By the Name of ALLAH the Most Gracious the Most Merciful

Parathyroid Gland

د . أحمد اسامة حسن

Specialist in General Surgery & Laparoscopic Surgery

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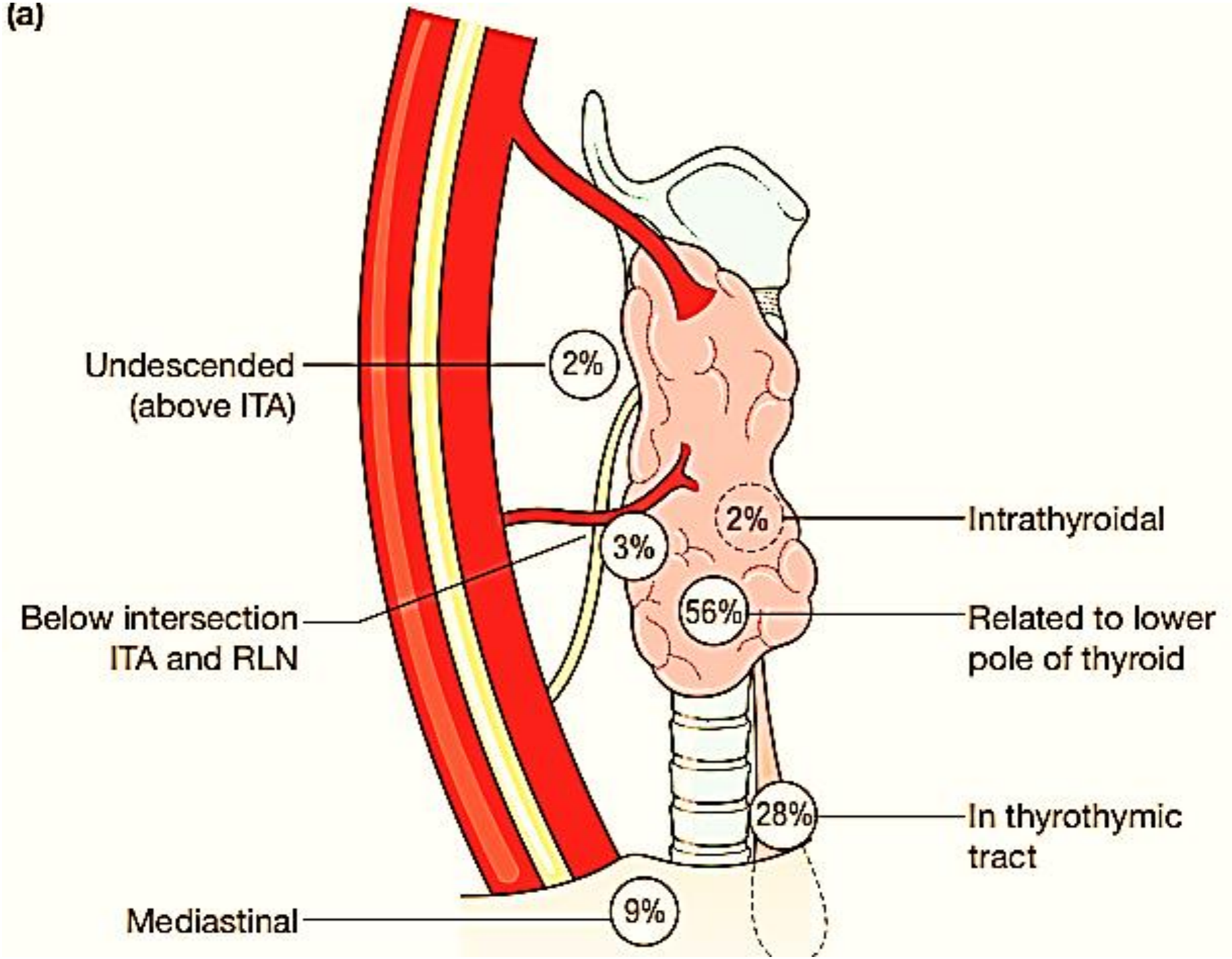
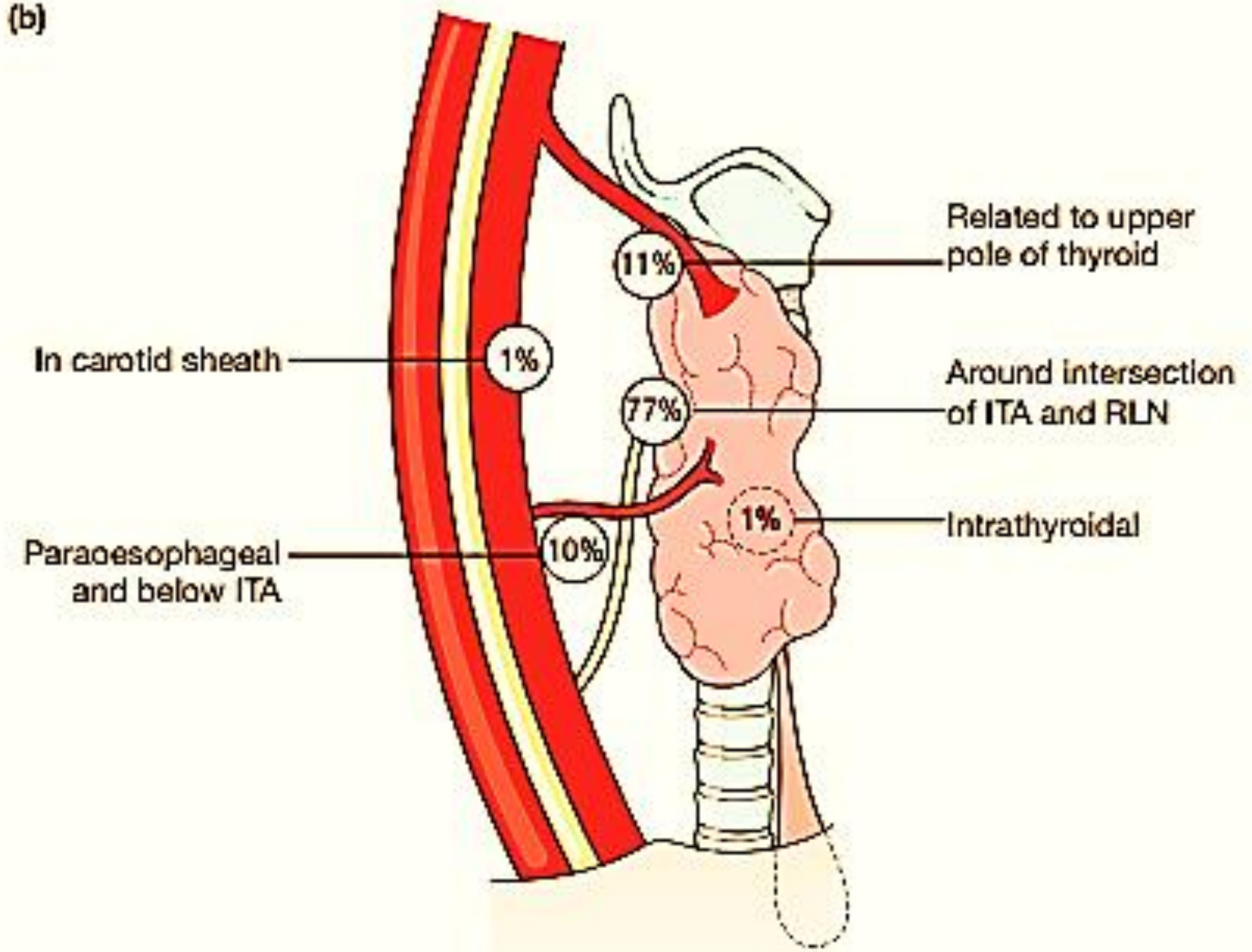
Parathyroid Gland

- CLINICAL ANATOMY.
- CALCIUM AND PARATHYROID HORMONE REGULATION
- PRIMARY HYPERPARATHYROIDISM .
- SECONDARY HYPERPARATHYROIDISM .
- TERTIARY HYPERPARATHYROIDISM.
- PARATHYROID CARCINOMA .
- PERSISTENT HYPERPARATHYROIDISM
- RECURRENT HYPERPARATHYROIDISM.


(a)
Undescended (above ITA)
2%
Intrathyroidal
2%
3%
Below intersection ITA and RLN
56%
Related to lower pole of thyroid
28%
In thyrothymic tract
Mediastinal
9%


(b)
Related to upper pole of thyroid
11%
In carotid sheath
1%
Around intersection of ITA and RLN
77%
Intrathyroidal
1%
Paraoesophageal and below ITA
10%

CALCIUM AND PARATHYROID HORMONE REGULATION

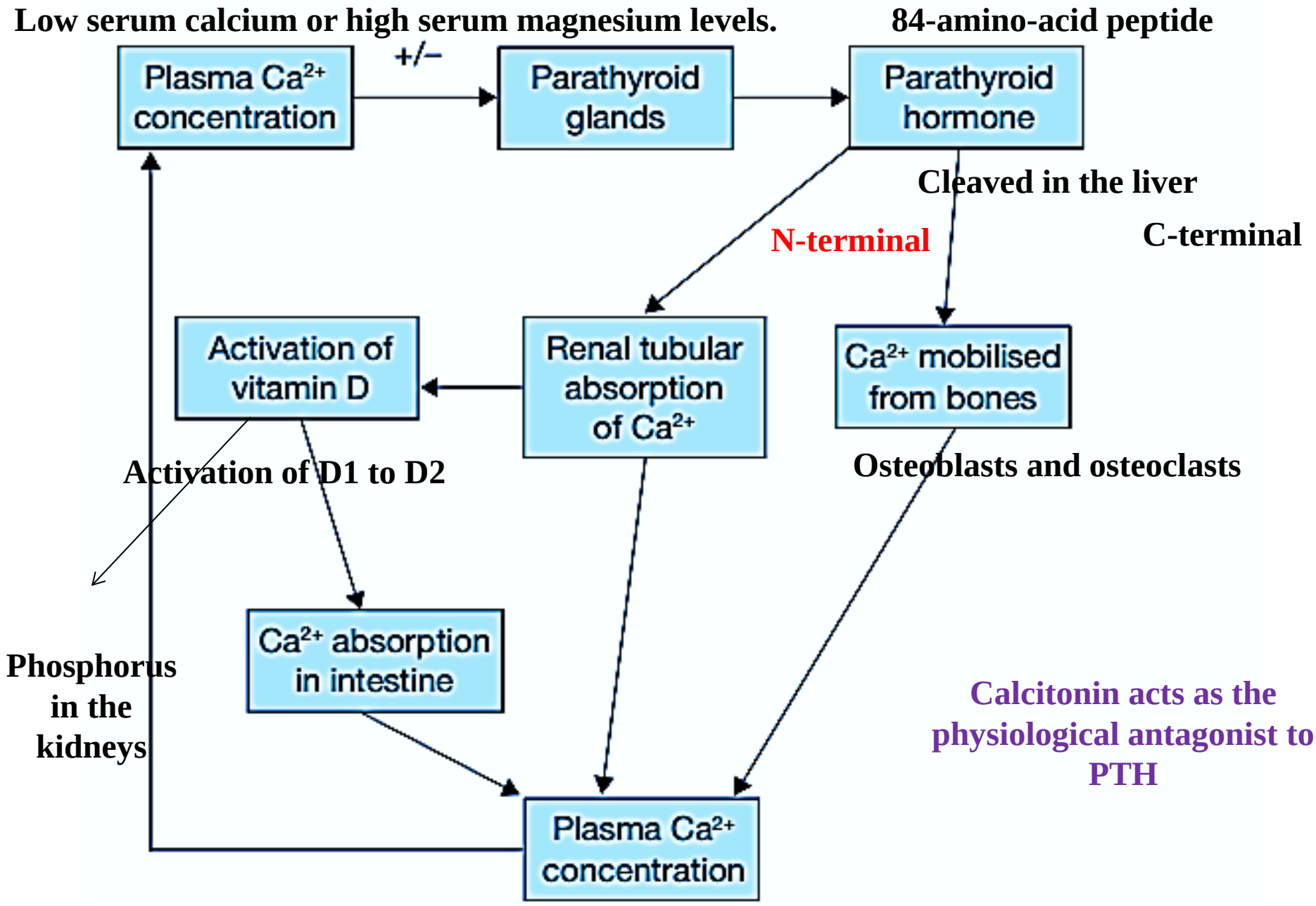


Figure 56.2 The actions of parathyroid hormone.

PRIMARY HYPERPARATHYROIDISM

- Hypercalcaemic crisis.
- Pathology.
- Diagnosis.
- Localisation studies.
- Ultrasonography.
- Nuclear medicine-based studies (sestamibi scanning).
- Four-dimensional computed tomography scanning/positron emission tomography– computed tomography.
- Magnetic Resonance Imaging,
- Parathyroid angiography and venous sampling for parathyroid hormone.
- Management strategies (Surgical & medical).
- Special cases (Lithium, Familial syndromes).

PRIMARY HYPERPARATHYROIDISM

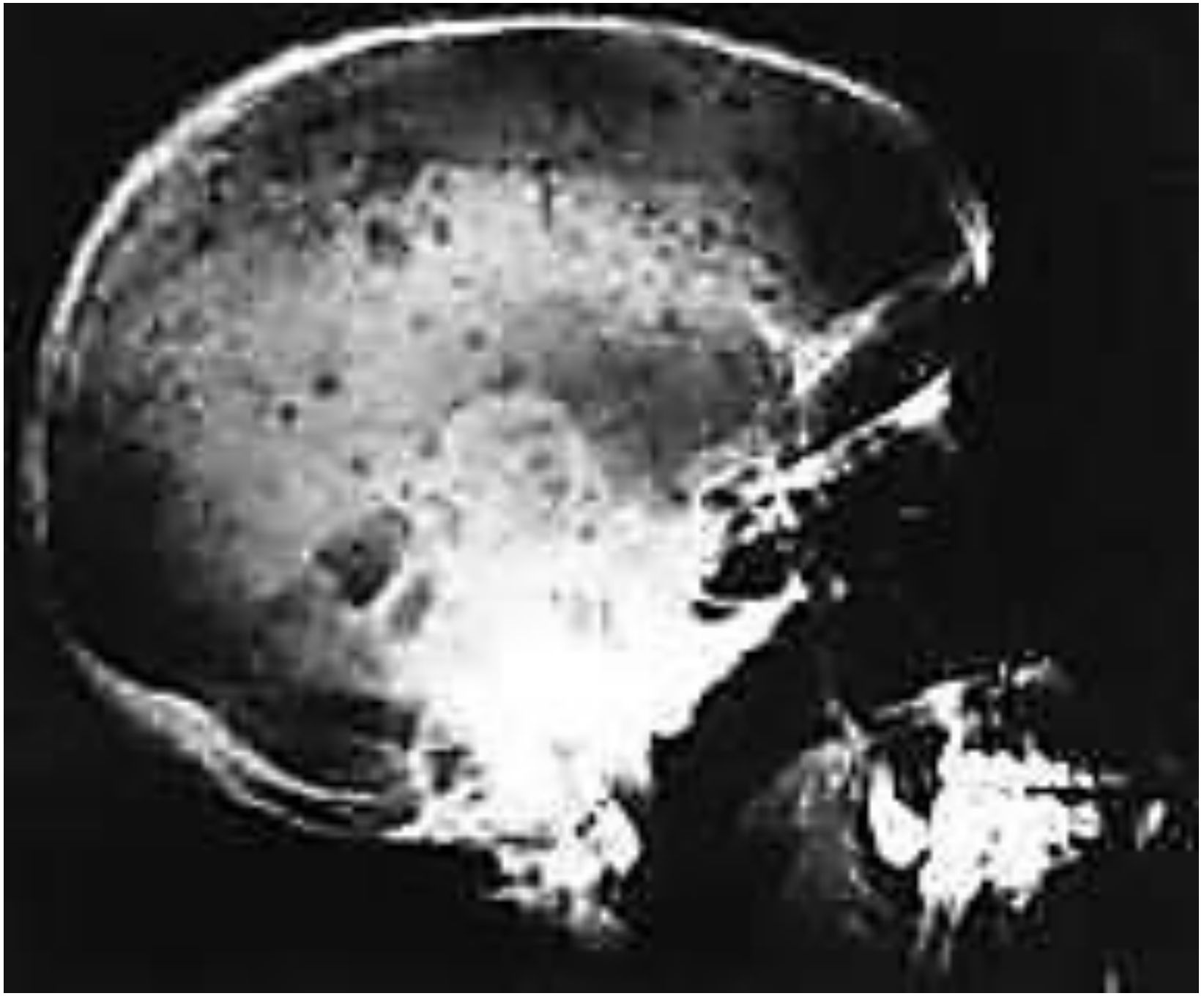
Hypercalcaemia in the presence of an unsuppressed and therefore relatively, or absolutely, elevated PTH level.

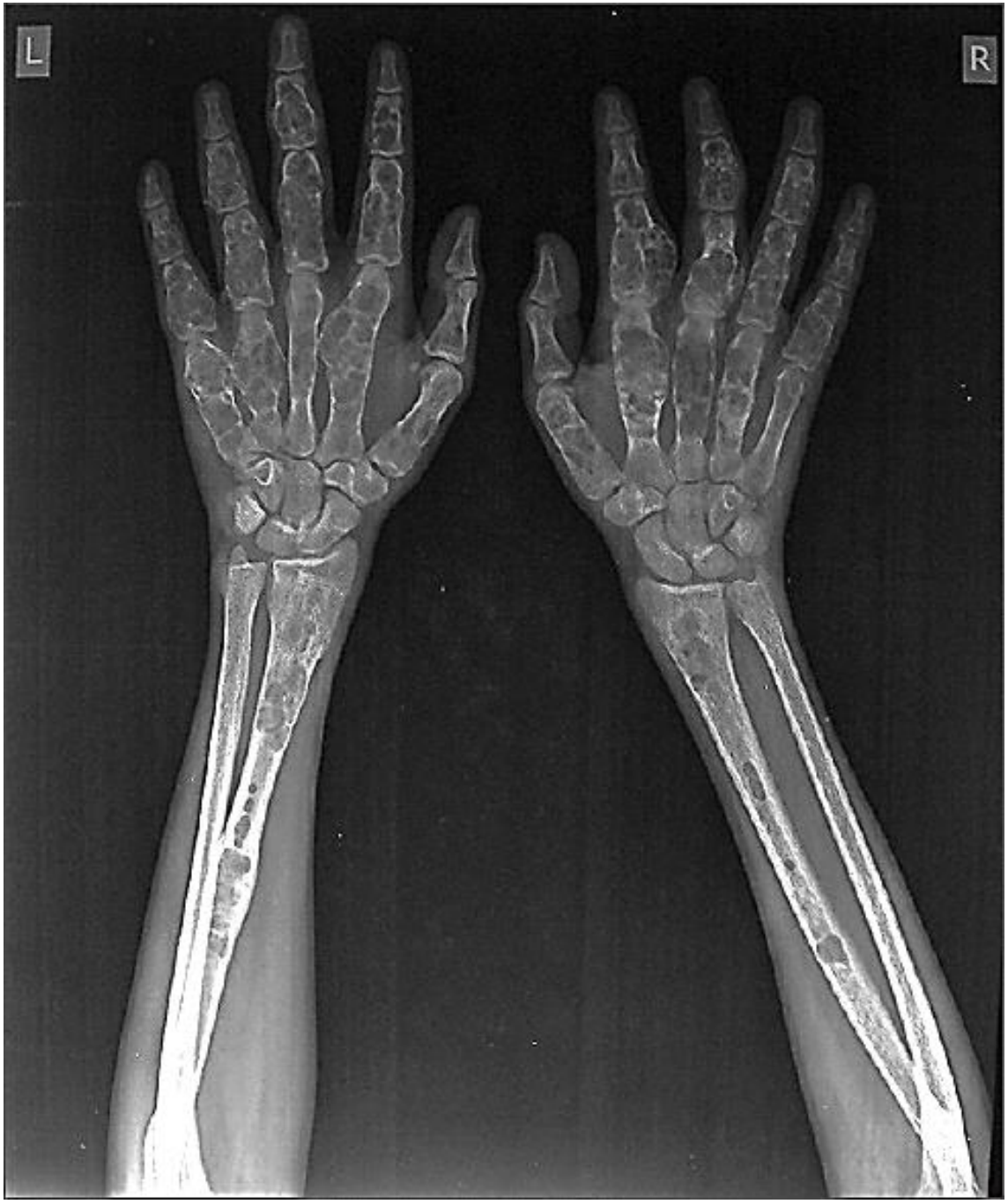
Patients usually present in the fifth or sixth decades and there is a female predominance with a ratio of 3:1.

- Presentation is now typically asymptomatic rather than the classical ‘bones, stones, abdominal groans and psychiatric overtones’
- The diagnosis of PHPT is a biochemical one

  (an elevated ionised calcium with an inappropriately elevated/not suppressed PTH level)
- Sestamibi and focused neck ultrasonography are the first-line radiological investigations.

- The early descriptions of patients with PHPT were dominated by those with osteitis fibrosa cystica. Brown tumours of the long bones and associated subperiosteal bone reabsorption, distal tapering of the clavicles and the classical ‘salt and pepper’ erosions of the skull were typical findings.
- Over 80% of patients had associated renal stones.
- Significant neuromuscular dysfunction and muscle weakness. This led to the traditional mnemonic that patients with PHPT presented with ‘bones, stones, abdominal groans and psychiatric overtones’.




L
R

R
a
b

TABLE 56.1 Causes of hypercalcaemia.

Endocrine	• Primary hyperparathyroidism • Thyrotoxicosis • Phaeochromocytoma
Renal failure	• Secondary hyperparathyroidism • Tertiary hyperparathyroidism
Malignant disease	• Skeletal metastatic disease • Multiple myeloma, lymphoma, leukaemia • Solid tumours (PTH-related peptide mediated): lung, renal, squamous cell carcinoma of the head and neck, oesophagus, genital tract
Nutritional	• Excessive vitamin D ingestion • Vitamin A intoxication • Milk-alkali syndrome • Aluminium intoxication
Granulomatous	• Sarcoidosis • Tuberculosis
Inherited disease	• Hypercalciuric hypercalcaemia
Immobilisation	
Paget's disease	
Drug related	• Lithium

- Presentation
- Patients are typically identified incidentally with an elevated total calcium or following routine assessment of bone densitometry (DEXA scan).
- Vague constitutional symptoms, such as fatigue, muscle weakness, depression or some mild memory impairment on questioning.
- Renal stones remains the most common clinical manifestation of symptomatic PHPT.

- Increasingly, postmenopausal osteopenia or osteoporosis in the distal one-third of the radius with a minimal reduction in the lumbar spine, which prompts further investigation.
- This distribution arises as PTH appears to be catabolic at cortical sites (distal one-third of the radius) and anabolic at cancellous sites (lumbar spine).
- It may present with pancreatitis, although it is rarely seen in patients with milder forms of the disease.
- Hypertension and peptic ulcer disease, are often encountered.

- Clinical examination is usually normal.
- Band keratopathy, pathognomonic of the disease and due to deposition of calcium phosphate crystals in the cornea, is now rarely identified.
- The differential diagnosis includes other causes of hypercalcaemia, which are usually readily distinguishable (Table).
- Widespread malignancy has to be excluded, in which patients will typically have other symptoms.
- The exception to this rule is multiple myeloma, in which hypercalcaemia can be the presenting complaint.

Hypercalcaemic crisis

Presentation and Management

- **Hypercalcaemia**: is documented in 0.5% of the general population and in up to 5% of hospitalised patients. The vast majority are asymptomatic with a mild to moderate elevation of serum calcium (<3 mmol/L and 3–3.5 mmol/L, respectively) and respond to treatment of the underlying aetiology with associated dietary modification.
- A small proportion of patients will present symptomatically with a total calcium of >3.5 mmol/L. This is referred to as a hypercalcaemic crisis and requires aggressive medical management.
- Although symptoms can be varied, the typical presentation is of acute confusion, abdominal pain, vomiting, dehydration and anuria. Prolongation of the PR interval with a shortened QT interval on (ECG) prior to potentially lethal cardiac arrhythmias. Where the calcium is >4.5 mmol/L, coma and cardiac arrest can occur.

- **Treatment revolves** around increasing renal excretion of calcium, reducing skeletal release of calcium and treatment of the underlying cause.
- Aggressive rehydration plays a pivotal role.

Typically, 200–500 mL/h of normal saline is given to maintain a urine output >100 mL/h, with the caveat that this may be modified to account for associated patient comorbidities.

- Once intravascular volume has been adequately restored, loop diuretics, (furosemide) to enhance the renal excretion of calcium.
- The majority of patients will have normalisation of their calcium with these simple measures.

- In patients with advanced malignancy and a serum calcium level >3 mmol/L, agents that blunt the release of calcium from skeletal stores may be required.
- First-line treatment includes administration of
- **Bisphosphonates**. (sustained action) These are pyrophosphate analogues that inhibit osteoclast activity in areas of high bone turnover. In the acute setting, these are given intravenously owing to poor absorption in the gastrointestinal tract.
- **Calcitonin** can be used to both decrease osteoclastic activity and increase renal excretion of calcium. It has a short duration of action and is usually used as a bridge to reduce calcium until the sustained action of the bisphosphonates is seen.
- Finally, **Glucocorticoids** (prednisolone) to enhance the action of calcitonin. They increase calciuresis and decrease intestinal absorption of calcium. As a result, they may also play a role in diseases associated with vitamin D excess.

Diagnosis

- When confirmed biochemically, should **localisation** studies be undertaken .
- PHPT is defined as an elevated total, or more specifically ionised, calcium in the presence of an inappropriately elevated or unsuppressed PTH. It is associated with a low serum phosphate in the setting of normal creatinine and vitamin D levels; 24-hour urinary excretion of calcium may be normal or
- Alkaline phosphatase may be elevated in patients in whom there is concomitant bone disease.

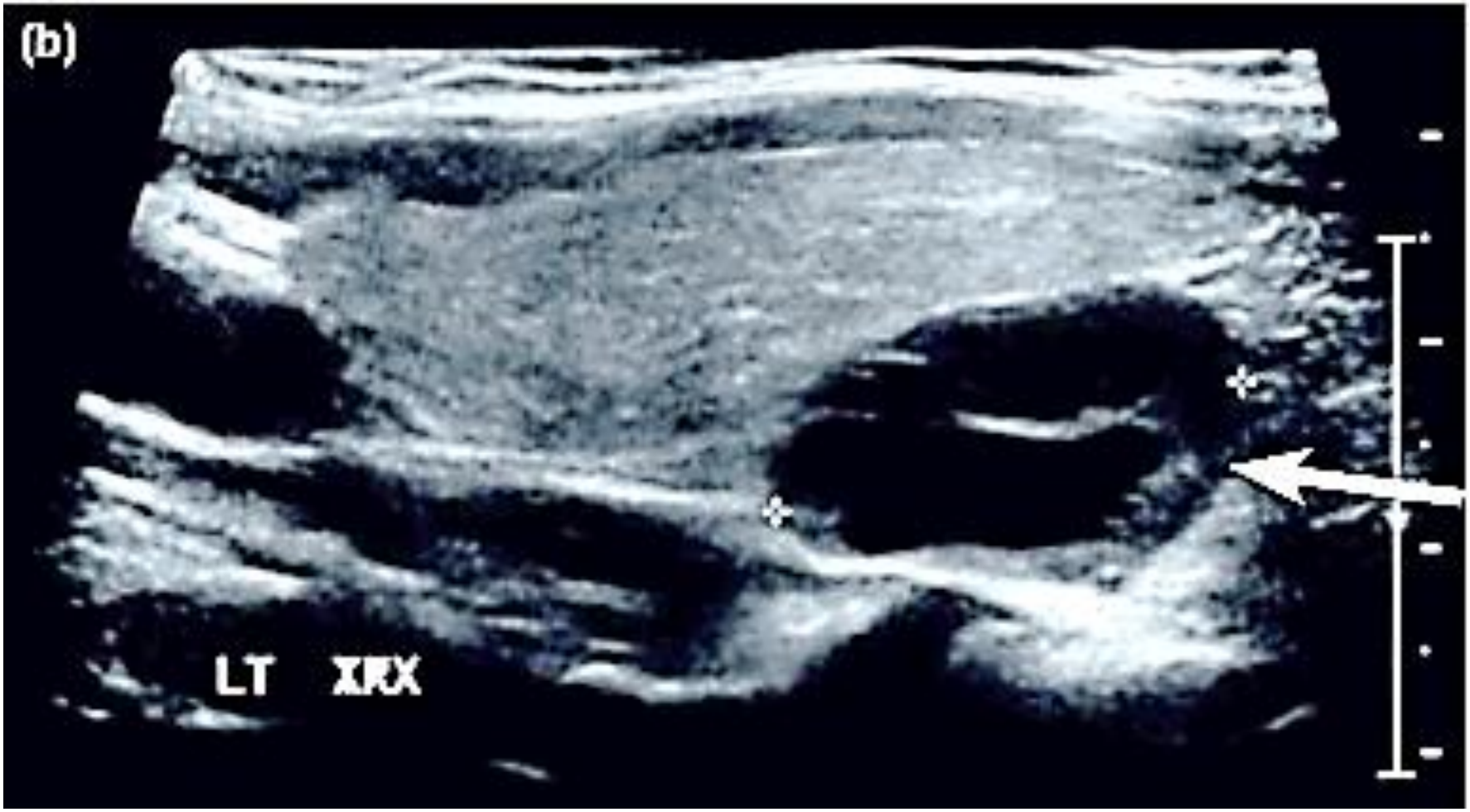
- It is important to perform a 24-hour urinary collection to rule out the presence of the rare familial hypocalciuric hypercalcaemia (FHH).
- This is important to recognise preoperatively as the surgeon should anticipate significant postoperative hypocalcaemia due to the development of hungry bone syndrome.

Localisation studies

Positive imaging does not confirm the diagnosis and negative findings cannot rule it out.

- Non-invasive radiology includes nuclear medicine-based studies, ultrasonography and fourdimensional (4D) computed tomography (CT) scanning.
- Invasive imaging is largely reserved for reoperative surgery and includes ultrasound or CT-guided fine-needle aspiration with concomitant PTH assays, parathyroid angiography or selective venous sampling for the PTH gradient.

Ultrasonography



Right inferior adenoma

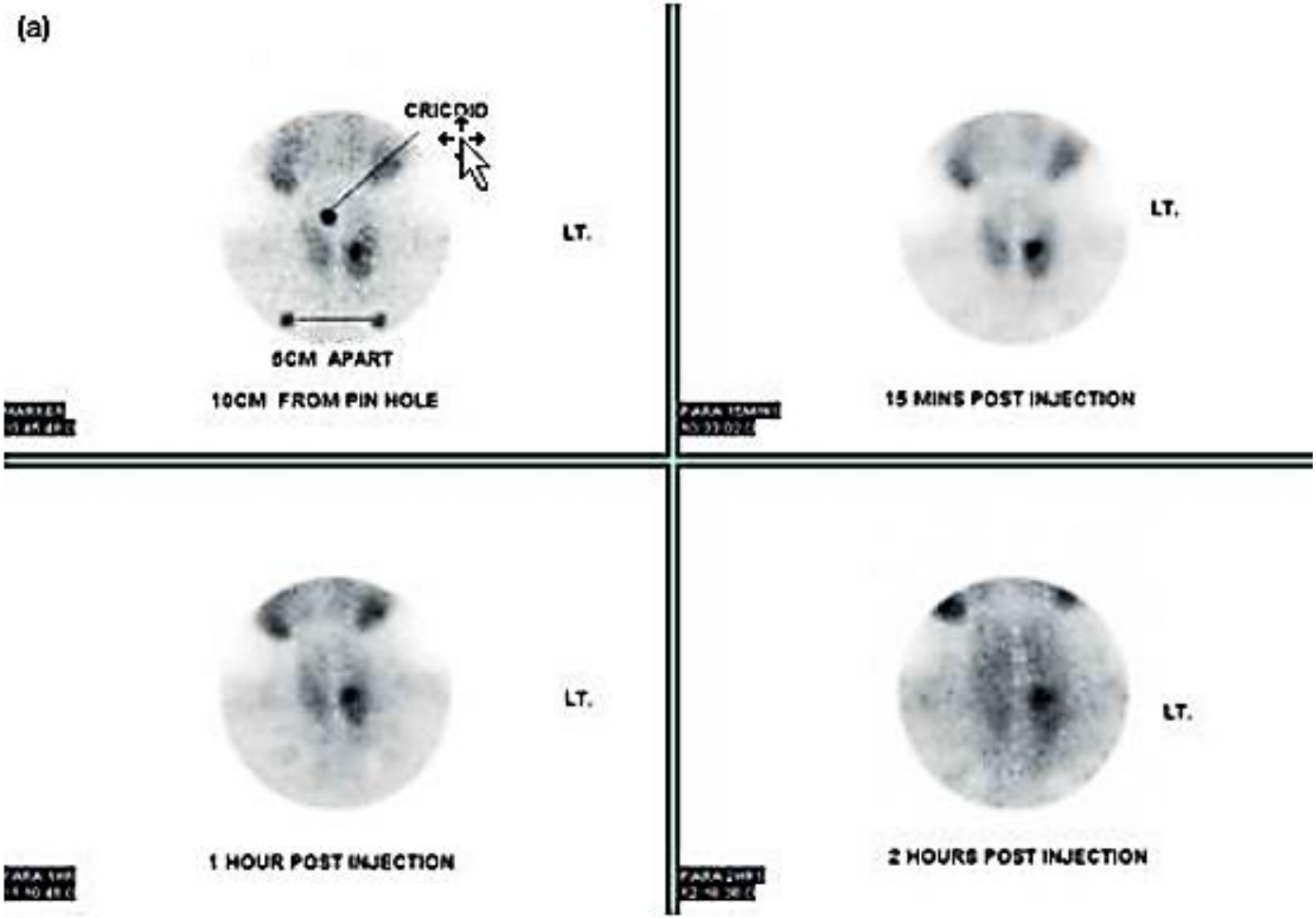
Ultrasonography

- Ultrasonography is a non-invasive, inexpensive method of imaging the parathyroid glands.
- Parathyroid adenomas are typically oval or elongated, bi- or multilobed hypoechoic structures. Rarely, adenomas may be cystic or heterogeneous in nature.
- Giant adenomas are over 3 cm in size.
- It helps to identify and facilitate biopsy of any concomitant thyroid pathology. However, ultrasonography is operator, lesion size and location dependent.

- Ultrasonography may miss adenomas located in retro-oesophageal, retrosternal or retrotracheal areas.
- It can also be difficult to differentiate between a small parathyroid gland and a normal-appearing lymph node.

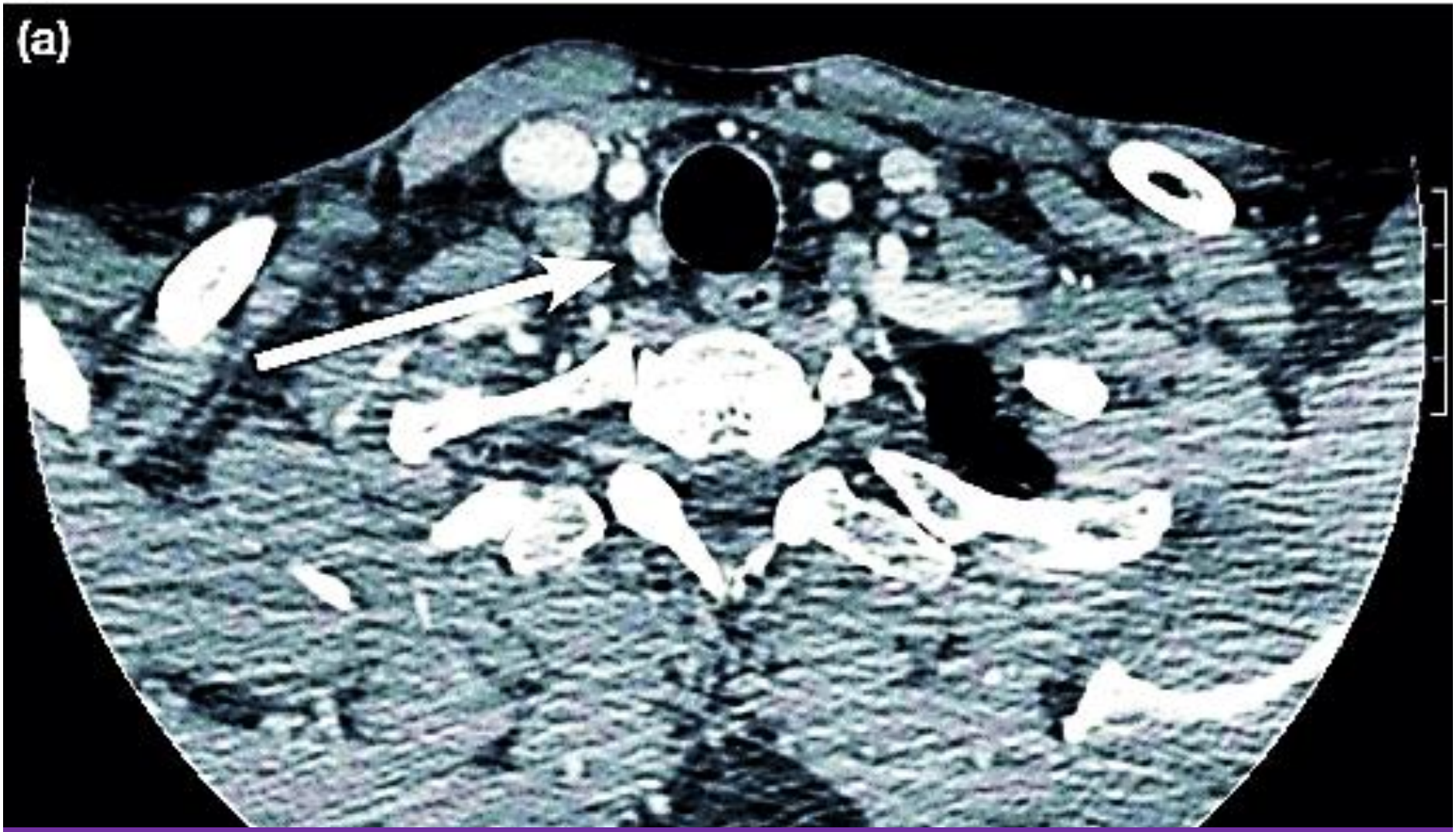
Nuclear medicine-based studies (sestamibi scanning)

(a)

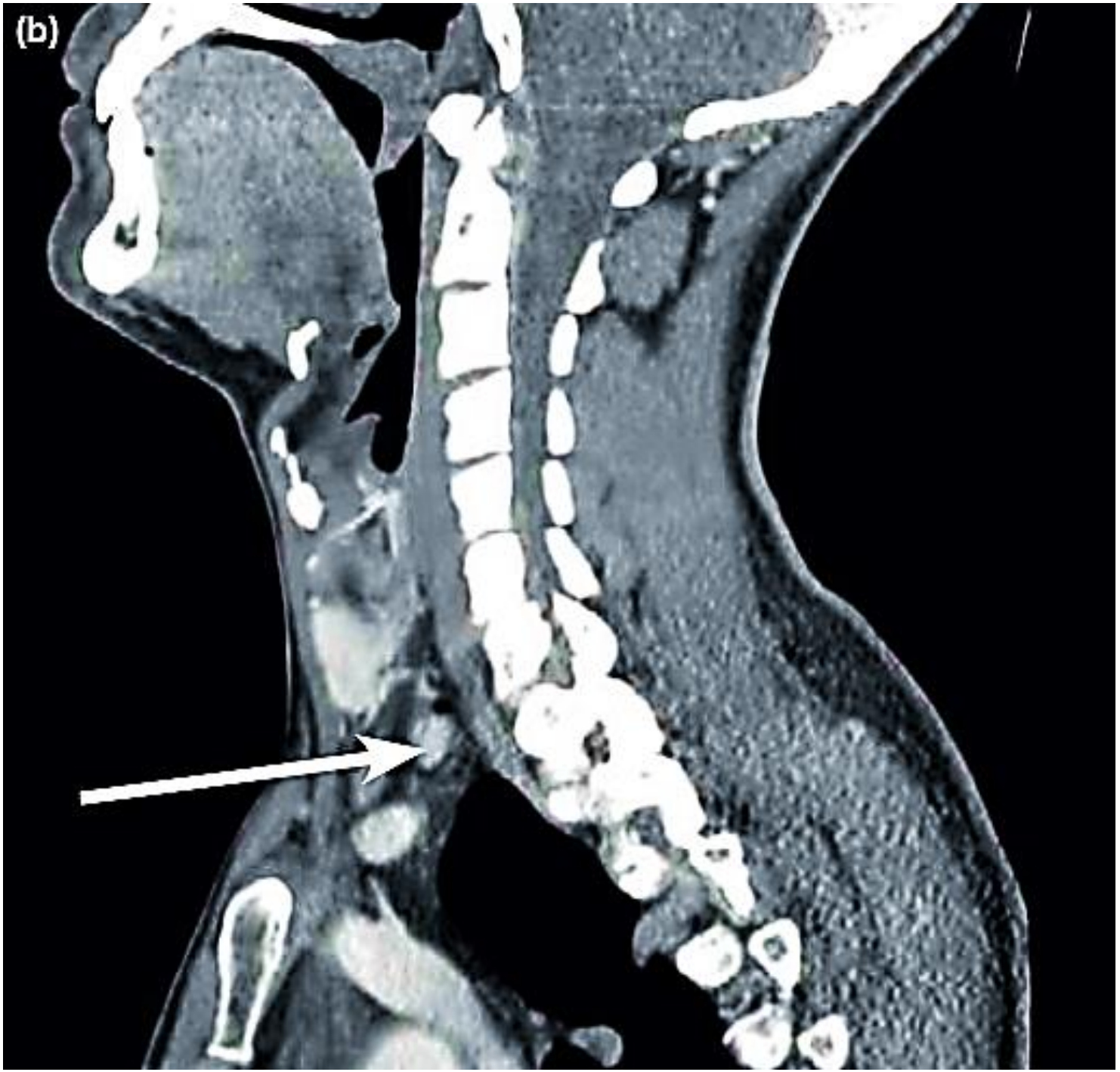

CRICOID
LT.
6CM APART
10CM FROM PIN HOLE
LT.
15 MINS POST INJECTION
LT.
1 HOUR POST INJECTION
LT.
2 HOURS POST INJECTION

- The use of sestamibi (2-methoxy-2-methylpropylisonitrile [MIBI]) for parathyroid localisation is regarded as the most accurate and reliable method, safe and reproducible and, while it has a sensitivity and specificity similar to ultrasonography, it may image glands in ectopic positions better .
- **Sestamibi** accumulates in mitochondria and therefore washes out at differential rates depending on the number of mitochondria within individual tissues.
- Parathyroid adenomas often have a high concentration of oxyphilic cells with high mitochondrial content. (a slow washout in comparism with the thyroid gland

- There are three different protocols for sestamibi scanning. The sensitivity and specificity of sestamibi, regardless of the protocol used, are 79% and 90%, respectively.
- False positives are rare but may arise from some solid thyroid nodules, such as Hürthle cell nodules, that are associated with high oxyphilic content. These can be reduced by the addition of a thyroid-specific radioactive tracer, such as 99Tc-pertechnetate and subsequent subtraction images.



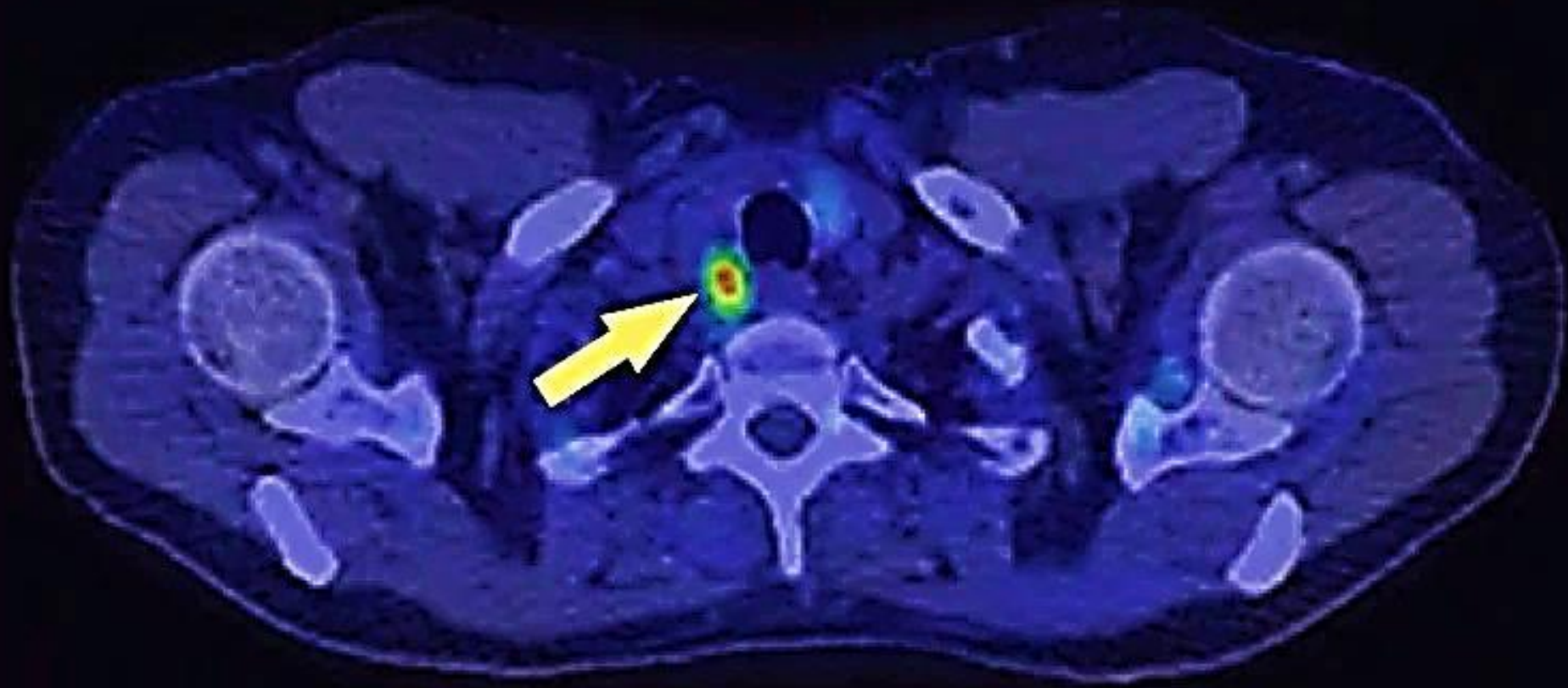
Four-dimensional computed tomography scanning demonstrating a right inferior parathyroid adenoma


(b)

Four-dimensional computed tomography scanning/positron emission tomography– computed tomography

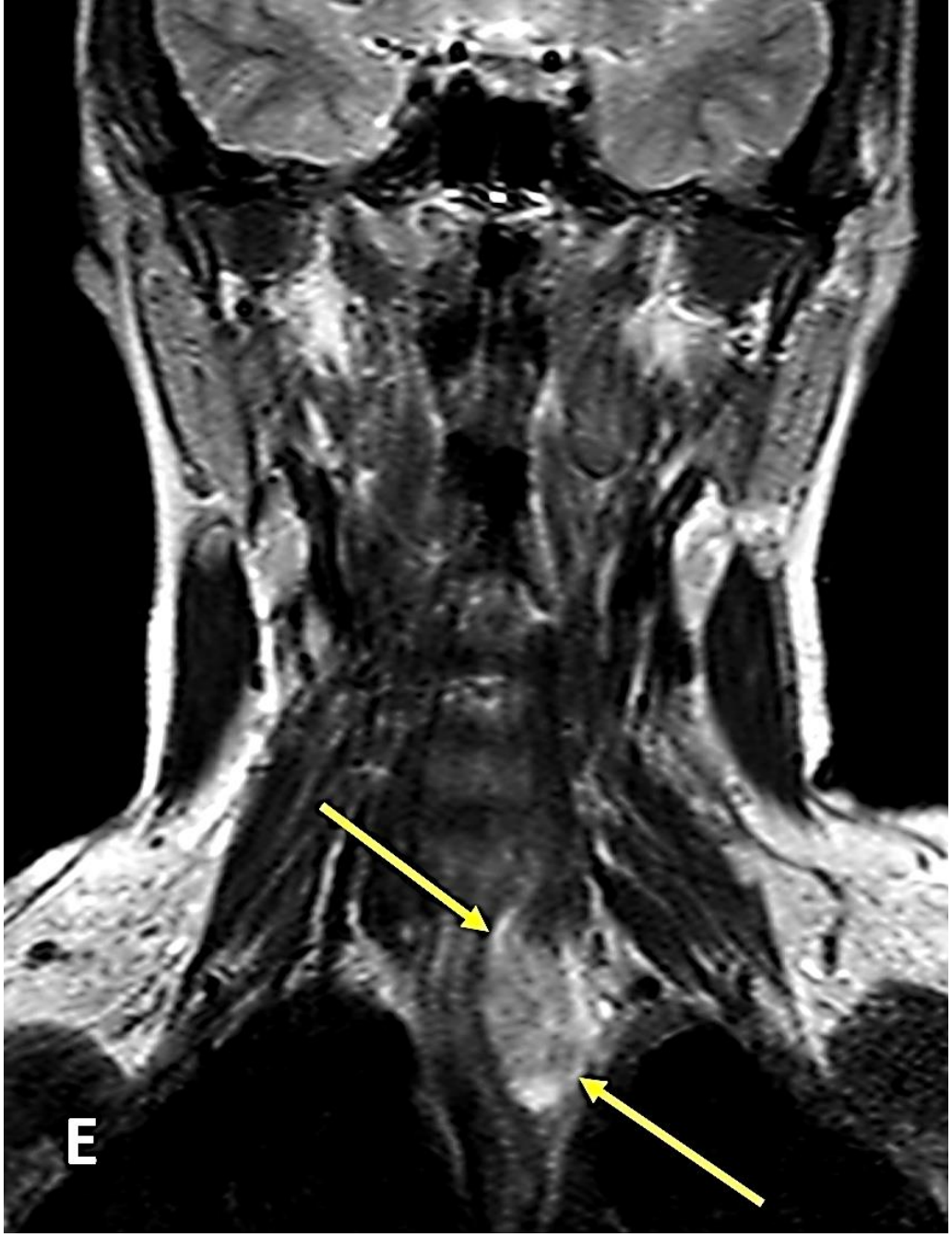
- It gives both anatomical and functional information about the parathyroid glands, allows hyperfunctioning glands to be differentiated from lymph nodes that demonstrate a progressive enhancement pattern.
- The potential disadvantage of 4D-CT scanning is the higher radiation dose .
- Positron emission tomography (PET) scanning remains expensive and is not widely available. (18F-fluorocholine PET with the addition of CT scanning for localisation of ectopic adenomas).

Positron emission tomography (PET) scanning



Magnetic Resonance Imaging

- Is not commonly used to image the parathyroid glands. However, on T2-weighted images, enlarged parathyroid glands demonstrate significantly increased intensity.
- In reoperative cases or where the adenoma is located in the mediastinum.
- It is expensive, the resolution for normal glands or adenomas <5 mm is poor, it can be difficult to localise superior glands because it is obscured by the thyroid gland.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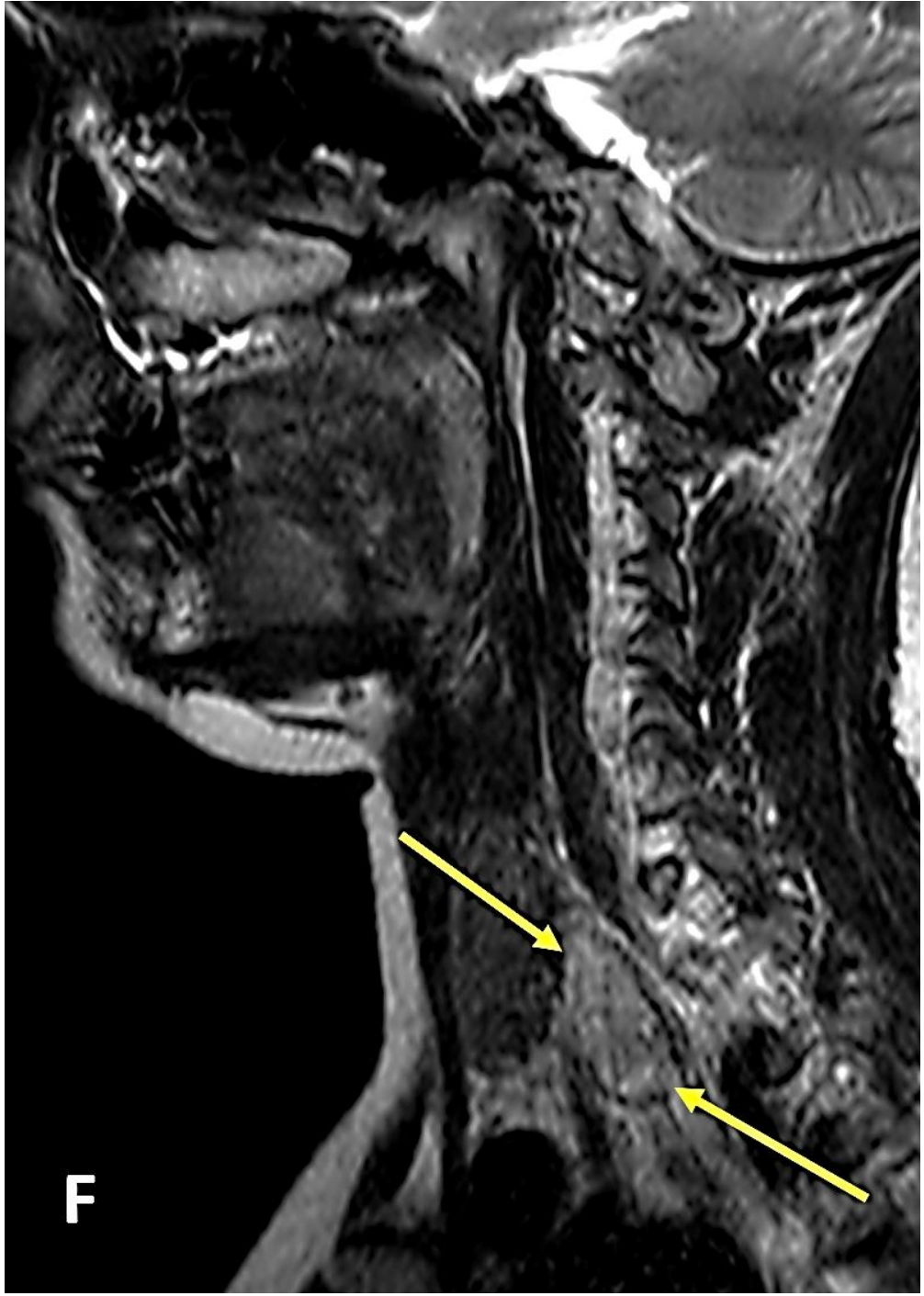
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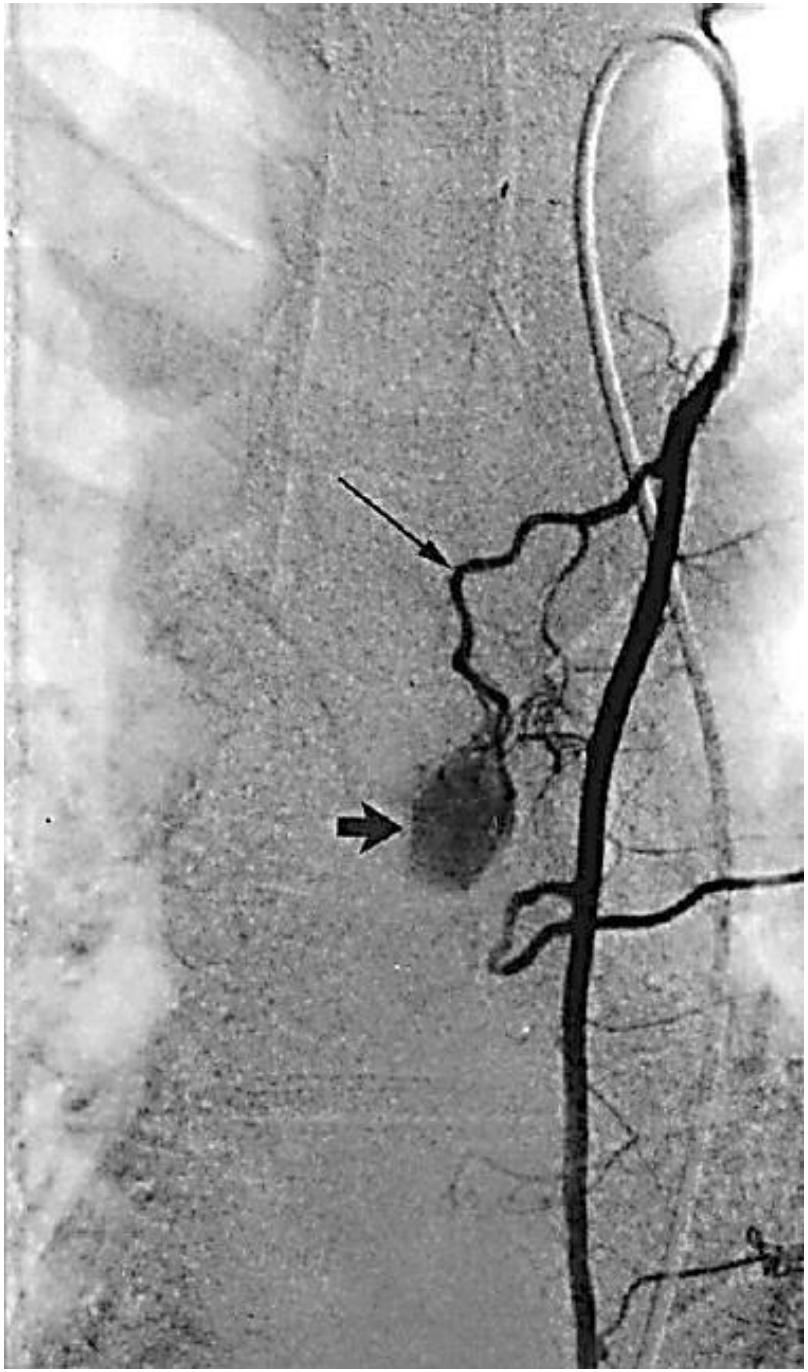
- **Parathyroid angiography** is reserved for reoperative cases and is now rarely required owing to improvements in non-invasive imaging modalities.
- Vascular parathyroid adenomas appear as a persistent oval or round ‘stain’ on angiography.



- **Selective venous sampling** for PTH can allow accurate localisation of adenomas .
- is established when there is a twofold drop in the PTH between the sampled blood and the serum PTH.

Management strategies

- Medical
- Surgical (MIS, Bilateral neck exploration).

Medical Management

- **For unfit** or who have contraindications to surgical intervention, in patients with failed surgical intervention or in the long-term management of parathyroid carcinoma.
- The aims are **to prevent skeletal complications** (improve bone mineral density and reduce fracture risk) and to stabilise biochemical parameters.

- **Bisphosphonates** : They inhibit osteoclast activity and apoptosis, thereby increasing bone mineralisation and reducing bone turnover.
- **Denosumab** is a monoclonal antibody that works as a receptor activator of nuclear factor- κB (RANK) ligand inhibitor. (it may be a valid treatment option for patients in whom surgery is undesirable).

Hormone replacement therapy (HRT) and selective oestrogen receptor antagonists

- (**HRT**) has been shown to improve bone mineral density and reduce the associated fracture risk in postmenopausal women by reducing bone turnover.
- **Selective oestrogen receptor antagonists** (SERMs) is that they should confer the benefits of HRT but without the potential adverse vascular and breast effects

Calcimimetics

- Calcimimetics, such as **cinacalcet**, amplify the sensitivity of the calcium-sensing receptor to extracellular calcium, altering the set point and thereby decreasing PTH production.

1. The treatment of severe hypercalcaemia in patients with PHPT who were unfit for parathyroidectomy.
2. Normalisation of serum calcium levels can be achieved with a similar reduction in the level of PTH, although not to within the normal range.

Surgical management

- The mainstay of treatment for PHPT is surgery, addressing the underlying aetiology and allowing not only resolution of biochemical abnormalities but also sustained improvements in end-organ damage.
- Traditionally a bilateral cervical exploration was performed with reported cure rates of 95–98%. With improvements in preoperative radiological localisation, a more minimally invasive approach has been developed and widely adopted
- All symptomatic patients should be offered surgery. An expert panel published recommendations on which asymptomatic patients should be considered for surgical intervention

Guidelines from the American Association of Endocrine Surgeons

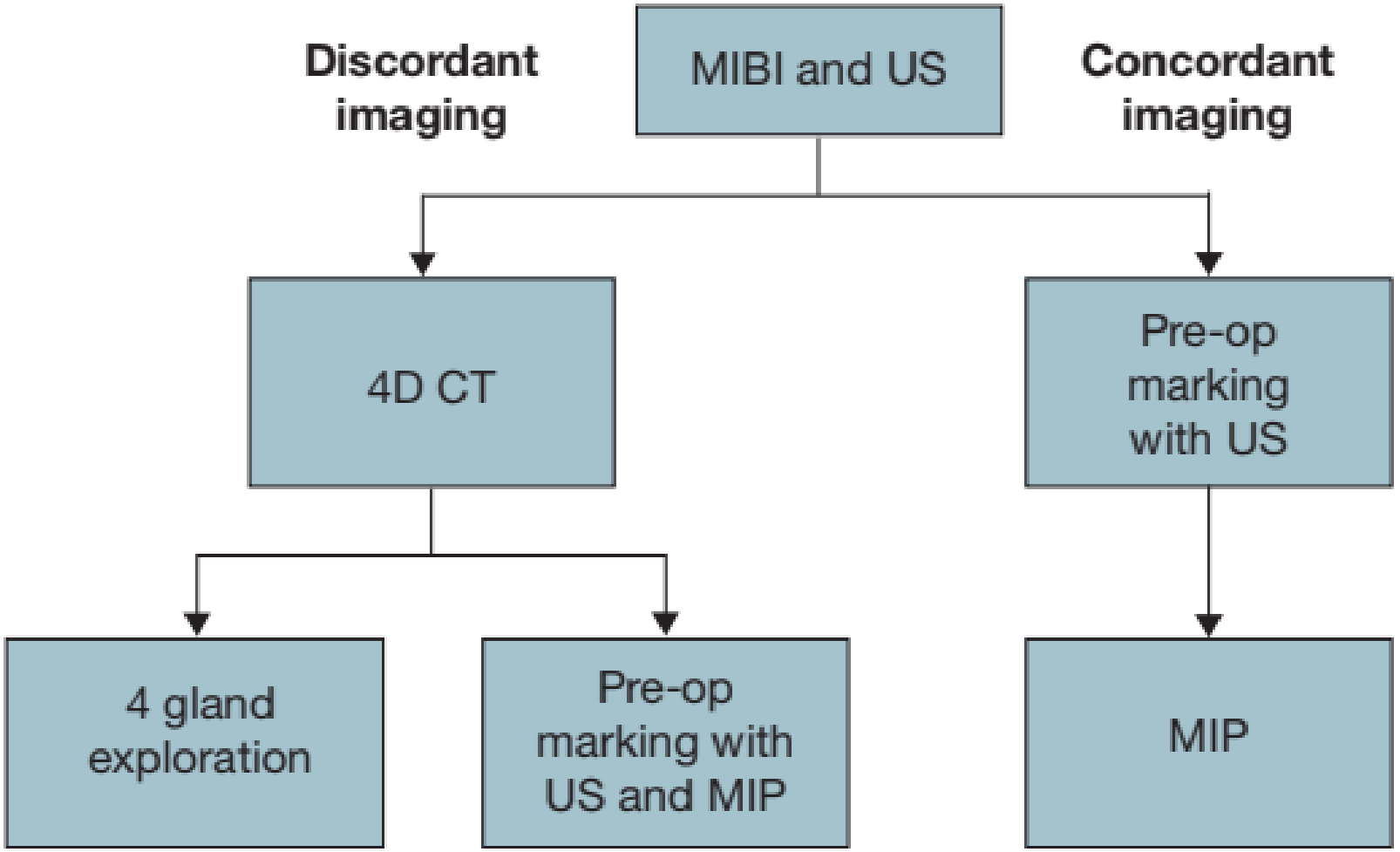
- These included patients with cognitive or psychiatric symptoms attributable to PHPT, cardiovascular disease (excluding hypertension) and more non-specific symptoms, such as muscle weakness, impaired functional capacity and abnormal sleep patterns.

- When criteria have been met and where a single adenoma has been confidently identified by radiological means, a minimally invasive parathyroidectomy may be offered.

TABLE 56.2 Consensus guidelines for surgical intervention in asymptomatic primary hyperparathyroidism.

Measurement of serum calcium	0.25 mmol/L (1.0 mg/dL) above the upper limit of normal
Skeletal	• BMD by DEXA; T score –2.5 at lumbar spine, total hip, femoral neck or distal one-third of radius • Vertebral fracture
Renal	• Creatinine clearance <60 mL/min • 24-hour urinary calcium >10 mmol/dL (>400 mL/day) or increased risk of stone formation by risk analysis
Age	<50 years

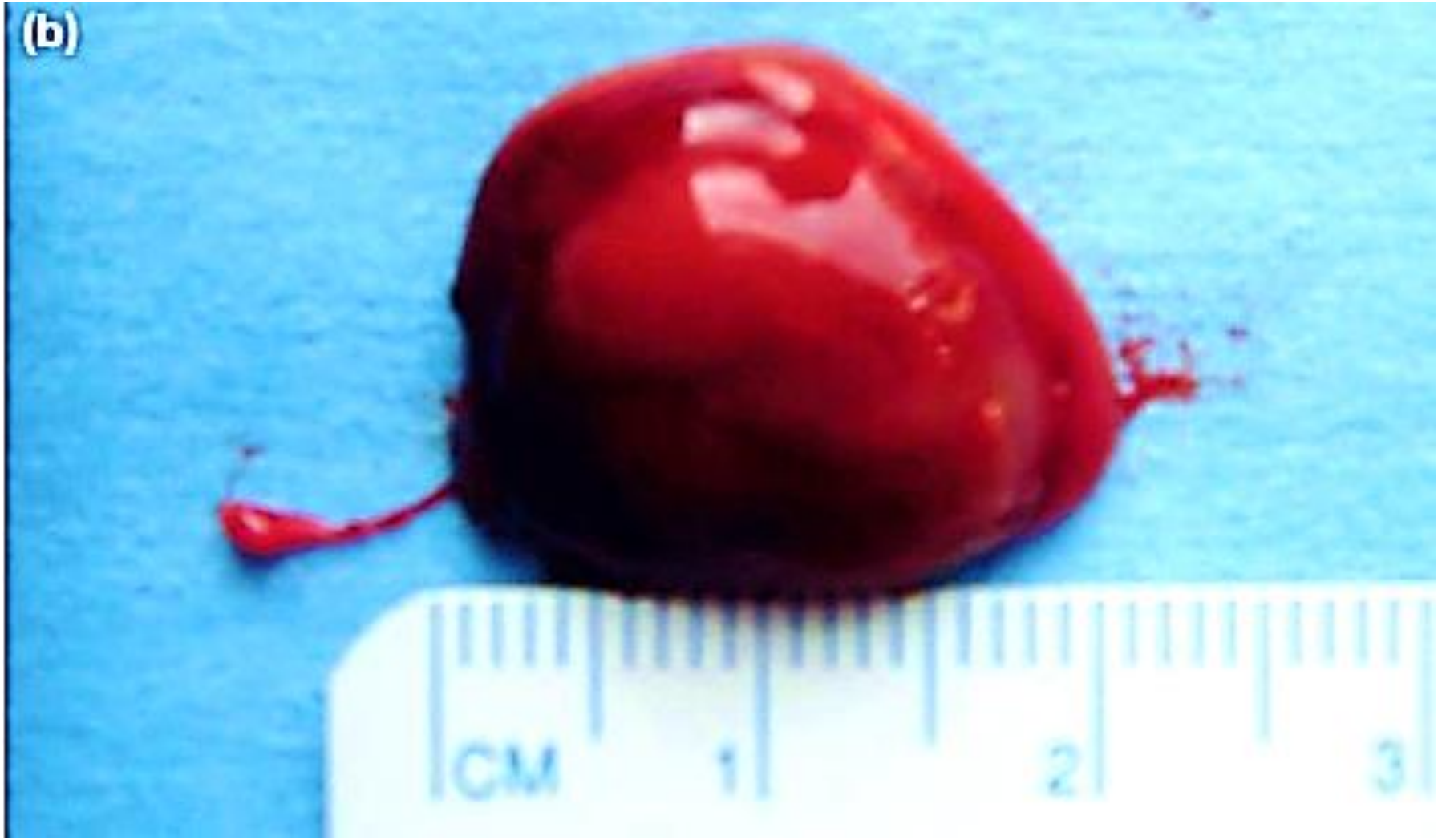
BMD, bone mineral density; DEXA, bone densitometry.
Adapted from Bilezikian *et al*. (2014).



Localisation paradigm and management strategies. 4D CT, four-dimensional computed tomography; MIBI, 2-methoxy-2-methylpropylisonitrile; MIP, minimally invasive parathyroidectomy; US, ultrasonography.

- Where imaging fails to identify any parathyroid abnormalities, then a bilateral neck exploration and a three-and-a-half-gland parathyroidectomy or a four-gland parathyroidectomy and autotransplantation should be performed.
- Consent for a parathyroidectomy must include the possibility of recurrent laryngeal nerve damage (risk <1%), permanent hypoparathyroidism (requiring lifelong calcium and vitamin D supplementation; risk 0.5%) and persistent (5%) or recurrent hyperparathyroidism.
- Persistent disease is defined as an elevated serum calcium within 6 weeks of surgical intervention and recurrent disease is defined as an increase in calcium levels after 6 months but with an intervening period of normocalcaemia.


(a)
MIP Central incision less than 3 cm in length


(b)
CM
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2
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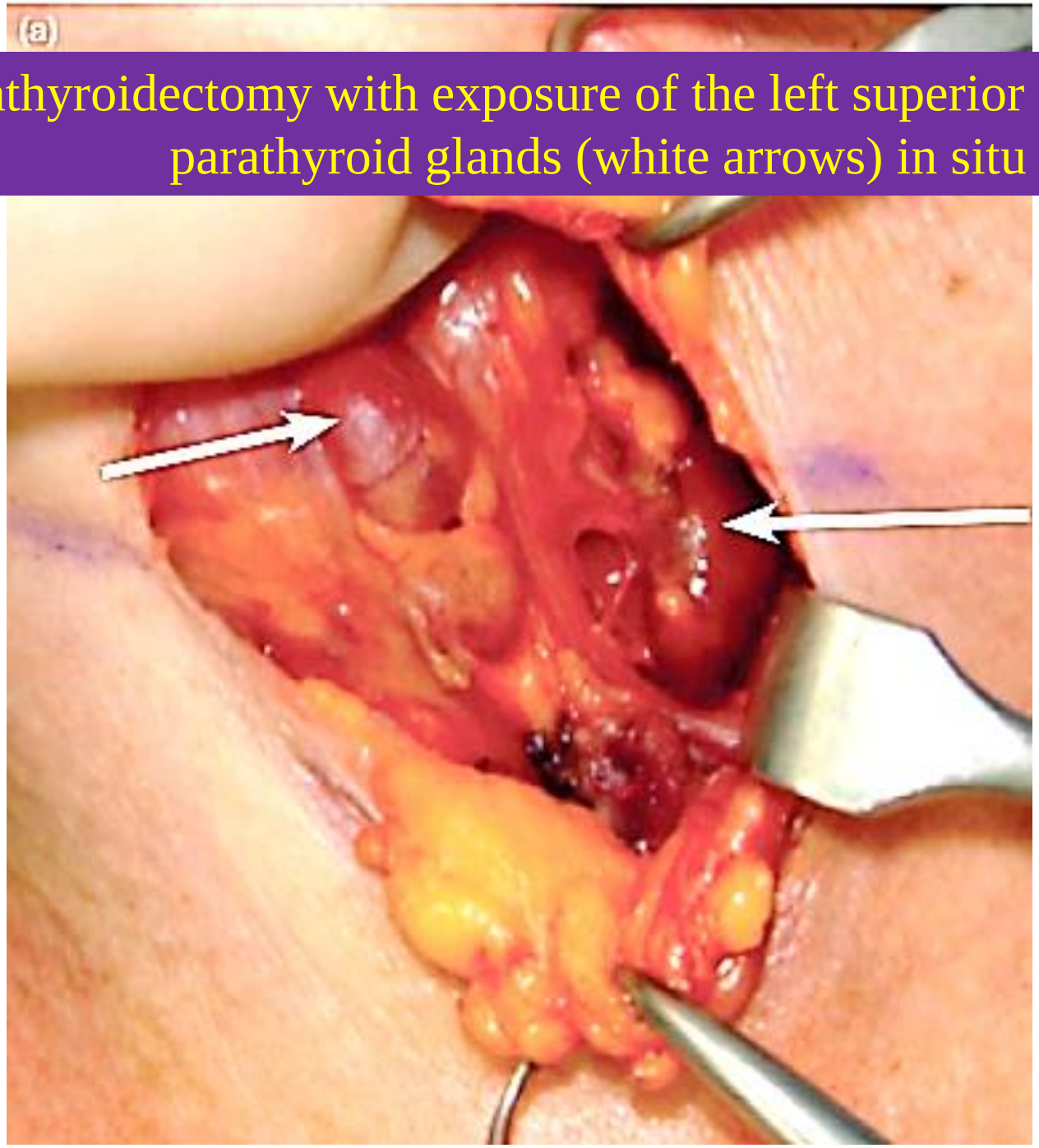
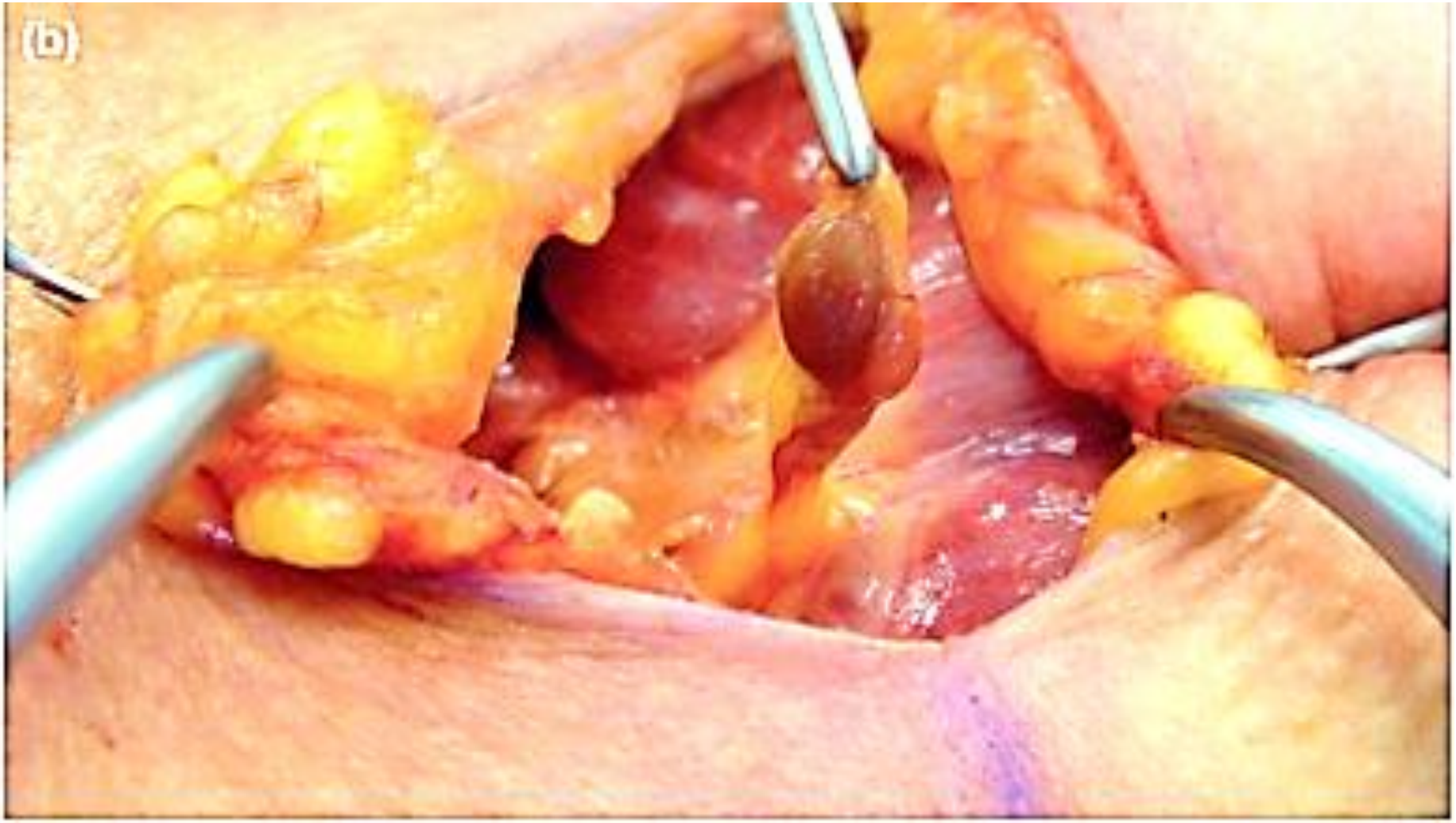
Parathyroidectomy with exposure of the left superior and inferior parathyroid glands (white arrows) in situ




(b)

- **Minimally invasive (focused) parathyroidectomy**
- individuals with PHPT have a single adenoma.
- it commonly refers to the removal of a localised abnormal parathyroid gland through an incision less than 3 cm in length .
- The term encompasses open approaches (central and lateral incisions) and video-assisted and radioguided parathyroidectomies.
- A number of randomised studies have shown that the focused approach has similar cure rates to a cervical exploration but with reduced rates of postoperative hypocalcaemia, shorter operating times, potentially less pain and better cosmesis.

- The need to convert to a cervical exploration may be guided by the use of intraoperative PTH measurements.
- The basic concept is that the half-life of circulating PTH is 3–5 minutes and there should therefore be a significant drop detected in the plasma PTH following resection of a single adenoma. If no such drop is detected, then multigland disease may be suspected and conversion to a bilateral neck exploration should be considered.
- The Miami criteria were developed to determine the extent of resection. A drop in the PTH into the normal range and to less than half the maximum preoperative PTH at 10 minutes appears to accurately predict single-gland disease .

Bilateral neck exploration

- A traditional cervical neck exploration is required where imaging is negative or discordant, in MEN (type 1 or type 2A) or in lithium-induced PHPT.
- A transverse collar (Kocher’s) incision .
- Identification of the recurrent laryngeal .
- All four glands are identified. Three and a half glands are resected, with half of a vascularised parathyroid left in situ. The other half of the gland should be sent for frozen section to confirm the presence of parathyroid tissue

- .Ideally the most normal-appearing parathyroid is left in situ. With this caveat in mind, where possible an inferior gland should be left.It is marked with a non-absorbable suture to aid identification in the presence of recurrent disease, where resection can be achieved without increasing the risk of damage to the recurrent laryngeal nerve.
- Alternatively, all four glands can be resected and a forearm autotransplant created. Small pieces of parathyroid are sutured into pockets created in the brachioradialis muscle.
- Cure rates and rates of persistent and recurrent disease appear to be similar, regardless of the type of procedure used.
- However, in recurrent disease it can be difficult to identify the location of the recurrent tissue when an autotransplant is performed.

Thymectomy and resection of mediastinal adenomas

- The incidence of clinically significant supernumerary glands is increased in patients with multigland disease or those with hereditary syndromes.
- A thymectomy should be routinely undertaken for patients with MEN1-associated PHPT or in secondary hyperparathyroidism.
- A cervical thymectomy is performed by dissecting close to the thymic capsule, exploring the cervical part of the gland. The mediastinal part of the gland can be removed by gentle upwards traction, with ligation of the veins draining into the innominate vein.

- The end of the gland is tapered and rarely requires formal ligation.
- A median sternotomy is not required where a prophylactic thymectomy is being performed.
- Mediastinal adenomas are rare, accounting for less than 1% of all parathyroid adenomas. They will be typically identified on preoperative imaging.
- Resection can be achieved either by an open sternotomy or increasingly by a thoracoscopic approach. A minimally invasive approach can be particularly effective where the abnormal gland lies immediately deep to the mediastinal pleura. It can confer significant advantages in length of hospital stay and complication rates.

Post operative complications

Permanent hypoparathyroidism

Reccurent Laryngeal Nerve Injury

Permanent hypoparathyroidism

The continuing need for calcium and/or vitamin D replacement at 1 year postoperatively.

- It is a rare complication when surgery is undertaken for PHPT (0.5%), but in secondary hyperparathyroidism it can range from 4% to 12%.
- Symptoms include mild circumoral or digital numbness and paraesthesia, carpopedal or laryngeal spasms and cardiac arrhythmias.
- Chvostek's and Trousseau's signs may be elicited.
- Chvostek's sign refers to contraction of the ipsilateral facial muscles on percussion of the facial nerve below the zygoma.
- Trousseau's sign refers to the development of carpopedal spasm secondary to occlusion of the arm (usually with a blood pressure cuff).

- Biochemical investigations include total and ionised calcium levels as well as serum magnesium levels. An ECG may demonstrate a prolonged QT interval or QRS complex changes.
- Mild hypocalcaemia can be treated with oral calcium and vitamin D supplementation. Acute symptomatic hypocalcaemia is an emergency and should be corrected with intravenous as well as oral calcium and vitamin D replacement. Traditionally, 10 mL of 10% calcium gluconate is administered slowly intravenously. Supplemental magnesium may also be required, owing to the synergistic action of transporters for calcium and magnesium.

Reccurent Laryngeal Nerve Injury

- Unilateral.
- Bilateral

SPECIAL CASES

- Lithium-induced hyperparathyroidism
- Familial syndromes

Lithium-induced hyperparathyroidism

- 10–15% of patients treated with long-term lithium.
- Failure to suppress PTH. Hyperplasia all parathyroid tissue, or a single adenoma 33–49% of cases.
- It may be caused by interference with the parathyroid kinase C signal transduction system and the Wnt pathway.

- Biochemical abnormalities may resolve with discontinuation of lithium.
- Surgery is indicated where ongoing treatment with lithium is required or where abnormalities persist following withdrawal of lithium.
- Minimally invasive surgery is relatively contraindicated in these patients because of the high incidence of multigland disease. Excision, however, should be limited to those glands that are obviously enlarged at exploration rather than a formal three-and-a-half-gland excision.

Familial Hereditary PHPT Syndromes (FHH)

- PHPT occurs as a central facet in multiple MEN type 1, type 4, type 2A, HPT-JT, autosomal dominant mild hyperparathyroidism and FHH.

Familial isolated hyperparathyroidism

- Patients have PHPT without any other associated endocrinopathies.
- The underlying genetic abnormality has yet to be fully elucidated, but the syndrome has been linked to known mutations in the MEN1 gene, the HRPT2 gene as well as the calcium-sensing receptor gene. A significant proportion of patients will belong to the MEN 1 family, with documented recognised mutations but without expression of other endocrinopathies.
- Hyperparathyroidism should be treated with a formal bilateral neck exploration and management as per patients with MEN.

- MEN type 1-associated hyperparathyroidism
- A rare autosomal dominant syndrome consisting of tumours of the parathyroids, endocrine pancreas–duodenum and the pituitary (the three Ps).
- It can also be associated with adrenal adenomas or carcinoma, foregut carcinoids and lipomas.
- occur in the MEN1 gene, encoding the protein menin acts as a tumour suppressor.
- Patients typically present with young onset (20–30 years of age) of symptomatic hyperparathyroidism .

- In general, it is associated with the presence of multigland parathyroid disease and as such has mandated a bilateral cervical exploration with at least a subtotal parathyroidectomy and cervical thymectomy.
- A subtotal parathyroidectomy removes three and a half glands with half of the most normal-appearing parathyroid left in situ with a marking stitch to facilitate reoperative intervention.
- A total parathyroidectomy and forearm autotransplantation is an acceptable alternative.

MEN type 4-associated hyperparathyroidism

- An autosomal dominant syndrome that comprises the same combination of tumours as MEN type 1 but is a rarer cause of hereditary PHPT.
- It arises as a result of an inactivating pathogenic variant in the cyclin-dependent kinase inhibitor CDKN1B gene.
- It should be managed in the same fashion as MEN type 1.

MEN type 2A-associated hyperparathyroidism

- MEN type 2A consists of medullary thyroid carcinoma (MTC), unilateral or bilateral phaeochromocytomas and PHPT.
- PHPT occurs in approximately 20% of patients and is associated with mutations in codon 634 in the RET proto-oncogene.
- The majority of patients will be asymptomatic, with a mild elevation in calcium and asymmetrically enlarged parathyroid glands. It is extremely important that the presence of a phaeochromocytoma is excluded prior to surgical intervention.
- Surgery is usually performed for MTC, with the parathyroid enlargement often being a coincidental intraoperative .
- The primary aim of treatment is to avoid hypoparathyroidism. A conservative stance is adopted with resection of grossly enlarged glands, but with preservation of parathyroid tissue where possible and identification with a marking stitch in the neck.

Hyperparathyroidism–jaw tumour syndrome

- HPT-JT is a rare cause of PHPT. It arises as a result of inactivating mutations in the HRPT2/CDC73 gene on chromosome 1q21–q31, encoding parafibromin.
- It classically presents with early-onset PHPT (mean age of 32 years), the aetiology of which can be either single- or multigland disease but is predominantly cystic in nature. It presents with severe hypercalcaemia and is associated with an increased risk of an underlying parathyroid carcinoma.
- 40% of patients will have the pathognomonic ossifying jaw fibromas of the maxilla or mandible.

- Other associated abnormalities include renal pathology (hamartomas, polycystic kidney disease and adult Wilms' tumours) and female patients may have uterine malignancies. Surgical intervention involves removal of all enlarged parathyroid glands.
- Where there is concern for a parathyroid carcinoma, great care must be taken to avoid tumour spillage. Whether or not an en bloc resection of the enlarged suspicious parathyroid and the adjacent thyroid lobectomy is required remains controversial.

Autosomal dominant mild hyperparathyroidism

- This is a rare autosomal dominant syndrome presenting with hypercalcaemia and hypercalciuria.
- It is associated with a mutation in the calcium-sensing receptor gene.
- It typically presents in patients who are over 40 years of age and all patients have PHPT.
- Surgical intervention requires a bilateral neck exploration as it is associated with multigland disease.

Familial hypocalciuric hypercalcaemia

- FHH is not a surgical disease and therefore preoperative diagnosis is imperative for the surgeon.
- It arises as a result of heterozygous mutations in the calcium-sensing receptor gene on chromosome 3.
- Benign FHH typically presents with mild hypercalcaemia in young (<10 years of age) asymptomatic patients.
- Patients with FHH have a normal or slightly elevated PTH level, increased serum magnesium levels and hypocalciuria. A low urinary calcium–creatinine clearance ratio is used to discriminate between FHH and mild PHPT.
- Patients rarely require intervention and surgical intervention is not indicated.

Criteria for genetic testing (hereditary PHPT)

- The current NHS England National Genomic Test Directory testing criteria from March 2019 for familial hyperparathyroidism state that testing should be considered for patients with PHPT and a creatinine clearance ratio >0.02 who meet one of the following criteria:

- 1 presenting before the age of 35 years or
- 2 presenting before the age of 45 years with one of :

- a proven multigland involvement or
- b hyperplasia on histology or
- c ossifying fibroma(s) of the maxilla or mandible or
- d at least one first-degree relative with unexplained hyperparathyroidism.
- The testing criterion for FHH is a creatinine clearance ratio <0.02.

SECONDARY HYPERPARATHYROIDISM

- Definition and presentation.
- Calciphylaxis.
- Diagnosis.
- Management.

Definition

- A derangement in calcium homeostasis, which leads to a compensatory increase in PTH secretion
- Renal hyperparathyroidism (chronic kidney disease)
- Others (gastrointestinal malabsorption, vitamin D deficiency, liver disease or chronic lithium usage).

- Primarily due to underlying chronic kidney disease
- Associated with **parathyroid hyperplasia**
- Diagnosis is made biochemically with a hypocalcaemia or normocalcaemia and an elevated PTH. High phosphate levels and low vitamin D levels are seen
- No localisation studies are required
- **Mainstay of treatment is renal transplantation**. Medical management with calcium and vitamin D replacements and phosphate binders is a bridge to transplantation
- Use of calcimimetics has reduced the requirement for surgical intervention
- Subtotal parathyroidectomy remains the surgical intervention of choice when indicated

- Abnormalities in the renal tubular absorption of phosphate lead to Hyperphosphataemia, acting directly on the parathyroid cells and stimulates PTH secretion.
- (FGF23) phosphaturia hormone fibroblast growth factor 23 .This is progressively secreted from osteocytes to compensate for chronic phosphate retention that in turn leads to a reduction in 1,25-dihydroxyvitamin D, which by reducing the intestinal absorption of calcium also acts to increase secretion of PTH.
- There is a reduction in the expression of the vitamin D receptor and the calcium-sensing receptor, with associated skeletal resistance to PTH. These factors interact to form the complex pattern leading to progressive secondary hyperparathyroidism in the setting of chronic renal disease.

- The pathological characteristics associated with secondary hyperparathyroidism include: (hyperplasia, asymmetrical glandular enlargement or nodularity). When the parathyroid gland becomes nodular, it loses expression of the vitamin D receptor and the calcium sensing receptor gene. It has been proposed that nodular parathyroid glands may be resistant to calcimimetics and therefore refractory to medical management.

- **Calciphylaxis** (calcific uraemic arteriolopathy) is a syndrome of disseminated calcification resulting in both vascular calcification and skin necrosis. It accounts for approximately 4% of patients undergoing surgical intervention for secondary hyperparathyroidism.
- It presents with expanding painful cutaneous purpuric lesions, predominantly on the extremities, although they can also be seen on the lower abdomen. Leads to ischaemic necrosis and the development of gangrene, which in turn leads to overwhelming sepsis and death.
- Prognosis : is extremely poor, with a mortality of up to 87%.
- An urgent parathyroidectomy has been shown to decrease pain, improve wound healing and reduce the risk of amputation in these patients. It has also been associated with an increase in median survival.

Presentation

- Bone pain, with associated soft-tissue calcium deposits .

Diagnosis

- (Hypocalcaemia or normocalcaemia with an elevated PTH , high serum phosphate and a low vitamin D).
- Traditional plain rarely demonstrate the pathognomonic osteitis fibrosa cystica.
- Bone densitometry (DEXA scan) demonstrates osteopenia or osteoporosis.

- **Neck ultrasonography** (nodular hyperplasia who may be refractory to medical management).
- **Localisation studies** are not undertaken as minimally invasive surgery is not indicated. They are helpful in patients with recurrent disease in order to identify ectopic parathyroid tissue, especially in the mediastinum.
- **Selective venous sampling** In cases of recurrent disease, when there is no evidence of active disease in the neck and a previous allograft has been used to the forearm, selective venous sampling for PTH in the neck and the brachial vein on the side of the graft can be useful. This is known as the Casanova test and to prove that the recurrent disease is located in the grafted arm (graft hyperplasia) the ratio must be greater than 20:1.

Management OF Secondary HPT

- Renal transplantation remains the only definite treatment for secondary hyperparathyroidism.
- Other therapies to provide symptom relief.
- Standard management includes replacement of calcium and vitamin D and the reduction of phosphate levels by the use of phosphate binders.
- Treatment of this disease changed radically with the introduction of calcimimetic drugs, such as cinacalcet.
- Calcimimetics alter the set point of the calcium-sensing receptor, thereby reducing the constant stimulation of the parathyroid glands and lowering the PTH level. This obviously does not address the underlying renal disease. It remains controversial as to which patients may benefit from the use of calcimimetics and which patients may benefit from earlier surgical intervention.

- Indications for pursuing medical management include those patients who are deemed non-surgical candidates by reason of medical comorbidities. Similarly, where there is persistent or recurrent disease, the origin of which cannot be clearly elucidated, surgical management should be avoided.
- However, there are definite indications for surgical intervention in secondary hyperparathyroidism , although these have been modified to reflect the current use, where available, of calcimimetics .

- There are a wide variety of operations that can be utilised for the management of secondary hyperparathyroidism, none of which appears significantly superior in terms of clinical outcomes (persistent or recurrent disease).
- These include a subtotal parathyroidectomy, a total parathyroidectomy with autograft or a total parathyroidectomy without autograft.
- Cryopreservation of resected tissue, where available, should be performed in cases of significant postoperative hypocalcaemia. The first two procedures are most widely accepted and the type of operation performed depends upon the surgeon.

- **A subtotal parathyroidectomy** is where three and a half parathyroid glands are excised, with the remnant being marked with a non-absorbable stitch to facilitate identification in the event of recurrent disease.
- **A biopsy** of the final gland that is to be left in situ is mandatory to confirm the presence of residual parathyroid tissue.
- Ideally an inferior gland is left in situ to facilitate reoperative surgery and minimise potential damage to the recurrent laryngeal nerve in that setting .
- **A total parathyroidectomy with a forearm autograft** involves removal of all parathyroid tissue in the neck, with reimplantation of a small amount of morcellated tissue within a pocket formed in the brachioradialis muscle.
- Overall, regardless of the operative approach utilised the cure rate ranges between 90% and 96%, with similar complication rates. A randomised study looking at 40 patients who underwent either a subtotal or total parathyroidectomy with autotransplant demonstrated no significant difference between the two operations in terms of efficacy and recurrence rate .

- The response to surgical intervention is often dramatic.
- The biochemical parameters may resolve almost immediately and appear to be sustained for up to 3 years postoperatively.
- Symptoms of improvements: (bone pain, pruritus, fatigue and depression).
- Finally, bone metabolism is improved with an approximate 10% increase in trabecular bone, with almost immediate suppression of bone resorption and acceleration of new bone formation.

Indications for surgical intervention in secondary hyperparathyroidism.

- **Essential components**

1. Persistently high serum level of intact PTH >500 pg/mL

2. Hyperphosphataemia (serum PO4 >6 mg/dL) or hypercalcaemia (serum Ca >2.5 mmol/L or 10 mg/dL) which is refractory to medical management

3. Estimated volume of the largest gland >300–500 mm^3 or long axis >1 cm.

- **Clinical findings**

If patients have one of these symptoms, parathyroidectomy should be recommended:

- Severe osteitis fibrosa with associated high bone turnover
- Subjective symptoms (bone and joint pain, arthralgia, muscle weakness, irritability, pruritus, depression) .
- Progressive ectopic calcificationcation
- Calciphylaxis
- Progressive reduction in bone mineral content
- Anaemia resistant to ESA
- Dilated cardiomyopathy/cardiac failure

ESA, erythropoietin-stimulating agent; PTH, parathyroid hormone

Proposed indications for surgical management of secondary hyperparathyroidism (SHPT) in the era of calcimimetics.

- When SHPT is refractory to vitamin D replacement or vitamin D analogues and prolonged survival is anticipated
- Severely impaired quality of life owing to either SHPT or intolerance to calcimimetics
- When sufncient reduction in parathyroid hormone cannot be achieved with use of calcimimetics
- Thyroid surgery is also required (thyroid carcinoma).

TERTIARY HYPERPARATHYROIDISM

Is a persistent autonomous hypercalcaemic hyperparathyroidism occurring after kidney transplantation.

A number of proposed factors may prevent involution of the hyperplastic parathyroid glands following resolution of the underlying renal impairment :

- Impaired graft function,
- Non-suppressible PTH secretion.
- Slow involution of enlarged glands .
- Insufficient calcitriol conversion by the transplanted kidney (hydroxylase).

- Biochemically(an elevated total or ionised calcium, with an elevated or unsuppressed PTH and a reduced phosphate occurring at least 1 year post renal transplantation.
- Differentiation from PHPT can be difficult.
- Treatment (control of hypercalcaemia).
- Surgury is the definitive treatment. Subtotal parathyroidectomy or total parathyroidectomy with autotransplantation .

Indications for surgical intervention in tertiary hyperparathyroidism

- Subacute severe hypercalcaemia (>3 mmol/L)
- Impaired graft function
- Nodular hyperplasia of the parathyroid gland(s)
- Progressive symptoms (>2 years following transplantation)
  - Worsening bone disease (pain, fracture, bone loss)
  - Renal stones/nephrocalcinosis
  - Soft-tissue or vascular calcifications

PERSISTENT HYPERPARATHYROIDISM

- An elevated calcium within 6 weeks of surgical intervention, due to technical error during the first operation (a missed adenoma or asymmetrical disease).

- All preoperative biochemistry, radiological imaging, intraoperative findings and pathology must be carefully reviewed.
- Investigations: repeat imaging of the neck and mediastinum :(sestamibi, ultrasonography and 4D-CT scanning).
- Surgery ([MIP] / bilateral exploration).
- Complications (Recurrent laryngeal nerve damage and permanent hypocalcaemia.

RECURRENT HYPERPARATHYROIDISM

- Hypercalcaemia occurring 6 months after surgery but with an intervening period of normocalcaemia.

Common causes include

- Missed pathology at the first operation.
- Hyperplasia in remaining or autotransplanted tissue.
- Parathyromatosis (disseminated parathyroid tissue within the soft tissues of the neck and superior mediastinum owing to rupture of the parathyroid gland during the primary surgery.) .
- Very rarely, the development of a second parathyroid adenoma.

- Surgical intervention is guided by the radiological imaging.
- Post op complications rates are higher in re-operative surgery.

PARATHYROID CARCINOMA

- It is an indolent but progressive disease.
- It remains difficult to diagnose preoperatively as it biochemically resembles PHPT. Metastatic spread can occur to the lungs, liver and bones.
- Treatment : Hypercalcaemia and Surgery for primary presentations and locally recurrent disease.
- Complete resection **(**R0) to avoide spillage to prevent seeding and thus recurrent disease and cervical lymph node mapping for excision. (local recurrence rates).
- Histological confirmation : remains difficult. (invasion of the surrounding soft tissue and/or metastatic disease).
- Parafibromin immunohistochemistry and immunohistochemistry for PGP 9.5. should be considered for genetic screening.

- Adjuvant chemotherapy has not been shown to confer a disease-free or overall survival benefit.
- External beam radiotherapy .
- Recurrence rates range from 33% to 80% in the first 3 years.
- Overall survival (5 years (90%) and 10 years (49–77%)).

PRAISE BE TO ALLAH