or a value in the normal range below 7.6 pmol/L ...'
Riss et al. [40]	'...A final IOPTH $< 35 \text{ pg/mL}$ or a $>90\%$ decrease from baseline was predictive of a successful operation...'

Static PTH

- Continued exploration is mandatory with conversion to bilateral neck exploration
- Intraoperative ultrasound or bilateral jugular vein sampling
- The most advantageous time to cure pHPT is during the first operation

Postoperative care

- Complications:
 - Hematoma
 - Wound infection
 - Recurrent or superior laryngeal nerve injury
 - Hypoparathyroidism
 - Transient hypocalcemia

Postoperative care

- Patient is monitored for 1-4h for absence of neck hematoma
- Oral calcium/vitamin D supplementation for 2-4 weeks to avoid symptoms of transient hypocalcemia
- Repeat bloodwork at 2 weeks and 6 months. Cure is defined as normalization at 6 months

Persistent or recurrent HPT

- Causes of failure:
 - Persistent disease
 - Serum Ca never normalises or returns to abnormal values within 6 months of abnormal
 - Recurrent disease
 - Hypercalcemia reappears more than 6 months after apparently curative surgery

- The most common cause of persistent primary hyperparathyroidism is
 1. Parathyroid cancer
 2. Parathyroid hyperplasia
 3. Missed adenoma
 4. New adenoma

Persistent or recurrent HPT

Table 39.1 Causes of failed primary operations in HPT

Persistent HPT

Missed adenoma

Not identified or inadequately resected multiglandular disease

Supernumerary gland not identified

Incomplete excision of multilobated gland

Recurrent HPT

Insufficient four-gland visualization, hyperplasia not recognized, or inadequately resected

Growth of previously normal glands

Development of abnormality in supernumerary glands

Remnant hypertrophy in patients subjected to subtotal resection

Graft hypertrophy in patients subjected to total parathyroidectomy and autotransplantation

Persistent or recurrent HPT

- Persistent disease is implicated in 80-90% of reoperations
- Recurrence more common in patients with MEN1

Persistent or recurrent HPT

- Preoperative evaluation
 - Confirm \uparrow Ca and \uparrow PTH, exclude co-existing diseases (sarcoidosis, malignancy)

Persistent or recurrent HPT

- Indications for re-operation
- Symptomatic patients:
 - Parathyroid bone disease
 - Renal stones
 - Nephrocalcinosis
 - Renal function impairment
 - Pancreatitis
 - Cardiovascular disease
 - Peptic ulcer disease
 - Neuromuscular weakness
 - Psychiatric disability

Persistent or recurrent HPT

- Indications for re-operation
- Symptomatic patients
- Asymptomatic patients:
 - Patients younger than 50 years
 - Patients unwilling or unable to comply with annual biochemical surveillance
 - $\text{CrCl} < 60 \text{ ml/min}$
 - Bone mineral density T score less than -2.5 at any site
 - Previous fragility fracture
 - Total serum Ca $> 1.0 \text{ mg/dl}$ (0.25 mmol/l) above the upper normal limit

Persistent or recurrent HPT

- Timing of re-operation
 - Within 1 week if possible to avoid adhesions
 - Postpone until at least 3 months
- Approach
 - Dissection between anterior border of sternocleidomastoid and the poster border of the strap muscles can avoid scar tissue from the prior operation

Parathyroid carcinoma

- Accounts for only ~1% of HPTH
- 0.005% of NCDB cancer cases
- Etiology poorly understood
 - Head and neck radiation
 - Chronic stimulation from renal failure
 - Familial syndromes

Parathyroid carcinoma

- Histological diagnosis
 - Difficult without evidence of metastatic disease or invasion
 - Classic features: trabecular architecture, mitotic figures, thick fibrous bands, capsular and blood vessel invasion
 - Not always present or specific for malignant disease

Parathyroid carcinoma

- Clinical presentation

Table 38.1 The clinical and biochemical feature of parathyroid carcinoma compared to benign primary hyperparathyroidism

	Benign HPTH	Parathyroid carcinoma
Female to male	4 to 1	1 to 1
Average calcium (mmol/L)	2.7–2.9	3.75–4.0
Average PTH (ng/L)	<2× normal	>3–10× normal
Average age	Sixth decade	Fifth decade
Palpable mass (%)	<2	30–76
Osteitis fibrosa cystica (%)	5	40–75
Nephrolithiasis (%)	10–15	40
Renal and bone disease (%)	Rare	40–50
Asymptomatic (%)	80	2

Parathyroid carcinoma

Table 3. Trends in Parathyroid Cancer Staging and Treatment by Four-year Groupings, 1998–2003 (N = 224)

Characteristic	No. of Patients (%)				Total
	1988–1991	1992–1995	1996–1999	2000–2003	
Cancer stage					
Localized [†]	14 (58.3)	15 (46.9)	23 (47.9)	64 (53.3)	116
Regional disease	7 (29.2)	14 (43.8)	19 (39.6)	40 (33.3)	80
Distant metastases	1 (4.2)	2 (6.3)	2 (4.2)	5 (4.2)	10
Unstaged	2 (8.3)	1 (3.1)	4 (8.3)	11 (9.2)	18
Size of tumor, cm					
0–1.9	7 (29.2)	5 (15.6)	6 (12.5)	18 (15)	36
2–3.9	5 (20.8)	10 (31.3)	15 (31.3)	39 (32.5)	69
≥4	4 (16.7)	3 (9.4)	7 (14.6)	7 (5.8)	21
Not reported	8 (33.3)	14 (43.8)	20 (41.7)	56 (46.7)	98
Lymph node status					
Negative	13 (54.2)	17 (53.1)	28 (58.3)	83 (69.2)	141
Positive	1 (4.2)	2 (6.3)	1 (2.1)	5 (4.2)	9
Not reported	10 (41.7)	13 (40.6)	19 (39.6)	32 (26.7)	74

Parathyroid carcinoma

- Pre-operative imaging
 - U/S, CT, and MARI can demonstrate extent of the tumor, involvement of adjacent structures, and evidence of regional/distant metastases
 - Whole body sestamibi imaging can localize the primary tumor and also display distant metastases

Parathyroid carcinoma

- Surgical management
 - Simple parathyroidectomy vs en bloc resection
 - En bloc resection associated with lower risk of recurrence and death
 - Contralateral exploration for hyperplasia

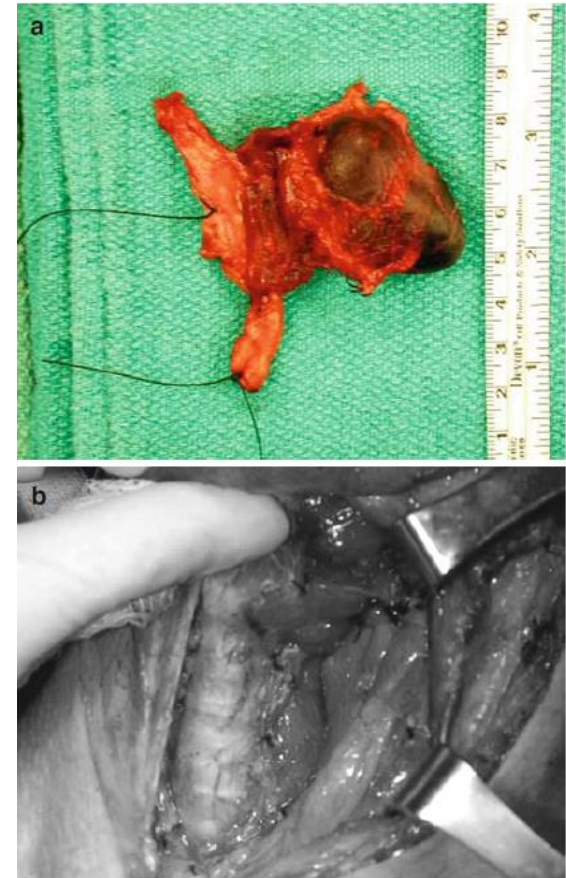


Fig. 38.7 (a) The en bloc surgical specimen. One suture is on the isthmus of the ipsilateral thyroid lobe. Two sutures mark the thymus and central compartment. (b) The residual tumor bed upon completion of the en bloc resection including the central compartment, ipsilateral thyroid lobe, and both the parathyroid carcinoma and normal ipsilateral gland

Parathyroid carcinoma

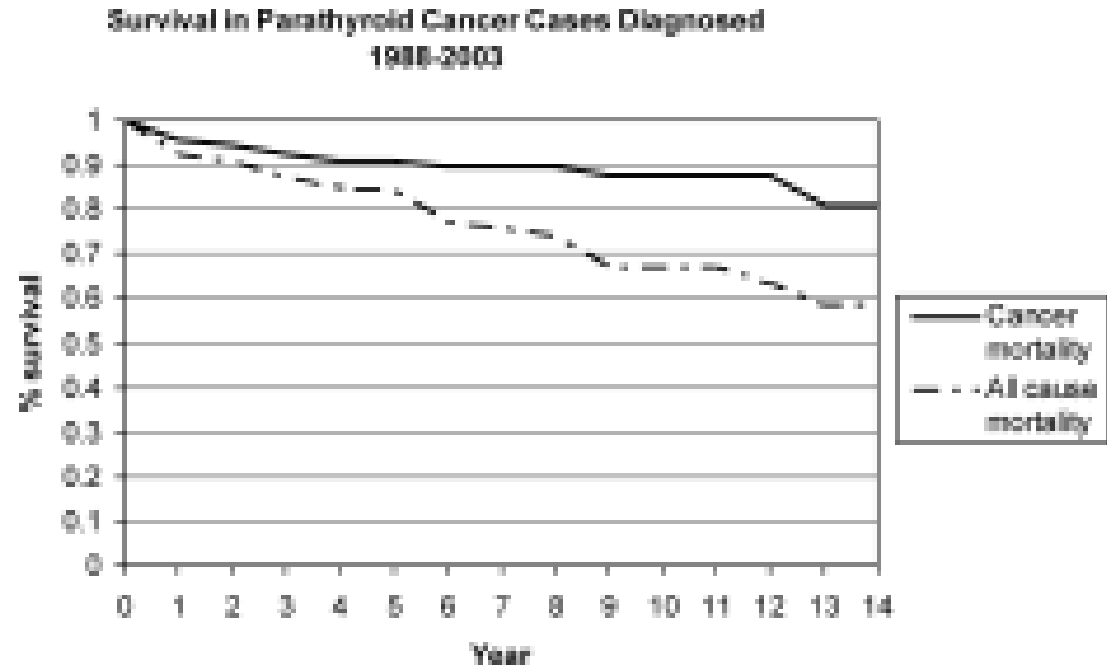
- Adjuvant therapy
 - Lower locoregional recurrence rate following adjuvant radiotherapy in small cohorts
 - No current role for chemotherapy

Parathyroid carcinoma

SEER database

10 year all-cause mortality = 33%

10-year cancer related mortality = 12.5%



Parathyroid carcinoma

- Recurrence is common (33%-78%)
- 10-year overall survival is high (50-70%)
- Male gender, vascular invasion, LN involvement, distant metastases, type of surgery associated with worse survival

Parathyroid carcinoma

- Patients usually die from metabolic complications of hypercalcemia
- Palliative therapy
 - Loop diuresis and rehydration
 - Bisphosphonates
 - Calcimimetics
 - Anti-PTH immunotherapy

Secondary Hyperparathyroidism

- Serum PTH levels rise once GFR falls below 60ml/min
- Up to 90% of patients with chronic renal failure have evidence of secondary HPT
- 2HPTH is almost universal in dialysis dependent CKD
- Normal parathyroid glands have the capacity to augment their mass by 10-100 fold in the setting of chronic hypocalcemia

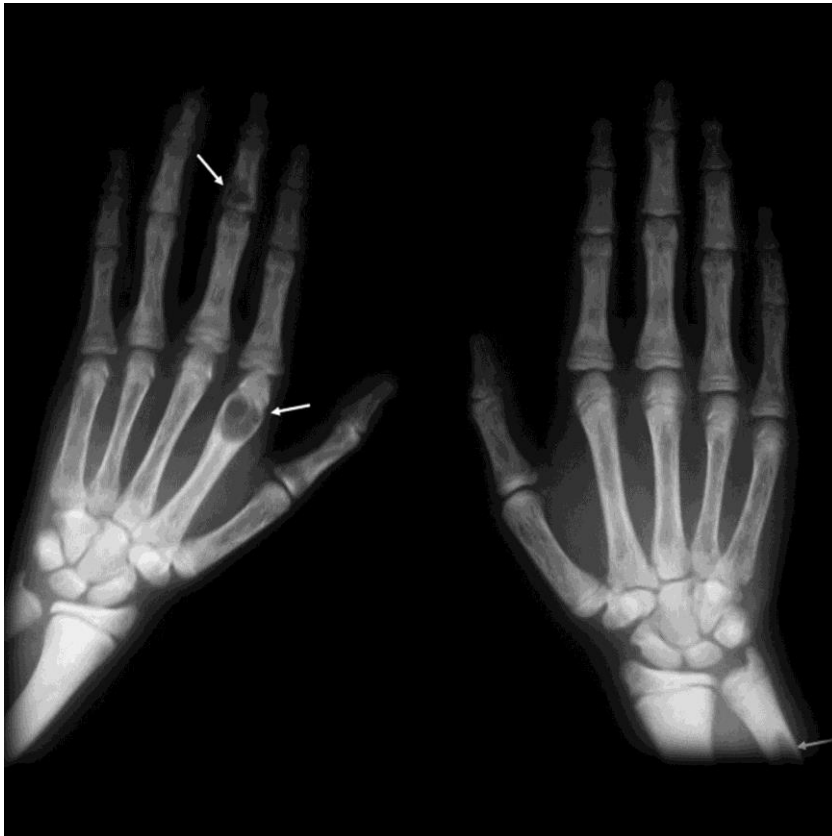
Pathophysiology

- Low calcium concentration increases both PTH release and PTH synthesis by post-transcriptional stabilization of PTH-coding RNA, which is mediated by membrane bound CaSR on the parathyroid cells.

Renal bone disease

- Osteitis fibrosa cystica
 - Caused by high bone turnover, as a consequence of increased PTH secretion
- Adynamic bone disease
 - Caused by low bone turnover, associated with low levels of serum PTH

Renal bone disease



- Parathyroidectomy is indicated in patients with secondary hyperparathyroidism who develop which of the following complications?
 1. Hypertension
 2. Serum Ca of $> 1\text{mg}$ over normal
 3. Nephrolithiasis
 4. Calciphylaxis
 5. Myocardial infarction

Calciophylaxis

- Calcification of the media of small to medium sized arteries
- Ischemic damage to dermis/epidermis
- Erythematous lesions → Nonhealing ulcers, gangrene
- Associated with 50% mortality
- Emergent indication for parathyroidectomy



Management

- Prevention of phosphate retention and hyperphosphatemia
- Judicious use of Vitamin D
- Calcimimetics

Management

- Bilateral neck exploration
- Subtotal parathyroidectomy
- Total parathyroidectomy with heterotopic autotransplantation
- High recurrence rate

Table 37.2 Target range of intact PTH by stage of CKD

Stage of chronic kidney disease	GFR range (ml/min/1.73 m ²)	Target intact PTH (pg/ml)
1	≥90 ml/min	Normal range
2	60–89 ml/min	Normal range
3	30–59 ml/min	35–70
4	15–29 ml/min	70–110
5	<15 ml/min or dialysis	150–300

Reproduced from National Kidney Foundation [24]

Tertiary Hyperparathyroidism

- Parathyroid glands become autonomous and hypercalcemia develops
- Persistent hypercalcemia seen in 8-53% of transplant recipients
- Multifactorial
 - Medications
 - Tubular injury
 - Rejection episodes

Tertiary Hyperparathyroidism

- Hypercalcemia may adversely affect renal graft function
- Most tertiary hyperparathyroidism will resolve after transplantation
- Medical treatment may be indicated in some cases

Table 37.1 Proposed indication for surgery in patients with 3HPTH after kidney transplantation

Indications
Persistent hypercalcaemia (>3–12 months after renal transplantation)
Persistent hypercalciuria
Renal phosphorus wasting
Low BMD
Nephrocalcinosis
Pruritus
Parathyroid glands weighing >500 mg as evaluated by US

Persistent hypercalcemia is the only major criteria, all others are minor criteria

BMD bone mineral density, *US* ultrasonography

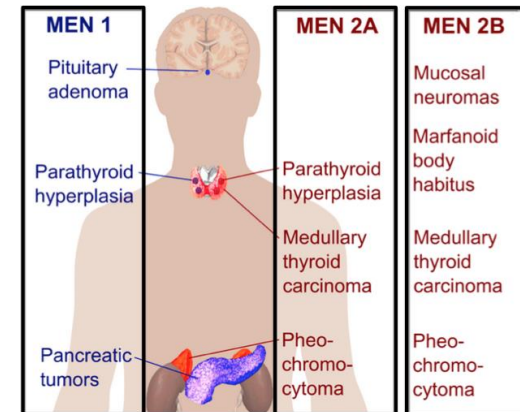
Familial syndromes

Table 39.2 Different entities of familial hyperparathyroidism, genetic characteristics, presentation of hyperparathyroidism, and associated features

Disorder	Inheritance	Responsible gene	Chromosomal location	HPT	Associated tumors
MEN1	AD	<i>MEN1</i>	11q13	High penetrance (~90%), multiglandular	Pituitary, EPT, adrenocortical, foregut carcinoid (thymic)
MEN2A	AD	<i>RET</i>	10q21	Low penetrance (~20%), multiglandular/adenoma	MTC, pheochromocytoma
HPT-JT	AD	<i>HRPT2</i>	1q21–q32	Cystic parathyroid tumors, 15% risk of carcinoma	Jaw tumors, renal lesions
FIHPT ^a	AD	<i>HRPT2</i>	1q21–q32	Adenoma/multi glandular	–
	AD	<i>MEN1</i>	11q13		–
	AD, AR	?	<i>2p13.3–14</i>		–
ADMH	AD	<i>CASR</i>	3q13–21	Multiglandular/adenoma	–
FHH	AD	<i>CASR</i>	3q13–21	Mildly hyperplastic	–
NSHPT	AR/AD	<i>CASR</i>	3q13–21	Markedly hyperplastic	–

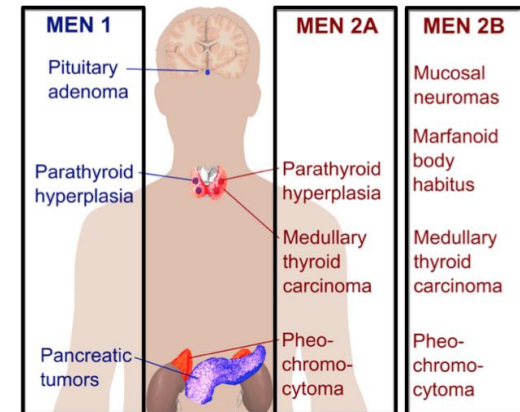
Familial syndromes

- Multiple Endocrine Neoplasia Type 1
 - Autosomal dominant
 - Mutation on 11q13
 - Three p's → tumors of parathyroid, endocrine pancreas, and anterior pituitary
 - Incidence 1 in 30, 000
 - An MEN1 case is defined as a patient who exhibits 2 of 3 principle MEN1 tumors
 - Familial MEN1 is defined as one MEN1 case and one 1st degree relative with 1 of 3 principle tumors



Familial syndromes

- Multiple Endocrine Neoplasia Type 1
 - Hyperparathyroidism is usually the first manifestation
 - Occurs in 3rd-5th decades of life
 - Asymmetrical hyperplasia with high incidence of supernumerary glands



Familial syndromes

- Multiple Endocrine Neoplasia Type 1

- Operative approach

- Subtotal parathyroidectomy vs total parathyroidectomy with heterotopic autotransplantation

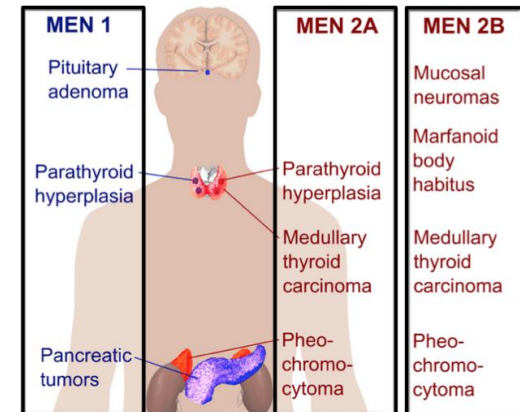
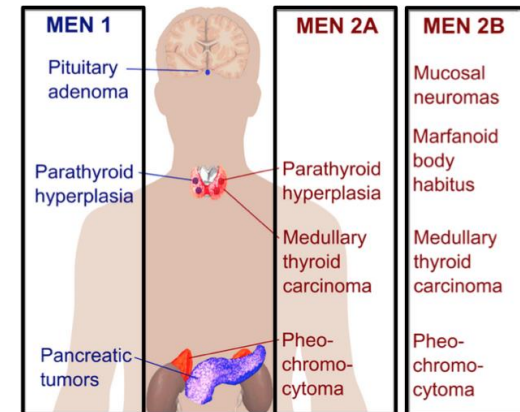


Figure 1- Implant with twenty sites.

Familial syndromes

- Multiple Endocrine Neoplasia Type 1
 - Operative approach
 - Subtotal parathyroidectomy vs total parathyroidectomy with heterotopic autotransplantation
 - Subtotal has ↑ persistence/recurrence but ↓ permanent hypoparathyroidism



Operative Considerations

- Parathyroidectomy for MEN1
 - Identification of all glands
 - Meticulous search for ectopic glands (up to 20% of MEN1 patients)
 - Thymus, mediastinum, carotid sheath, TE groove
 - Consider cervical thymectomy
 - Prevent persistent or recurrent HPTH, and thymic carcinoid tumors
 - Consider cryopreservation of parathyroid tissue

Operative Considerations

- Subtotal
 - Leave remnant approx. the size of a normal parathyroid (20-30mg)
 - Verify perfusion with bleeding from the transected surface
 - Preserve the single end-artery vascular supply
 - Prepare prior to resection of the remaining glands, in case the remnant becomes inschemic
 - Mark with nonabsorbable suture or clip
 - Consider suturing away from the RLN

Operative Considerations

- Total
 - Identification of all glands
 - Resection of at least 4 glands
 - Transplantation of 10-20 pieces (40-60mg) of fresh cut tissue into individual pockets in brachioradialis of non-dominant forearm
 - Can preform re-operative debulking under local anesthesia

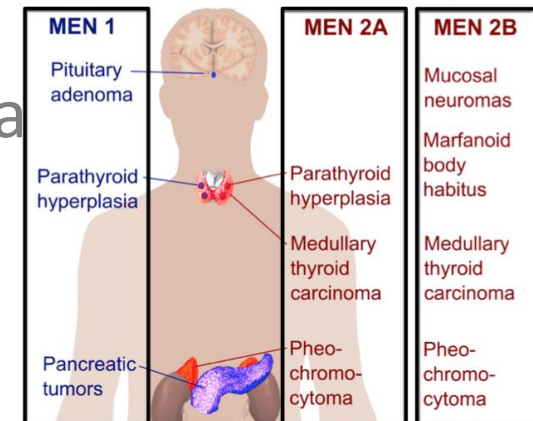


Figure 1- Implant with twenty sites.

- For patients undergoing parathyroidectomy for hyperparathyroidism associated with the MEN syndrome, the recurrence rate of hyperparathyroidism following removal of three glands is which?
 1. 1%
 2. 5.7%
 3. 11%
 4. 24%
 5. 50%

Familial syndromes

- Multiple Endocrine Neoplasia 2A
 - Involves mutation in RET proto-oncogene on chromosome 10
 - Hyperparathyroidism least common manifestation
 - Occurs in 20-30%
 - Tends to be milder and more often a compared to MEN1
 - More often due to single adenoma



Operative Considerations

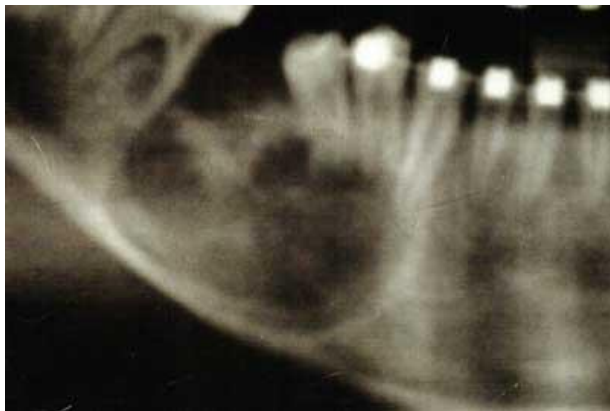
- Recognition of all glands is crucial
- Little data on extent of resection, but less aggressive resection seems sufficient and long term cure is possible
- Preservation of parathyroid function is possible due to the moderate nature of MEN2A

Familial syndromes

- Familial Isolated Hyperparathyroidism
 - Autosomal dominant inheritance mutations in MEN1, HRPT2, and CASR genes
 - Multigland hyperplasia is most common finding, solitary adenomas are found in up to 25% of patients
 - Increased risk of parathyroid carcinoma
- Autosomal Dominant mild HPT
 - Diffuse neoplasia common and typically radical resection required to prevent recurrence
- Familial Hypercalcemia with hypercalciuria
 - Most patients asymptomatic and do not benefit from resection
- Neonatal severe HPT
 - Severe hypercalcemia, very high PTH levels in neonate
 - Lethal unless total parathyroidectomy performed in first months of life

Familial syndromes

- Hyperparathyroidism jaw tumor syndrome
 - Autosomal dominant inheritance
 - Ossifying fibromas of the mandible and maxilla, renal cyst, renal hamartomas, and Wilms tumors
 - 10% incidence of parathyroid carcinomas
 - Treatment similar to MEN2A unless carcinoma suspected





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Treatment of the “missing” parathyroid

Answer: (E)

This patient has primary hyperparathyroidism. Nearly all hyperfunctioning glands are enlarged, so this patient is unlikely to have multi-gland hyperplasia and normal appearing tissue should not be excised. Since the thymus and side of the neck have been explored and ruled out, the next location is intra-thyroidal