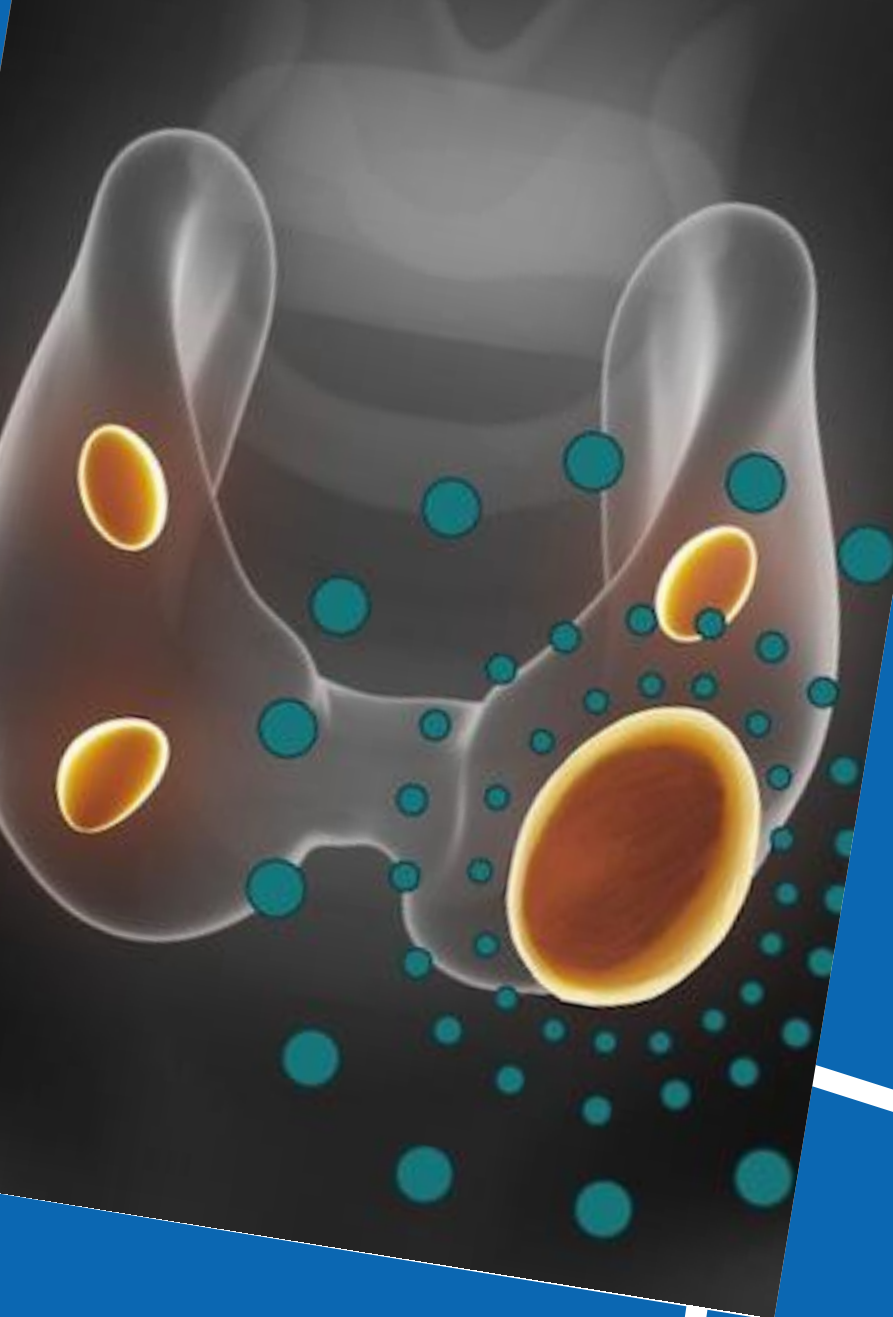




Imaging and parathyroid surgery

Dr A Buemi

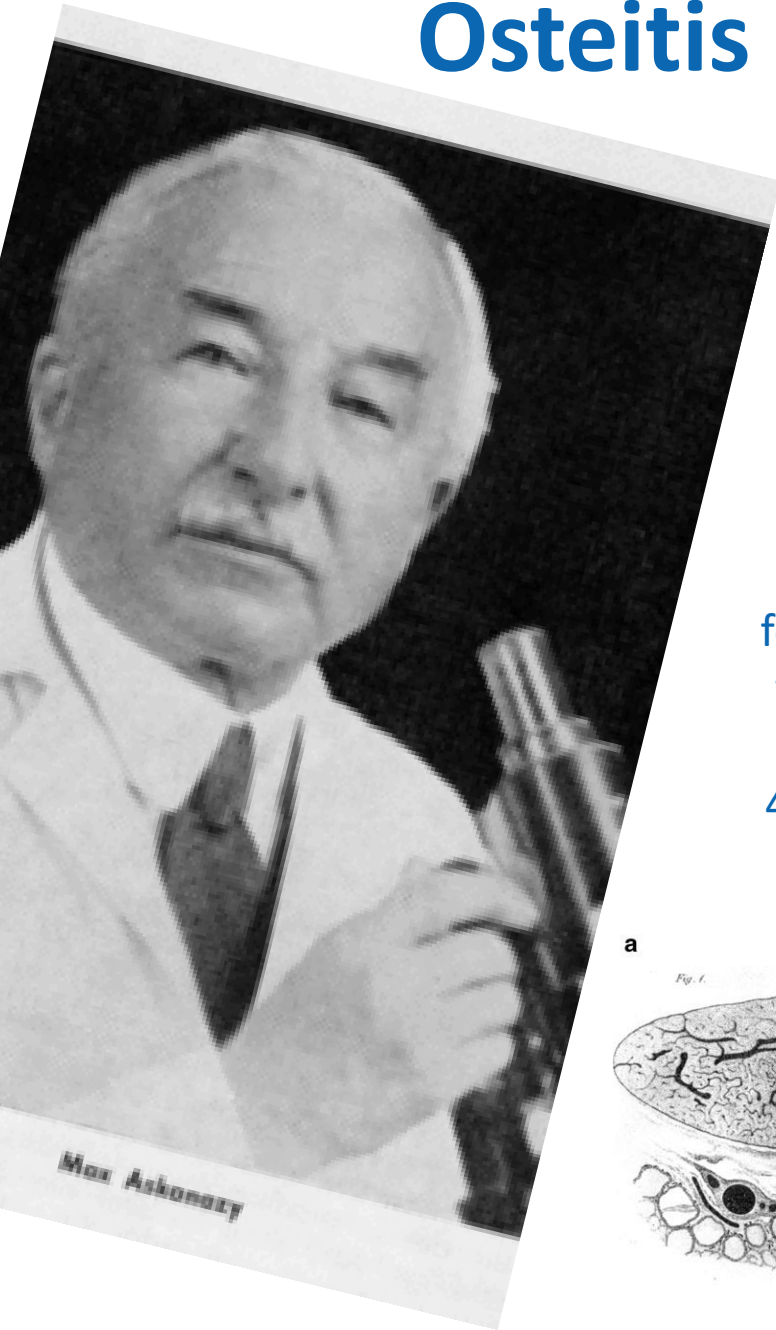
Osteitis Fibrosa Cystica

“at the left side of the neck below the thyroid gland a reddish brown lymph node is found...”

Von Recklinghausen, 1891

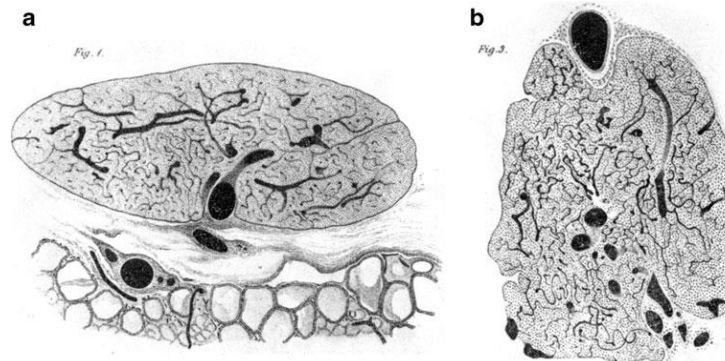


Osteitis Fibrosa Cystica



In 1904, **Max Askanazy** (1865–1940) from Bern published a classic case of osteitis fibrosa in a 51-year-old female patient who died from her illness.

At autopsy Askanazy found goiter of the right thyroid lobe and a soft **red-white tumor** of 4.5×2×2 cm fixed to the left lobe



Felix Mandl:
The first parathyroidectomy
July 30th 1925



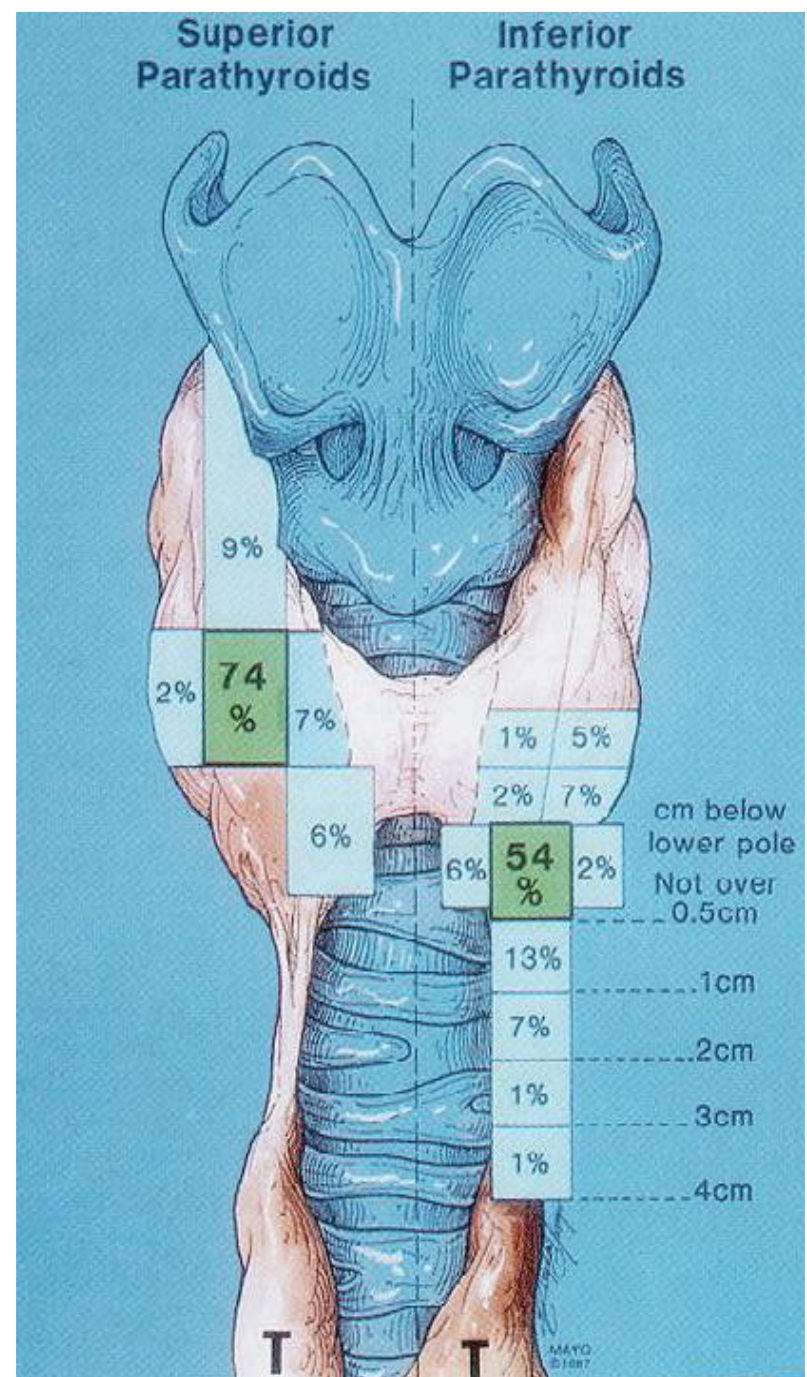
Captain Charles Martell before hyperparathyroidism and after the disease had affected his skeleton



Parathyroid Glands

- Usually four glands (15% of people have 2, 3, or 5)
- Ectopic glands occur in 20% of people
- Small (20-40 mg): about the size of a "grain of rice"

Usually located posterior to/or imbedded in the thyroid gland either mediastinum, tracheoesophageal groove, or thymus



Hyperparathyroidism types



- **Primary**- Most often caused by parathyroid adenoma, causing elevated parathyroid hormone (PTH) and serum calcium.
- **Secondary**- most often due to Chronic Kidney Disease (CKD), especially with an estimated glomerular filtration rate (eGFR) below 60.
 - Can also be caused by vitamin D deficiency, poor PO calcium intake or gastrointestinal loss (i.e. malabsorption).
- **Tertiary**- due to autonomous production of PTH in setting of longstanding CKD.

Differential Diagnosis of Confirmed Hyperparathyroidism

Mid-High Normal or Elevated PTH	
Primary hyperparathyroidism	Medications
• Sporadic	• Thiazide diuretics
-Adenoma (80-85%)	• Lithium
-Hyperplasia/ multiple glands (15-20%)	Chronic renal failure
-Carcinoma (<1%)	Aluminum
Familial	Tertiary hyperparathyroidism
• Isolated	Autoimmune hypocalciuric hypercalcemia
• MEN 1	
• MEN 2A	
• MEN4	
• Jaw Tumor Syndrome (CDC73)	
Familial benign hypocalciuric hypercalcemia	

PURPOSE OF PARATHYROID IMAGING:

IN SEARCH OF THAT “REDDISH
BROWN LYMPH NODE”!



The Captain Charles Martell lesson

Imaging in PHPT: What the Surgeon Wants to Know ?

Diagnosis?

Primary Hyperparathyroidism

Diagnosis

Primary Hyperparathyroidism Classical Laboratory Results

- **Calcium**
- **PTH**
 - Normal (20%) or elevated (80%)
 - Normal = usually upper 1/2 to 1/3 of reference range
- **Phosphorus**
 - Low in 25% in referral populations
- **Calcium creatinine clearance ratio**
 - $(U_{Ca} \times S_{Cr}) / (S_{Ca} \times U_{Cr}) < 0.01$ suggests familial benign hypocalciuric hypercalcemia
 - > 0.02 essentially rules out FBHH
- **25-D** low in 50% – worse hyperparathyroidism if severe

Imaging in PHPT: What the Surgeon Wants to Know ?

Diagnosis?

Biological

Risk stratification and
choice of treatment
(Medical vs Surgical)?

Primary Hyperparathyroidism Surgery

Symptomatic

1) All individuals with symptomatic PHPT should have surgery.

- Bone and muscle pain
- Polydipsia, polyuria, nocturia
- Abnormal fatigue, muscle weakness
- Anorexia, abdominal pain, weight loss, constipation
- Memory loss, concentration problems, anxiety, depression
- Pruritus

2) The vast majority of patients with PHPT (>90%) are symptomatic and some of these symptoms regress after curative surgery

Bilezikian JP et al: J Clin Endo Metab, 2014.

Primary Hyperparathyroidism Surgery

Asymptomatic

4th International Workshop on Asymptomatic Primary Hyperparathyroidism

- Age < 50 years
- Serum calcium >1 mg/dL (0.25 mM) upper limit of normal (ULN)
- Overt complication (Stones/Bones) includes radiographic stones (imaging recommended)
- 24-hour U-Ca >400 mg (10 mmol) and increased stone risk by biochemical stone risk analysis
- Calculated creatinine clearance <60 ml/min
- BMD with Z-score of ≤ -2.5 in premenopausal women or men <50 years or worse or T-score ≤ -2.5 in postmenopausal women and men over 50 years
- Vertebral fracture (morphometric) or fragility fracture

Bilezikian JP et al: J Clin Endo Metab, 2014.

Imaging in PHPT: What the Surgeon Wants to Know ?

Diagnosis?

Biological

Risk stratification?

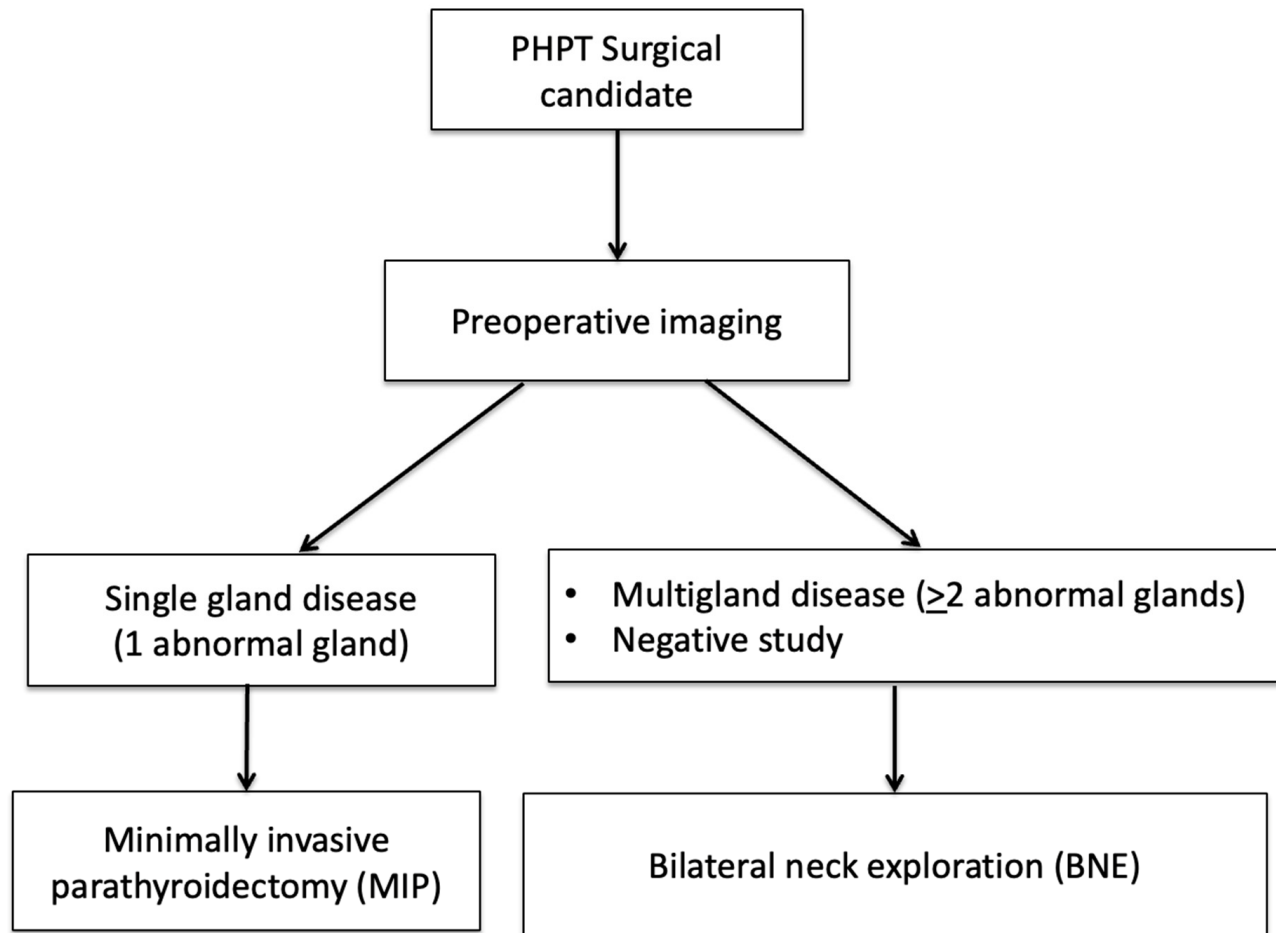
Clinical

Surgical planning?

Primary Hyperparathyroidism Localization

- Main benefit is to allow minimal access parathyroidectomy
- Parathyroid nuclear imaging or US are sensitive tests (identify 75-85%) for identifying the abnormal gland but institutional dependent based on skill/methods of team
- 4D Parathyroid CT
- ¹¹C Choline PET CT
 - Showing emerging benefit in localization

How imaging is used to guide parathyroid surgery?



Ultrasound semiology

Parathyroid Adenoma :

No concordance between size and shape and biological results

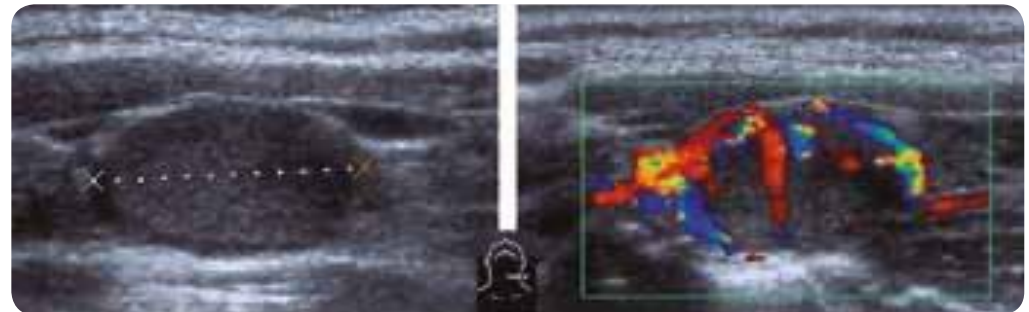
- Shape/Size:
Mostly oval, 0.7-4.1 +/-6.5 cm
- Echogenicity:
Hypoechoic (87%)- Isoechogenic (13%)
- Internal architecture:
Solid homogeneous (74%)-
heterogeneous: (19%)
Cystic: (6%)
- Interface:
75% when adenoma has contact
with thyroid



Endocr Pract. 2022 Jan;28(1):77-82.

Dynamic ultrasound aspects and colour Doppler

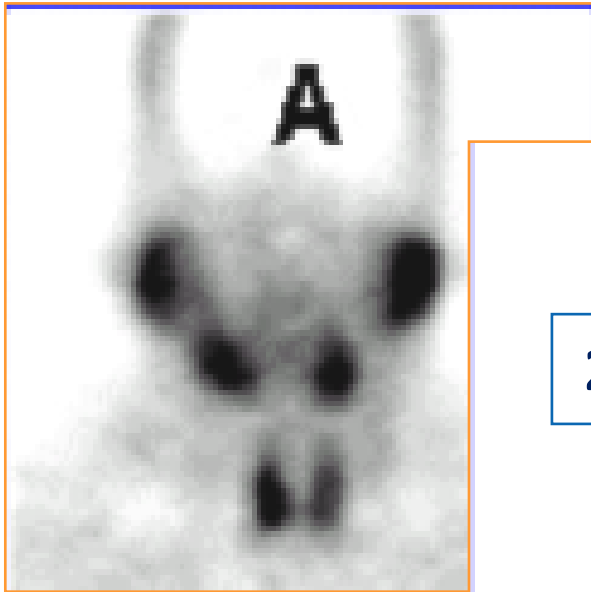
- Mobilise the patient's neck to clear a possible retro-tracheal adenoma
- Swallowing: the adenoma mobilises in 100% of cases ><adenopathy
- Vascularization
 - Moderately to richly vascularised (53%)
 - Weakly vascularised (21%)
 - Not vascularised (26%)



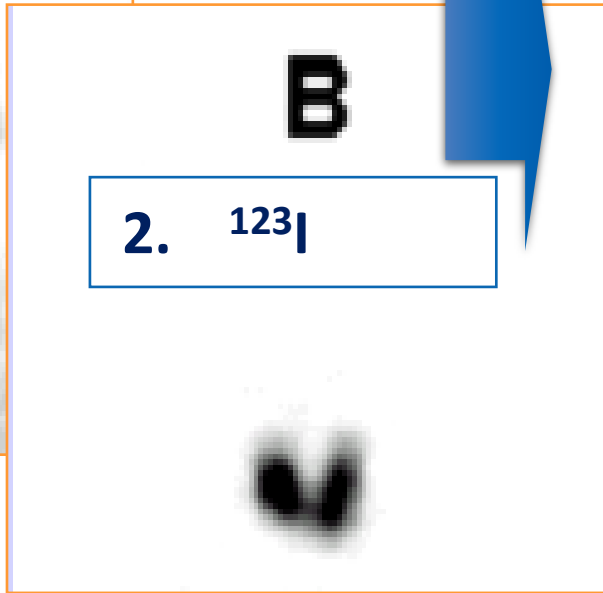
Radiol. 2018; 29(1): 4861-6

Parathyroid nuclear imaging

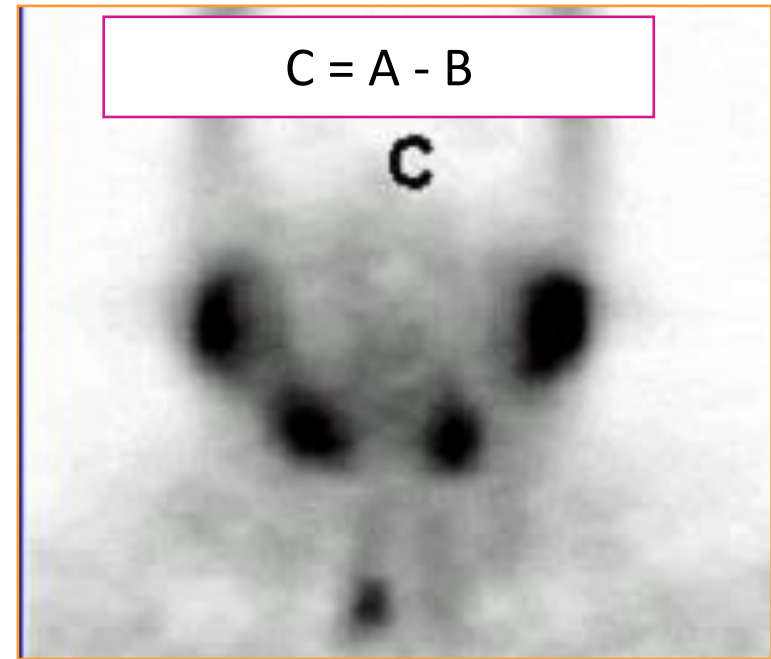
1. ^{99m}Tc - MIBI



2. ^{123}I



Subtraction technique



In the presence of concordance between scintigraphy and ultrasound, the positive predictive value for correct side localization of a parathyroid adenoma can be as high as 97 %

4D CT Scan

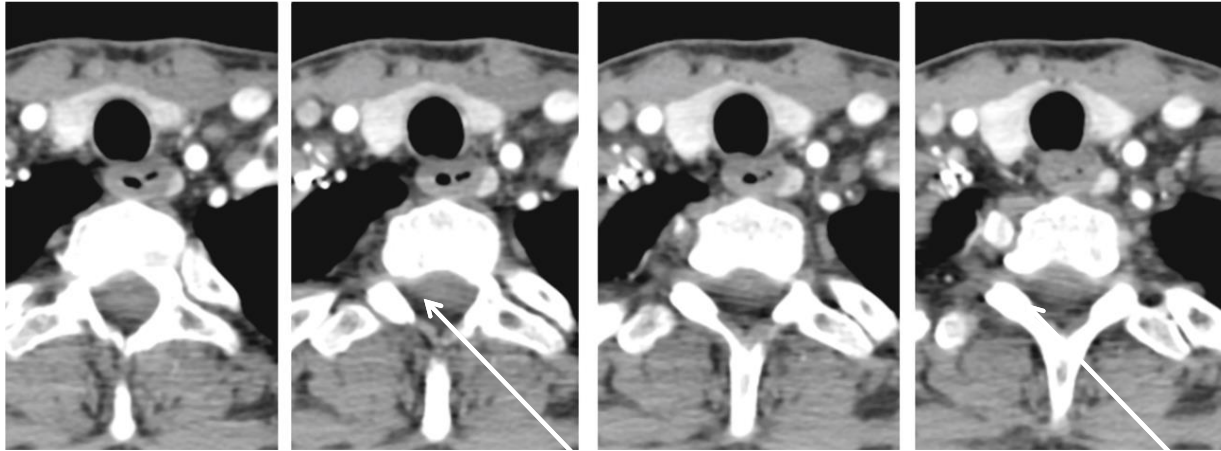


Table 3. Selected Cited Estimates for Accuracy of First-line Imaging Modalities for a Patient with De Novo 1°HPTH

	Sestamibi Scintigraphy	Ultrasound	4D-CT
Sensitivity (95% CI) (16)	78.9% (64–90.6%)	76.1% (70.4–81.4%)	89.4%
Positive predictive value (95% CI) (16)	90.7% (83.5–96.0%)	93.2% (90.7–95.3%)	93.5%
Localization–correct side (single adenoma)	68% (27)	74% (27)	93.9% (57)
Localization–correct quadrant (single adenoma)	50% (27)	72% (27)	85.7% (57)

J Clin Endocrinol Metab, March 2013, 98(3):902–912

Imaging modalities.

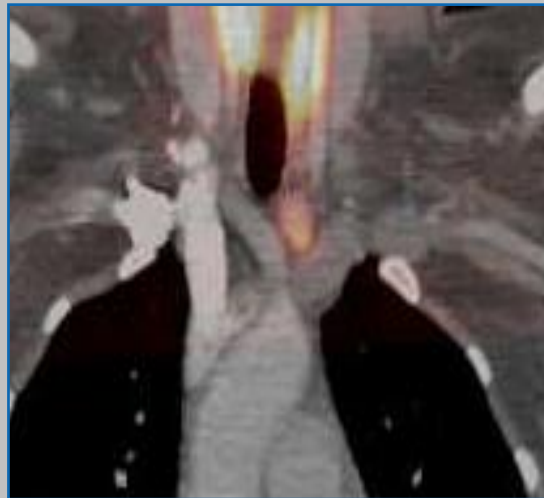
Diagnostic modality	Advantages	Disadvantages	Usefulness
Ultrasound	Widely available	Sensitivity operator dependent	As first imaging modality
	Cost-effective	Sensitivity diminished in presence of multinodular goiter, patient body habitus	
		Not good to locate ectopic glands	
		Limited in detecting multi-gland disease	
Sestamibi SPECT-CT	Functional and anatomical correlation	Not as widely available	As first imaging modality, or second line if ultrasound equivocal or non-localizing
		Expensive	
	Better for locating retropharyngeal or retroesophageal adenomas	Limited in detecting multi-gland disease	
		False-positive results in the setting of thyroiditis, thyroid cancer, adenomas	
4D-CT	Functional and anatomical correlation	Not as widely available	Re-operative setting
	Higher sensitivity for multi-gland disease than other modalities	Higher thyroid-specific radiation exposure	Inconclusive imaging with other modalities
4D-CT, four dimensional computed tomography; SPECT-CT, single-photon emission computed tomography fused with computed tomography scan.			

99mTC-sestaMIBI- scintigraphy with SPECT and low-dose CT



False Negative

Size of the adenoma
Multi-glandular lesions
High Vit D
Low blood calcium
P-gp and MRP (ABCB1, ABCC2)
Calcium channel blockers



False Positive

Thyroid nodule/cancer
Brown fat
Metastatic lesion

Parathyroid Venous Sampling

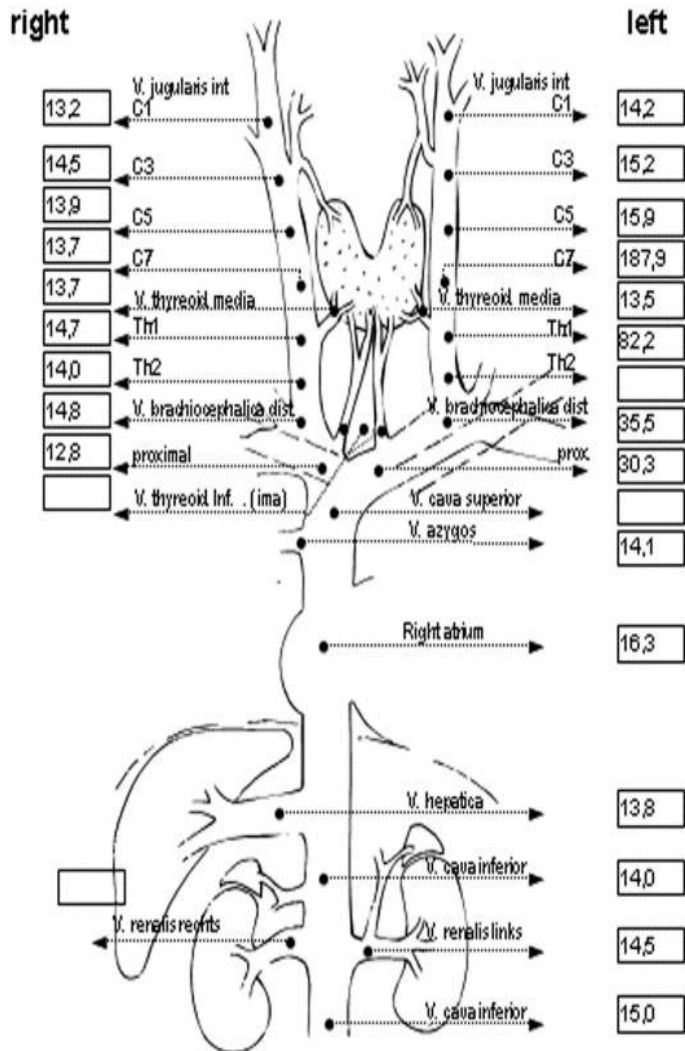


TABLE II.
Pooled Estimates for Subgroup Analysis by Diagnostic Tests.

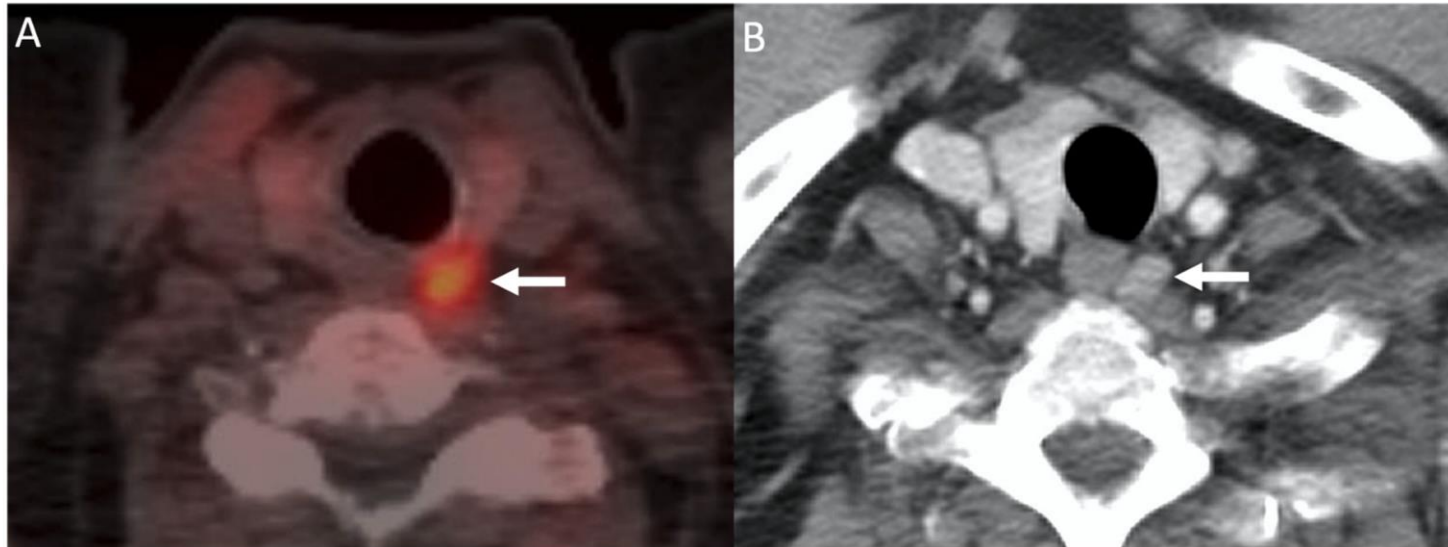
Diagnostic Test	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
sPVS						
SSVS	89 (85–93)	31 (21–43)	1.12 (0.86–1.46)	0.49 (0.16–1.50)	2.25 (0.49–10.2)	0.94 (0.86–1.0)
BIJVS	69 (63–74)	69 (59–77)	2.16 (0.78–5.98)	0.56 (0.28–1.12)	4.47 (0.83–23.8)	0.75 (0.61–0.9)
SVS	44 (27–62)	41 (15–72)	1.389 (0.34–5.59)	0.74 (0.50–1.08)	3.47 (0.36–32.9)	NA
Noninvasive						
Sestamibi	71 (66–75)	68 (61–74)	2.41 (1.23–4.73)	0.32 (0.10–0.98)	11.2 (2.91–43.58)	0.85 (0.78–0.92)
US	87 (80–91)	54 (48–60)	2.27 (1.18–4.37)	0.46 (0.16–1.35)	7.53 (1.08–52.8)	0.85 (0.75–0.95)
MRI	89 (82–94)	44 (32–56)	1.78 (0.55–5.84)	0.34 (0.03–4.20)	6.81 (0.11–437)	0.73 (0.38–1.0)
CT	100 (88–100)	79 (63–90)	3.75 (2.24–6.28)	0.14 (0.04–0.50)	44.5 (7.65–259)	0.88 (0.75–0.95)

- Sensitive and helpful modality that should be reserved to guide the surgical decision in recurrent or persistent PHPT when the preoperative localization is troublesome.
- Super-selective venous sampling had the highest sensitivity and accuracy.

Laryngoscope, 128:2662–2667, 2018

Other Newer Modalities

Choline PET/CT



Benefits

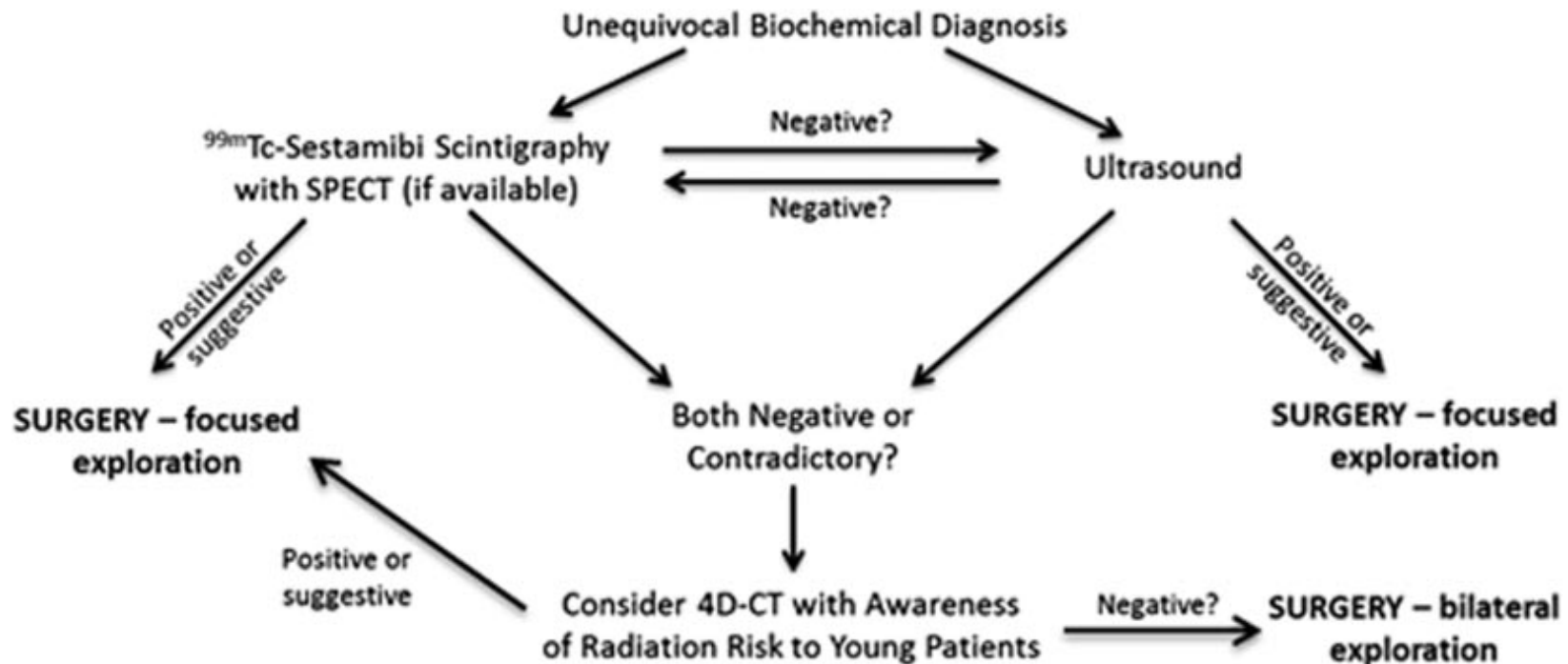
- Lower radiation
- «Patient- friendly»
- less false positive results than US and MIBI
- Cost-effectiveness analysis on patients with non-localized PHPT

Limitations

- no accepted standardized protocol for imaging timing, dynamic acquisition phases, or the radiotracer dose
- Cost
- research imaging technique

Tay,D.;Das,J.P.;Yeh,R. Preoperative Localization for Primary Hyperparathyroidism: A Clinical Review. *Biomedicines* **2021**, *9*, 390.

Imaging approach in an unexplored patient with a de novo diagnosis of primary hyperparathyroidism.



J Clin Endocrinol Metab, March 2013, 98(3):902–912

Primary Hyperparathyroidism

Persistent and Recurrent Disease

Definitions

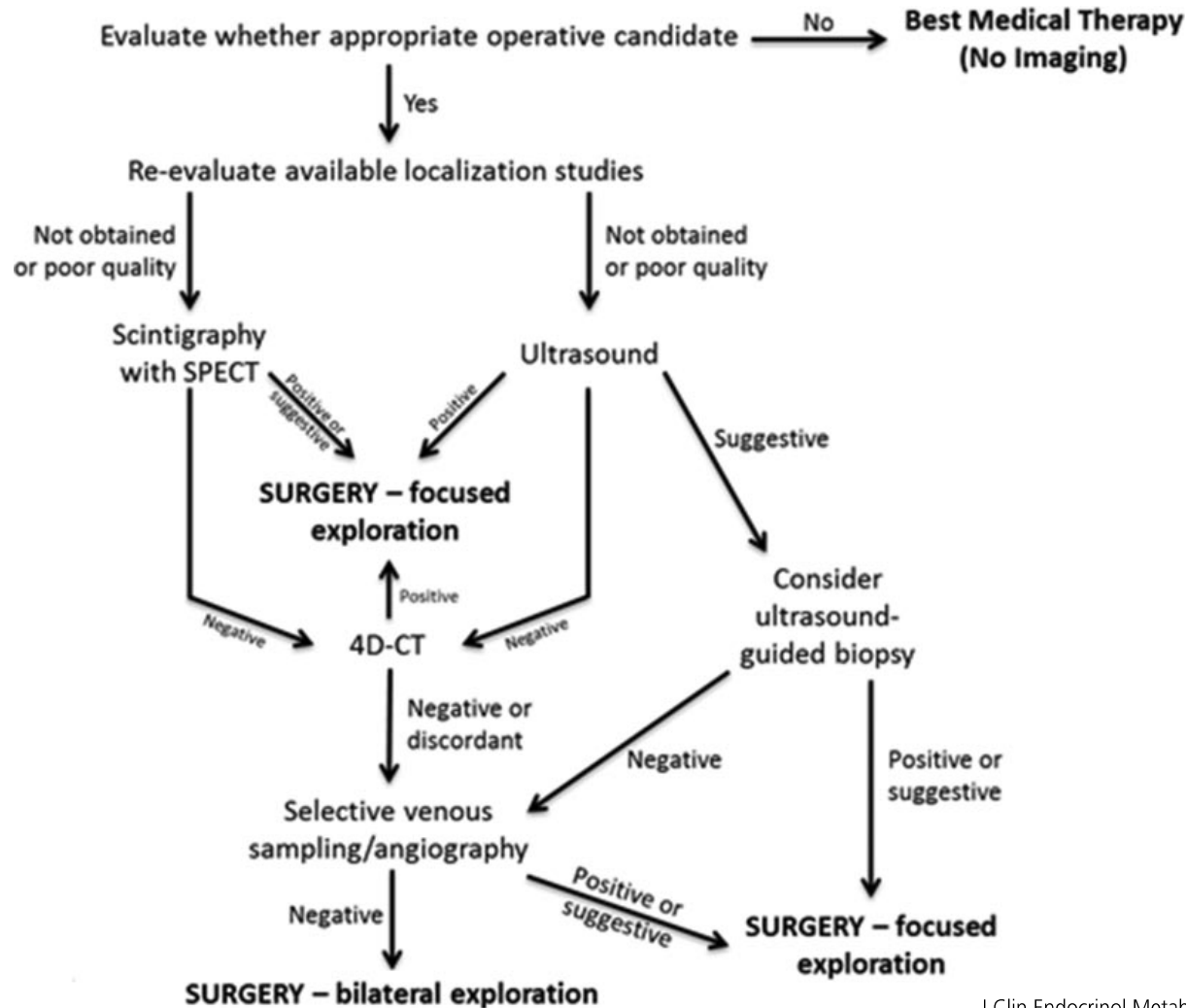
Persistent PHPT

- Fail of biochemical cure within six months after parathyroid surgery with **hypercalcemia** and inappropriate PTH

Recurrent PHPT

- Initial biochemical cure (normocalcemia) followed by **hypercalcemia** >six months after surgery with inappropriate PTH

Imaging approach for a patient requiring remedial cervical exploration



J Clin Endocrinol Metab, March 2013, 98(3):902–912

Role of Imaging and Secondary/Tertiary Hyperparathyroidism: A lesson from pathophysiology

Secondary hyperparathyroidism (SHPT) occurs when the parathyroid gland appropriately responds to a reduced level of extracellular calcium.

PTH concentrations rise, and calcium is mobilized by increasing intestinal absorption (via increase in calcitriol) and by increasing bone resorption.

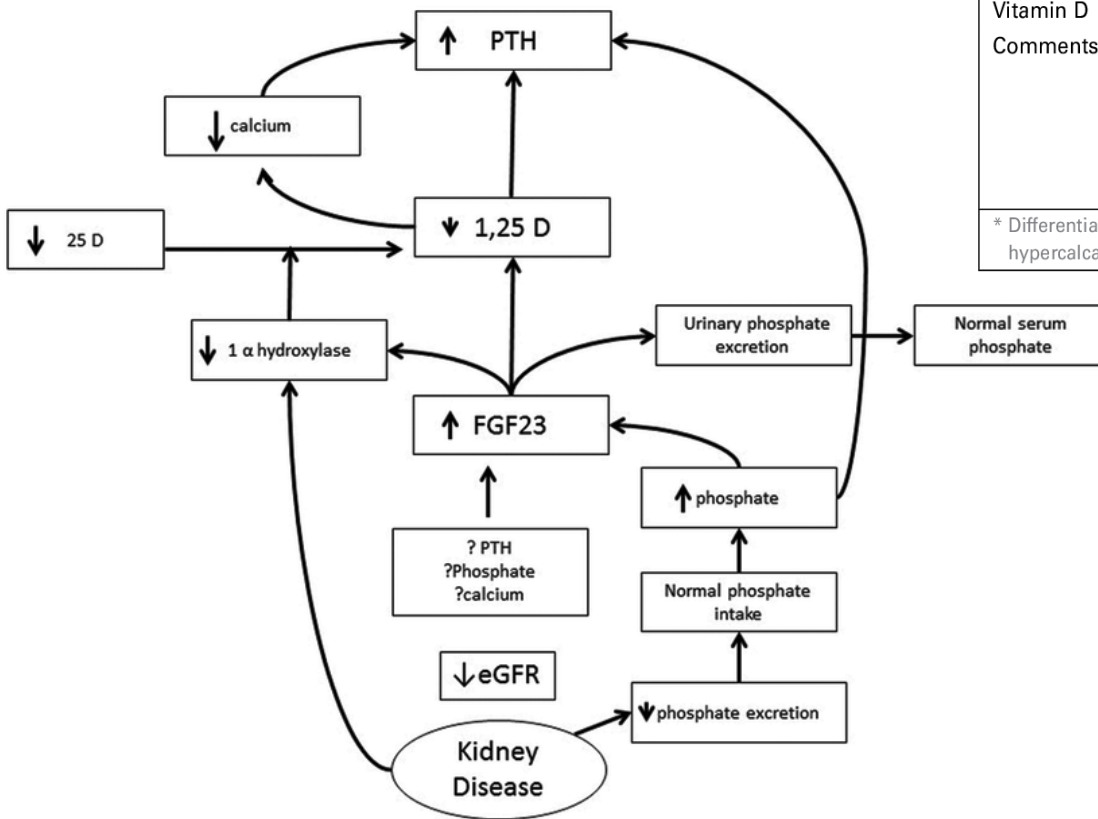
Thus, it is characterized biochemically by elevated PTH and normal or low serum calcium concentrations.

Tertiary (THPT) is due to autonomous production of PTH in setting of longstanding CKD.

Imaging in SHPT and THPT and: What the Surgeon Wants to Know ?

Diagnosis?

Pathogenesis of SHPT and THPT

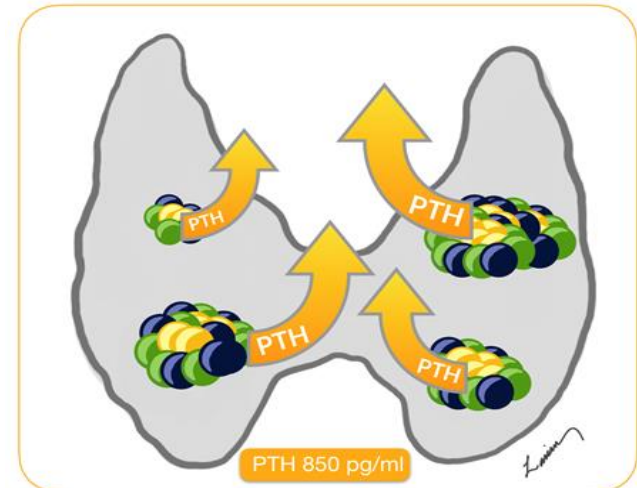


hyperparathyroidism

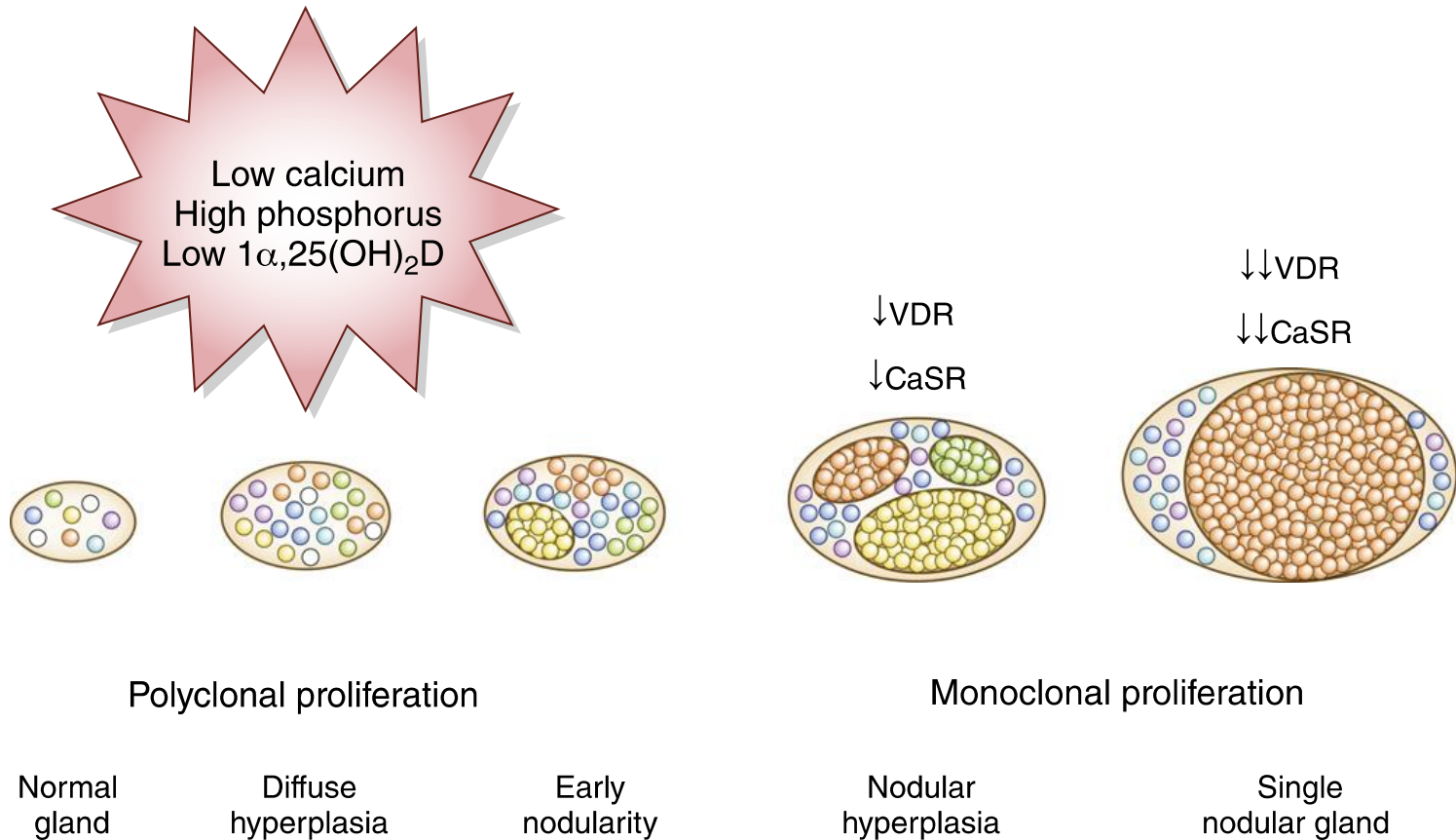
	Primary hyperparathyroidism	Secondary hyperparathyroidism	Tertiary hyperparathyroidism
PTH	↑	↑	↑↑↑
Ca ²⁺	↑ *	↓/N	↑
P0 ₄ ⁺	↓	↑/N	↑
Vitamin D	N/↓	↓↓↓	↓/N
Comments	In 85% a solitary parathyroid adenoma is present Important differential diagnosis is FHH (see Table 3)	Causes include: • chronic renal failure • vitamin D deficiency	Caused by: • end stage renal failure

* Differential diagnosis of hypercalcaemia includes drug induced (eg. lithium, thiazides) and hypercalcaemia of malignancy

Blackburn M, Diamond T. Primary hyperparathyroidism and familial hyperparathyroid syndromes. Aust Fam Physician. 2007 Dec;36(12):1029-33. PMID: 18075629.



Progression of parathyroid hyperplasia in secondary and tertiary hyperparathyroidism.



Imaging in SHPT and THPT: What the Surgeon Wants to Know ?

Diagnosis?

biological

Risk stratification?

Surgical Indications for Secondary Hyperparathyroidism

KDIGO guideline:

“consider parathyroidectomy in patients with stage 3-5D chronic kidney disease if severe hyperparathyroidism (parathyroid hormone [PTH] level > 800 pg/mL) does not respond to medical therapy”

- secondary hyperparathyroidism with hypercalcemia or hyperphosphatemia not controlled on medication alone
- osteoporosis (T-score > 2.5 standard deviations below mean)
- pathologic fractures
- ectopic soft tissue calcification (Surg Clin North Am 2009 Oct;89(5):1227full-text)
- calciophylaxis with raised levels of parathyroid hormone
- parathyroid hormone > 800 pg/mL
- myopathy
- severe vascular calcifications
- patient preference
- bone pain
- pruritus

Surgical Indications for Tertiary Hyperparathyroidism

Recommendations from European Best Practice Guidelines (EBPG) Expert Group on Renal Transplantation

- Main indication for parathyroidectomy in tertiary hyperparathyroidism is severity of accompanying hypercalcemia
- Consider observing patients with persistent tertiary hyperparathyroidism for 1 year after renal transplantation whenever possible to allow common post- transplantation imbalances to normalize via spontaneous involution (EBPG Level C)

- hypercalcemia
- persistent hypercalcemia
- severe osteopenia (low bone mineral density)
- symptomatic hyperparathyroidism
- bone and joint pain
- fatigue
- history of renal stone and/or nephrocalcinosis
- mental status changes
- pathologic bone fracture
- peptic ulcer disease
- renal phosphorus wasting (including hypophosphatemia)

Imaging in SHPT: What the Surgeon Wants to Know ?

Diagnosis?

biological

Risk stratification?

clinical

Surgical planning?

Surgical Strategy in SHPT and THPT

	total parathyroidectomy	total parathyroidectomy plus auto-transplantation	subtotal parathyroidectomy
Surgery Type	surgical removal of all 4 parathyroid glands	removal of all parathyroid glands autologous transplantation of 20-70 mg of glandular tissue	all but half of 1 parathyroid glands are removed
Advantage	reported to have lowest rate of recurrent secondary hyperparathyroidism	easily accessible parathyroid gland in case of recurrence	shorter period of postoperative hypoparathyroidism
Disadvantage	requires lifelong calcium and vitamin D replacement	longer operative time	need for neck re-exploration and associated risk of neurovascular injury or recurrence

Imaging in PHPT: What the Surgeon Wants to Know ?

Diagnosis?

biological

Risk stratification?

clinical

Surgical planning?

always an extensive surgery

Exclude an ectopy

Clinical Case

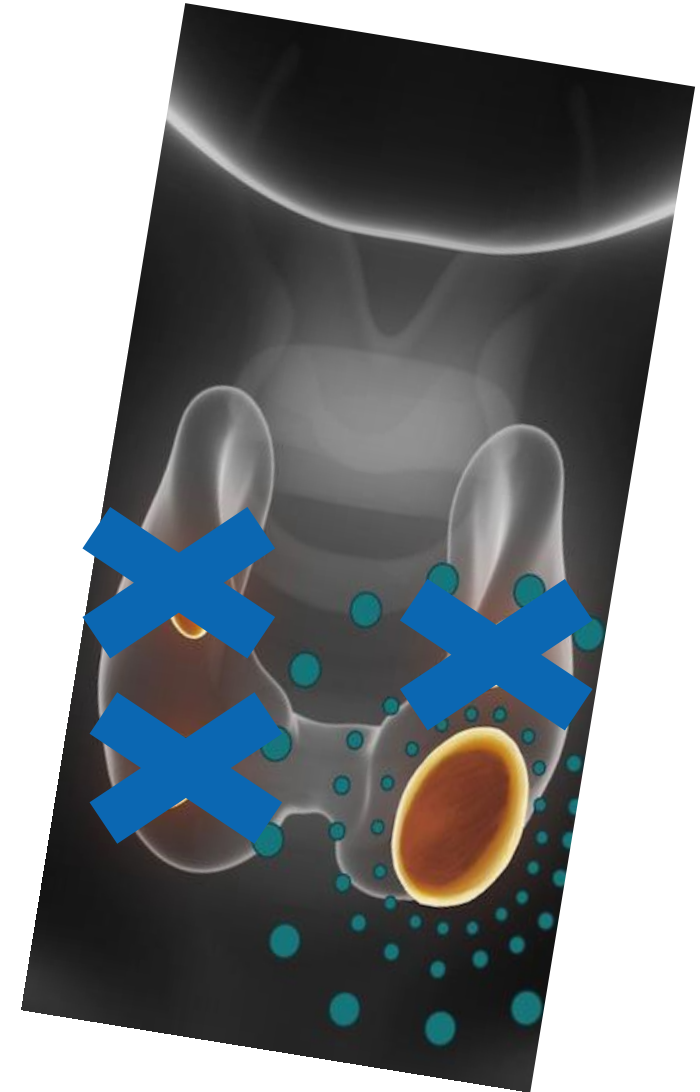
Mrs S, 44 y.o.

Initial nephropathy

PAX-2 mutation.

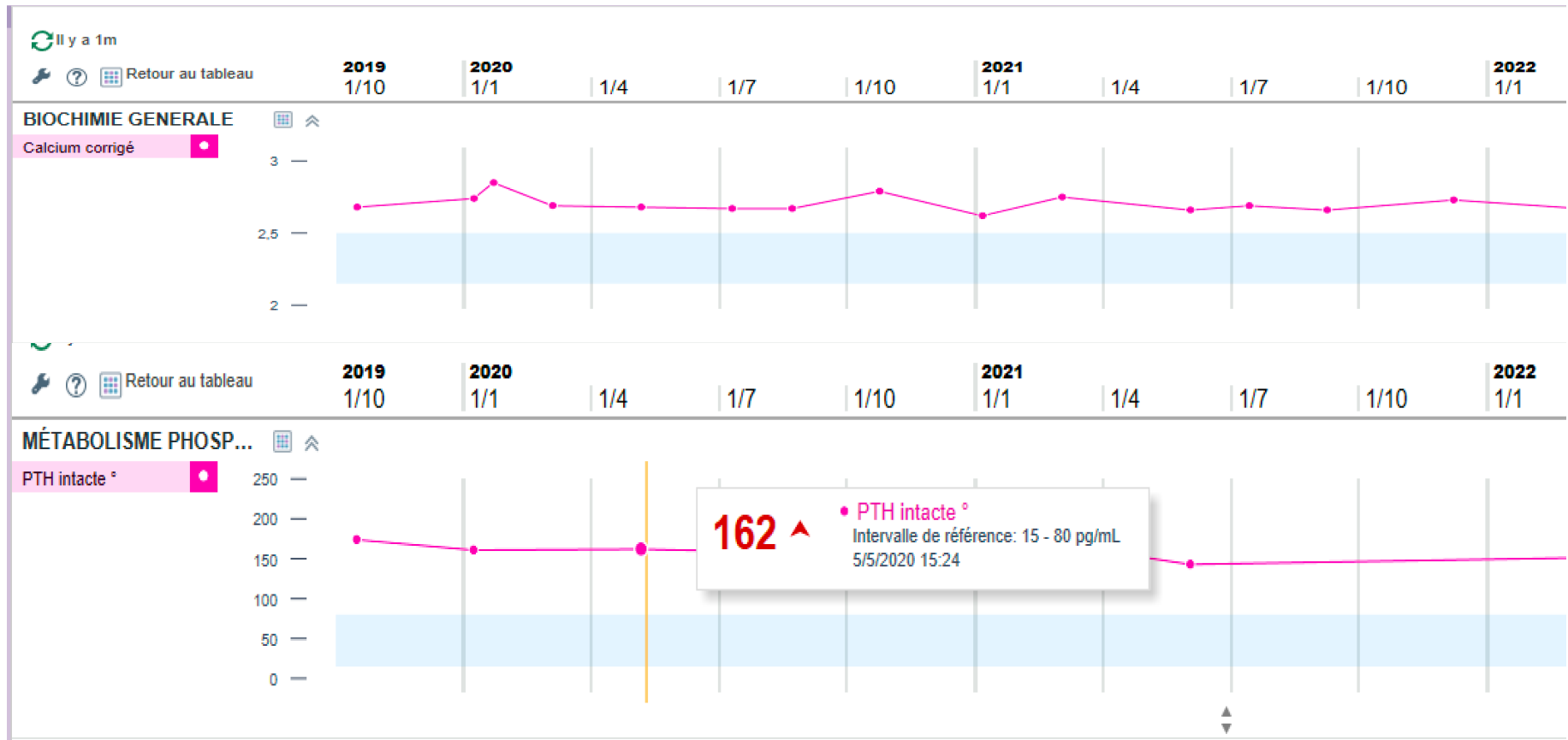
History of nephropathy

- 1992: discovery of a nephrotic syndrome in a context of pyelic bifidity.
- 1995: urgent hemodialysis for major hydrosodic overload.
- 15/04/1997: **1st renal transplant** from a deceased donor, complicated by a wall abscess and several acute rejections.
- 07/1998: hemodialysis restarting
- 8/1998: transplantectomy.
- 15/02/2012 **2° renal transplant** from a deceased donor
- **Parathyroid History**
- 12/1998: parathyroidectomy with negative preoperative imaging (US and NI)
- 3 glands were found
- 2021 Recurrence of THPT



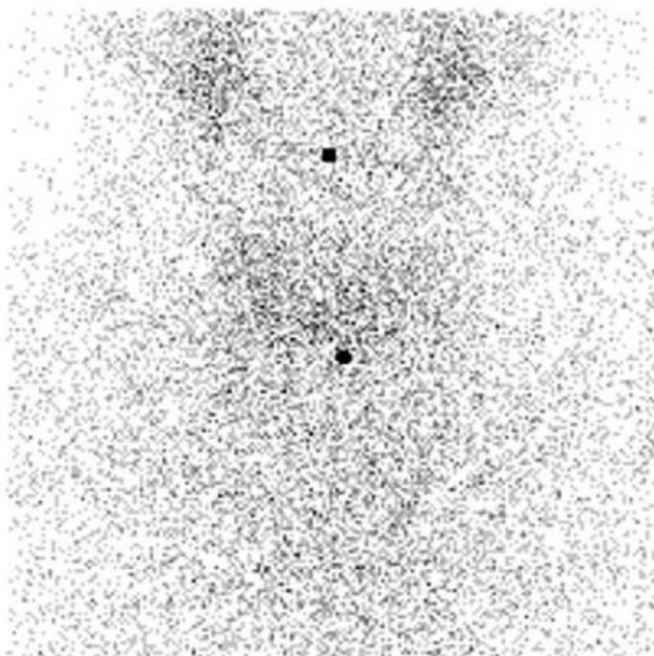
- **2021 Recurrence of THPT**
- **No tolerance to cinacalcet**
- **Complicated by**
 - bone and joint pain
 - fatigue
 - mental status changes

Lab results

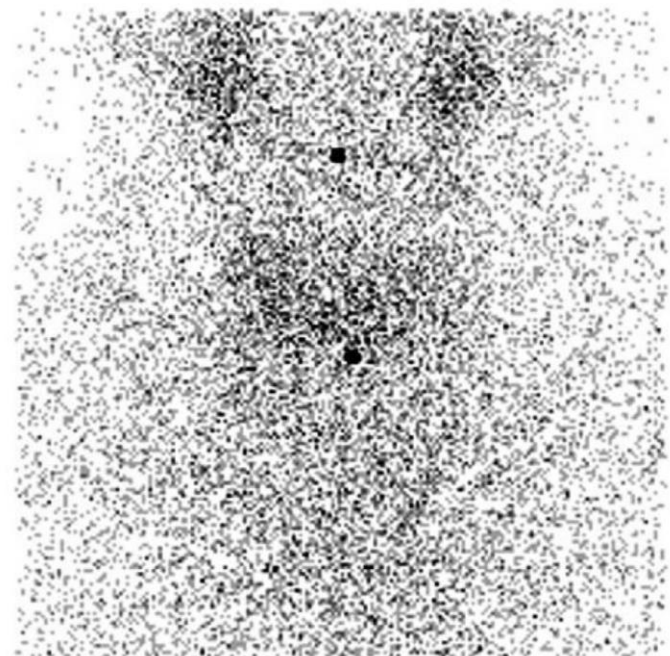


HPT Recurrence

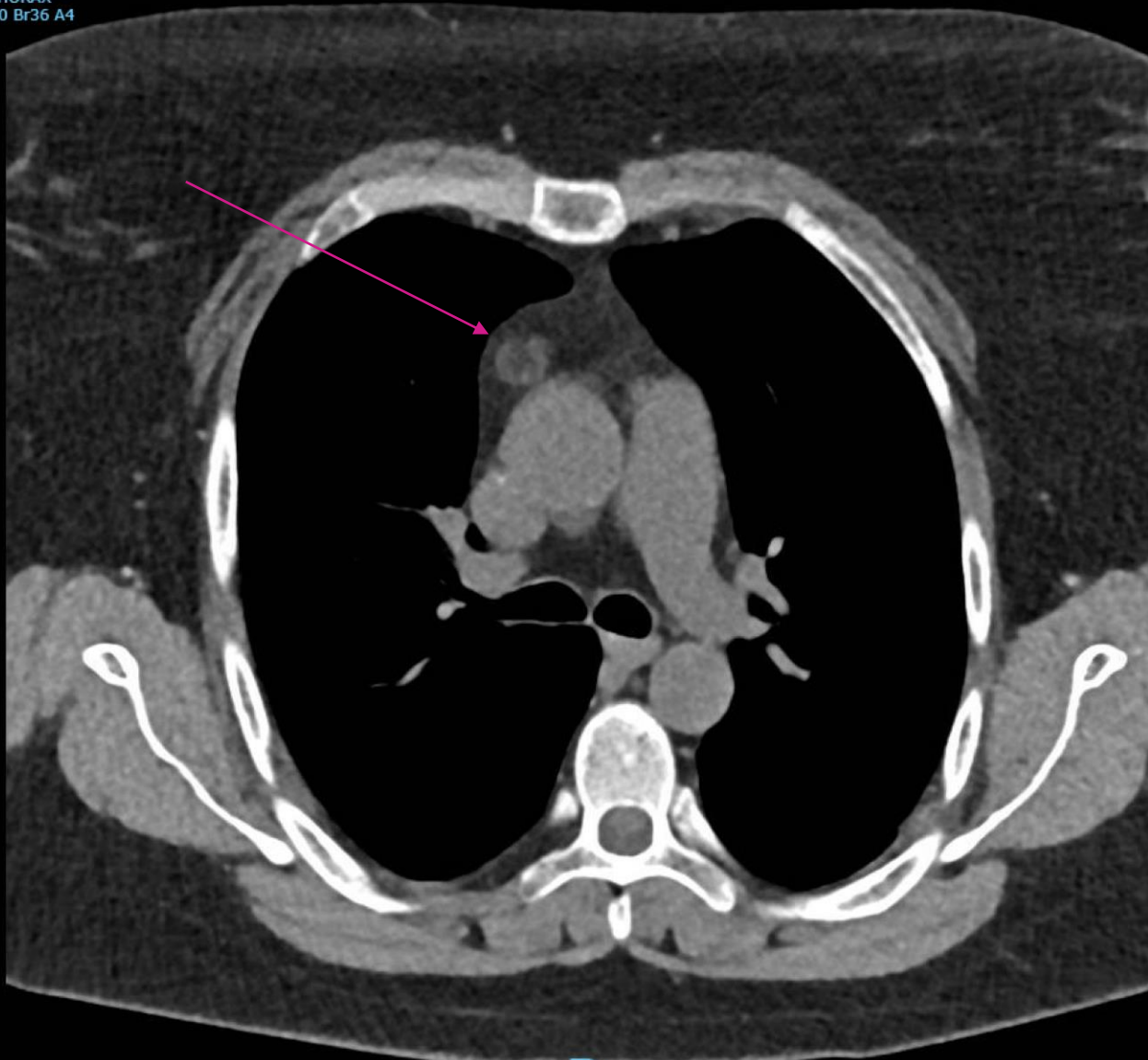
Preoperative Imaging



Tc99m

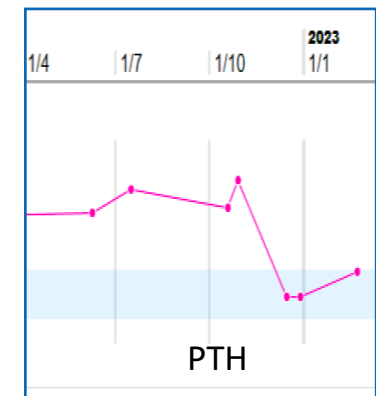
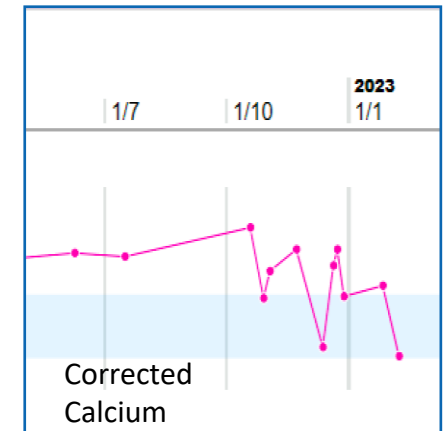
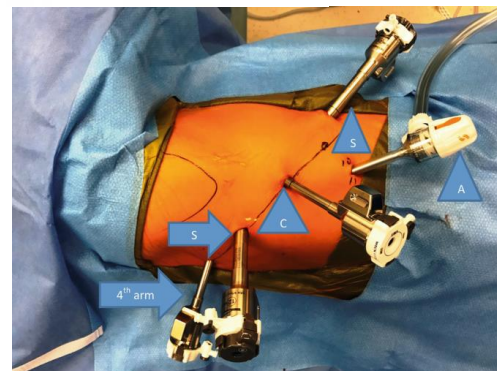
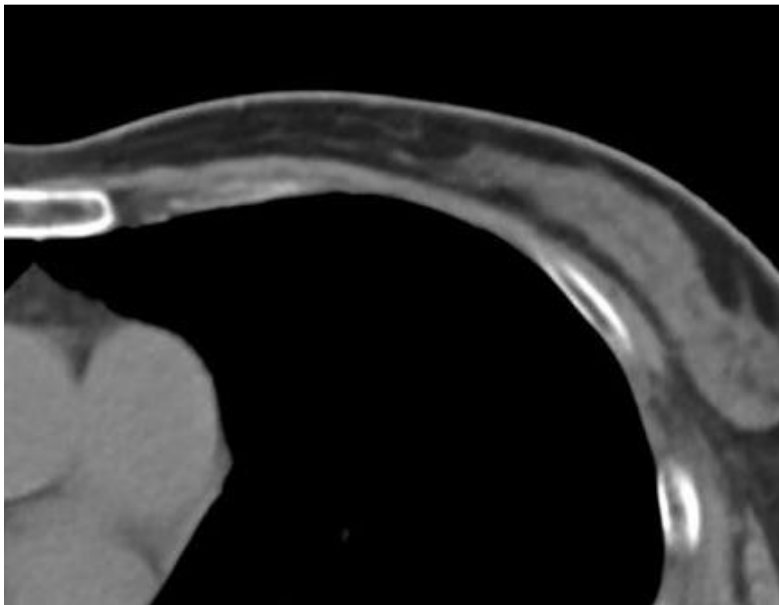


CT COU-THORAX
VOL 2,00 Br36 A4



12/12/2022 Da Vinci assisted surgery

- Total parathyroidectomy and reimplantation of a fragment in the forearm
- Recovered Day 5
- No side effects





**“The most important
preoperative localisation
challenge in HPT is to
locate the parathyroid
surgeon!”**

***John Doppman,
1975**