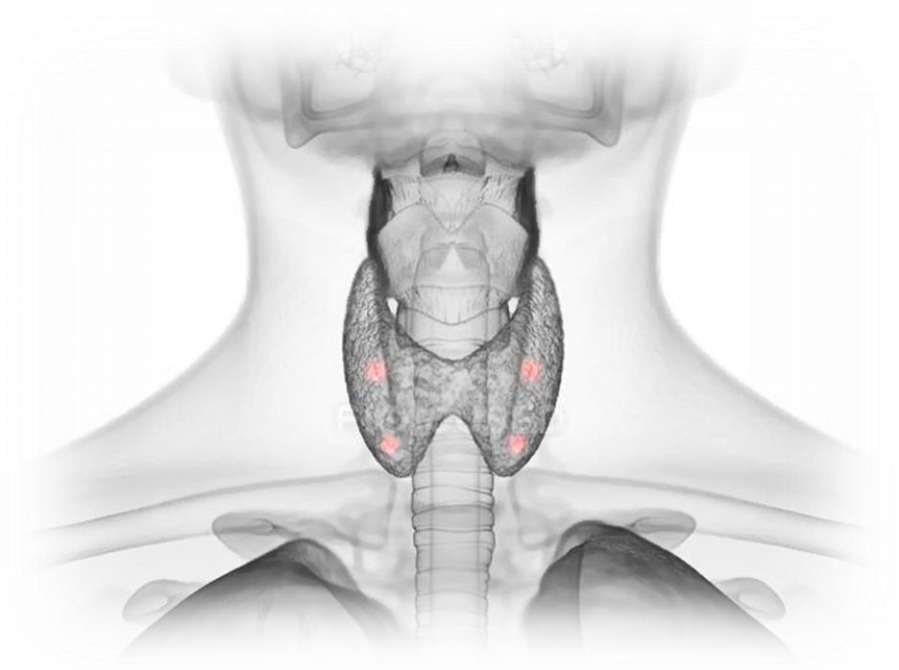
Universitat de Girona
Facultat de Medicina

Hospital Universitari de Girona
Doctor Josep Trueta



FINAL DEGREE PROJECT

University of Girona

November 2023

Surgical resolution of topographically diagnosed PHPT by 18F-choline PET/CT versus Tc99m sestaMIBI SPECT/TC: multicenter, randomized clinical trial.

Author: Inna Blokhina

Clinical tutor: Dr. Jordi Gironès Vilà

Methodological tutor: Dr. David Gallardo Giralt

I would like to express my gratitude to my clinical tutor, Dr. Jordi Gironès for all the help, patience and time dedicated throughout this final degree project.

Thanks to my methodological tutor, Dr. David Gallardo for all the help and methodological advice for the development of this project.

Finally, thanks to my family and friends for always being there, especially my mother Larisa for her support at all times.

It would not be the same without any of you.

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1. ABSTRACT

BACKGROUND:

Primary hyperthyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and elevated or inappropriately normal parathyroid hormone (PTH) levels. The most frequent case of autonomous PTH production is solitary parathyroid adenoma in 80% of cases.

Surgical treatment is the only definitive option for primary hyperparathyroidism. Once indicated, preoperative localization by nuclear medicine parathyroid imaging is a prerequisite before minimally invasive parathyroidectomy is performed.

Negativity and/or discrepancy in first-line tests (ultrasound and parathyroid Tc-99m MIBI SPECT/CT) requires repeat imaging tests or requesting second-line tests such as Choline PET/CT. In recent years, 18F-choline PET/CT has demonstrated great utility for the detection of single or multiglandular disease, superior to first-line imaging tests.

OBJECTIVE:

The main objective of the work are: to compare the surgical results in post-parathyroidectomy patients with 18F-Choline PET/CT localization imaging test versus Tc99m-MIBI SPECT/TC and to study the impact that all this has on the surgical management of the process, analyzing the benefit/cost ratio.

DESIGN AND SETTING:

This scientific study is a multicenter, open-label, parallel-group, prospective, randomized, controlled , interventional clinical trial, performed in University Hospital Doctor Josep Trueta and University Hospital Vall d'Hebron.

PARTICIPANTS:

The study includes patients diagnosed with symptomatic primary hyperparathyroidism, or asymptomatic patients who meet criteria to be candidates for parathyroidectomy.

METHODS:

120 patients will be recruited consecutively at the University Hospital Doctor Josep Trueta and the University Hospital Vall d'Hebron. They will be randomly divided into two groups, depending on the imaging test performed: A) In the first group Tc99m MIBI SPECT/, B) in the

second group PET/CT with 18F-Coline will be performed. Subsequently, patients in both groups will undergo selective parathyroidectomy and the surgical results in the two groups will be compared. Subjects will be followed up for 1 and 6 months.

KEYWORDS: primary hyperparathyroidism ; hypercalcemia; parathyroid hormone; 18F-Choline PET/CT ; Tc99m-MIBI SPECT/TC.

2. ABREVIATIONS:

PHPT	Primary hyperparathyroidism
PHT	Parathyroid hormone
US	Ultrasound
PET-CT	Positron Emission Tomography and Computed Tomography Scans.
MIP	Minimally invasive parathyroidectomy
FHH	Familial Hypocalciuric Hypercalcemia
NPHPT	Normocalcemic Hyperparathyroidism primary
NSHPT	Neonatal Severe Primary Hyperparathyroidism
DXA	Dual energy x-ray absorptiometry
MRI	Magnetic resonance imaging
PHTio	Intraoperative parathyroid hormone
PTX	Parathyroidectomy
VFA	Vertebral fracture assessment
TBS	Trabecular bone score
BMD	Bone mineral densitometry
SERMS	Selective estrogen receptor modulators
SPECT/TC	Single photon emission computed tomography/ computed tomography
MGD	Multiglandular disease
MIPR	Minimally invasive radioguided parathyroidectomy
Cr	Creatinine
RLN	Recurrent laryngeal nerve
CASR	Calcium-sensing receptor
VDR	Vitamin D receptor
OFC	Osteitis Fibrosa Cystica
HRpQCT	Hight-resolution peripheral quantitative computed tomography

3. INTRODUCCION:

3.1 PARATHYROID GLAND STRUCTURE AND FUNCTION:

The parathyroid glands are endocrine glands located behind the thyroid glands, but anterior to the rest of the neck. They are ovoid glands that weigh approximately 35 to 40 mg and measure between 3 and 8 mm (1).

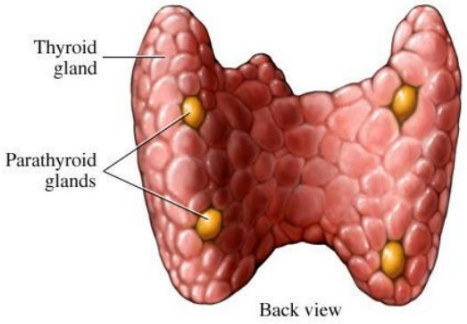


FIGURE 1. PARATHYROID GLAND ANATOMY. ADAPTED FROM (2).

Normally there are 4 parathyroid glands, 2 superior and 2 inferior:

- ***Superior parathyroid glands***: these glands are derived from the fourth pharyngeal pouch. They are located posterolateral to the superior pole of the thyroid, 1 cm above the junction of the recurrent laryngeal nerve (RLN) and the inferior thyroid artery. Classically they are found deep in the plane of the recurrent laryngeal nerve.
- ***Inferior parathyroid glands***: These glands are derived from the 3rd pharyngeal pouch. These glands are classically located near the inferior poles of the thyroid glands, 1 to 2 cm from the insertion of the inferior thyroid artery into the inferior pole of the thyroid. Their location is quite variable in comparison with the superior parathyroids, being either intrathyroidal or within the thymus or other mediastinal structures, and may even be found along the aortic arch (1,3).

Normally and most commonly there are 4 parathyroid glands, but in some cases there may be 5 or more glands, which are ***supernumerary glands***. They are usually quite small <5 mg, and their incidence ***is 13%.*** Also in rare circumstances less than 4 glands may be found.

Ectopic localization of parathyroid glands is quite common, up to ***16%.*** And the ectopic location includes: mediastinum, esophageal area and other locations in the lateral part of the neck (3) ***(Figure 2).***

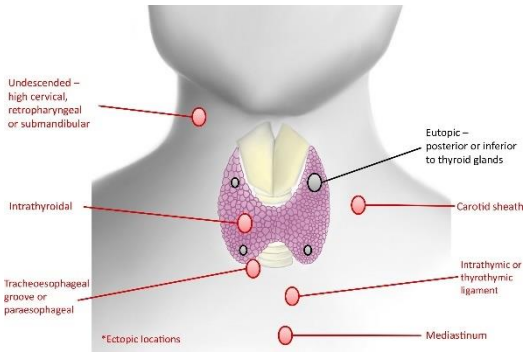


FIGURE 2. LOCATION OF ECTOPIC AND ECTOPIC PARATHYROID ADENOMAS. ADAPTED FROM (4).

Function: The primary function of the parathyroid glands is to regulate calcium and phosphorus homeostasis along with other hormones. When blood calcium levels decrease, a hormone called parathyroid hormone (PTH) is released (3). When secreted, PTH stimulates bone resorption, at the renal level it increases calcium tubular reabsorption and the synthesis of 1,25 dihydroxyvitamin D (1,25 OH 2D), which favors intestinal calcium absorption, but decreases renal tubular reabsorption of phosphorus and produces phosphaturia ***(Figure 3).***

The main regulators of PTH secretion are extracellular ionized calcium, whose increase activates the calcium-sensing receptor (CASR) and 1,25-dihydroxyvitamin D (1,25 (OH) 2D) which binds to the vitamin D receptor (VDR) and suppresses PTH expression. Other regulators that suppress PTH expression include serum phosphate and fibroblast growth factor 23 (FGF23) bound to fibroblast growth factor receptor 1 (FGFR1) (5,6).

Another existing molecule, called PTH-related proteins (PrPTH), has a structural similarity to PTH secreted by the parathyroid glands. PrPTH is produced by different tissues and, particularly, by neoplastic cells, being the mechanism responsible for most cases of tumor hypercalcemia. PTH and PrPTH bind to the same receptor, known as PTH1R, and activate it, however, the biological responses may be different (5).

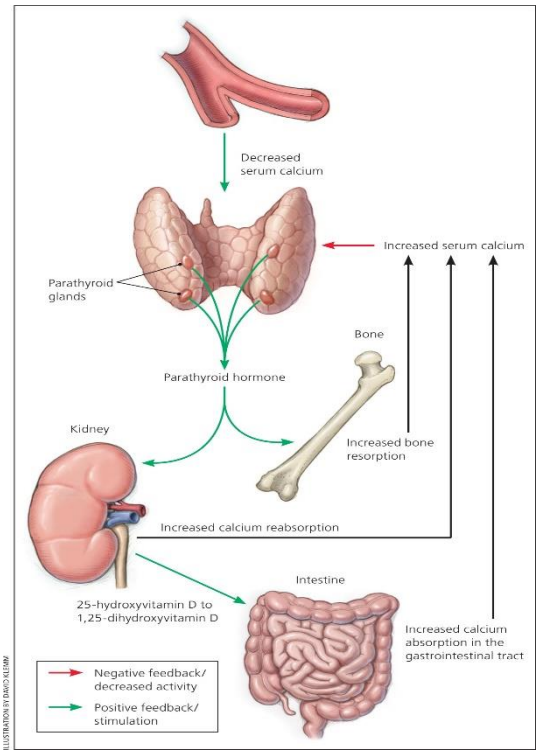


FIGURE 3 . CONTROL OF MINERAL METABOLISM BY PARATHYROID HORMONE (PTH). ADAPTED FROM (7).

3.2 DEFINITION OF PRIMARY HYPERPARATHYROIDISM.

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder after diabetes and thyroid disease, and is the most common cause of hypercalcemia. It is characterized by elevated serum calcium levels and elevated or inappropriately normal levels of parathyroid hormone which, acting on its target organs (bone and kidney), increases calcium concentrations in the extracellular space ***(Figure 4)*** (8,9). This increase in PTH secretion is autonomous and is not inhibited by the activation of CaSRs in the parathyroids (5).

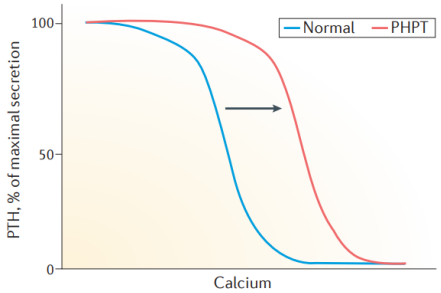


FIGURE 4. RELATIONSHIP BETWEEN SERUM LEVELS OF CALCIUM AND PTH. ADAPTED FROM (8).
RED LINE: PATIENTS WITH PRIMARY HYPERPARATHYROIDISM, BLUE LINE: NORMAL INDIVIDUALS
PHPT RESULTS IN A SHIFT OF THE CURVE TO THE RIGHT. INCREASED LEVELS OF CALCIUM ARE NEEDED TO SUPPRESS PTH LEVELS IN PHPT.

3.3 EPIDEMIOLOGY.

The epidemiology of PHPT has changed substantially since the initial reports demonstrating classical complications in severe disease. The incidence increased in 1970 after the introduction of ***automated chemistry panels*** that detected hypercalcemia to be a prevalent condition (6%) in asymptomatic adults (10,11).

The overall ***prevalence*** of PHPT from 2007 to 2018 was 0.84% and was higher in women (1.18%) than men (0.48%), but an increased prevalence was also appreciated, with an estimated overall prevalence of 1.02% (10). In the United States as of 2010 the overall age-adjusted prevalence rate was of 233 per 100,000 in women and 85 per 100,000 in men, with the highest overall prevalence in white and black women ages 70 to 79, with rates of 1409, and 1110 per 100,000 respectively (12,13).

Incidence estimates of PHPT range from ~0.4 to 82 cases per 100,000 inhabitants (5,14,15) . Women are more affected than men in a 3:1 ratio. The incidence increases in perimenopausal or postmenopausal women, it also increases in women ≥50 years, but not in men (6,12).
A recent Spanish study estimates an incidence of ***9.95 cases/100,000 per year*** in our environment (5,8,16).

3.4 ETIOLOGY

PHPT is caused by a solitary parathyroid ***adenoma in 80%*** of cases, while hyperplasia of four-gland accounts for 10–15%, multiple adenomas for 5% and parathyroid cancer for <1% of cases (8,17) .
Most cases of PPH are sporadic (95%), without an identifiable etiological factor or family history or involvement of other endocrine glands. However, risk factors such as age, female sex, chronic use of lithium or exposure to ionizing radiation have been identified (18,19).
The incidence of hereditary forms of PHPT does not exceed 10% of the population with PHPT. The genetic form of PHPT may be isolated to the parathyroid glands or may be part of a multiglandular endocrine syndrome . Some mutations affecting oncogenes or tumor suppressor genes have been described (11,19) ***(ANNEX 1).***

3.5 CLINICAL PHENOTYPES OF PHPT:

The clinical presentation of PHPT depends on the severity and chronicity of the disease.

There are 3 clinical phenotypes of PHPT:

1. ***Symptomatic*** or classical PHPT– multisystem disorder characterized skeletal and/or renal complications. Renal involvement predominates with asymptomatic nephrolithiasis (5-20%) accompanied by significant hypercalciuria in approximately 40% of cases, and other symptoms secondary to hypercalcemia (13,18).
2. ***Asymptomatic PHPT*** (>80%) – with typical biochemical abnormalities but without evident symptoms or signs.

a) with target organ involvement (detected by additional tests),

b) without target organ involvement.

The diagnosis is usually accidental, due to the detection of hypercalcemia in a routine analyses (albumin-adjusted serum calcium < 1 mg/dl above upper limit of normal) (13). These patients present trabecular and cortical osteoporosis with greater frequency (15%) and, therefore, greater risk of pathological fractures of the vertebral column and in distal sections of long bones. Asymptomatic renal lithiasis is also detected in up to 7% from the patients (18).

3. ***Normocalcemic PHPT*** (with or without skeletal or renal complications).

It has a prevalence of ***0.4-3.1%*** . NPHPT is characterized by persistently normal albumin-adjusted total and ionized serum calcium levels <9 mg/dl , normal 25 (OH)D levels and 24-hour urinary calcium excretion , accompanied by elevated levels of PTH on at least two consecutive measurements, over a 3-month to 6-month period (20). For its correct diagnosis ,all causes of secondary hyperparathyroidism (including chronic kidney disease stage ≥ 3 , vitamin D deficiency, calcium malabsorption, use of bisphosphonates or denosumab) should be ruled out. The clinical features of NPHPT can be similar to the ones described in PHPT (skeletal, renal complications, and nonclassical manifestations). (5,13,18)

3.6 CLINICAL MANIFESTATIONS AND COMPLICATIONS:

The form of clinical presentation has changed in recent decades. Previously, the diagnosis of PHPT was made when there were severe complications of the disease, but currently, through biochemical blood analyzes that include serum calcium levels, which allows an earlier diagnosis in its asymptomatic form in 80% (10,11).

We can differentiate the symptoms directly related to increase in PTH such as renal involvement and bone resorption, while the symptoms attributable to hypercalcemia would include more nonspecific symptoms such as weakness, fatigue, depression, anorexia and others (21). However, the specific manifestations of PHPT are nephrolithiasis and osteitis fibrosa cystica, which characterize the classic phenotype of the disease (5).

3.6.1 CLASSICAL MANIFESTATIONS:

- *Renal:*

Hypercalciuria is a known risk factor for the formation of ***kidney stones***. Calcium nephrolithiasis, consisting of calcium oxalate or calcium phosphate stones, with a prevalence that ranges between 5% and 55%. Other renal symptoms include polyuria, nephrocalcinosis, deterioration of renal function (19).

- *Skeletal:*

Skeletal involvement is a hallmark feature of PHPT, even in its mild forms. ***Osteoporosis*** is present in 50-65% of patients with PHPT, other conditions such as chondrocalcinosis, pseudogout, synovitis, sacroiliitis and fractures have also been found (13).

In severe forms of PHPT, bone pain and classic but rare radiological features of ***osteitis fibrosa cystica (OFC)*** can be found together with brown tumors, which account for 2%-5%.

The other radiological signs of PHPT what we can find include a "salt and pepper skull" pattern, gradual involvement of the distal clavicle, subperiosteal bone resorption, and cysts in the long bones, pelvis, and distal phalanges(17).

These alterations are explained by bone resorption and a decrease in bone mineral density (BMD), mainly at the cortical site (1/3 of the distal radius) and less at the trabecular site (lumbar spine) assessed by dual energy X-ray absorptiometry DXA (13).

However, assessment of bone structure by two other modalities, HRpQCT and trabecular bone score (TBS), have shown alterations in bone microstructure in both the trabecular and cortical compartments, and both indices correlate with the risk of fracture independent of BMD values (13,17).

3.6.2 NON-CLASSICAL MANIFESTATIONS:

- Cardiovascular disease:

Both , hypercalcemia and parathyroid hormone (PTH) could affect the CV system. PTH causes vasodilation, affects blood pressure, has indirect chronotropic and ionotropic effects on the

heart, and may act as a "hypertrophic factor" on cardiomyocytes. On the other hand, calcium also affects cardiac contractility and vasodilation (24). Cardiovascular symptoms due to these two conditions include cardiac arrythmias, hypertension, left ventricular hypertrophy, vascular stiffness, atherosclerosis, ventricular premature beats, shortening of the QT-interval and can also cause the formation of cardiovascular risk such as hyperuricemia, hyperlipidemia or insulin resistance (13).

- Gastrointestinal:

Gastrointestinal (GI) manifestations have been described in patients with symptomatic PHPT, including abdominal pain, anorexia, constipation, nausea, vomiting, peptic ulceration, cholelithiasis, and pancreatitis (22).
Patients with celiac disease are at increased risk of developing PHPT, possibly due to chronic vitamin D deficiency (8).

- Neuromuscular:

Neuromuscular involvement, with a wide spectrum of manifestations, ranges from approximately ***13% to 93%*** in patients with PHPT (20).
Manifestations comprise a spectrum of symptoms and conditions including muscle weakness, fatigue, postural instability, cramps, paresthesia and proximal muscle atrophy (particularly in the lower extremities) , some of these manifestations may be seen in non-PTH-mediated hypercalcemic states (13).
Joint involvement has also been described in PHPT, in particularly chondrocalcinosis, ranging from approximately 9 to 40%. Other joint manifestations: joint pain, gout, chondrocalcinosis, erosive arthritis, pseudogout, spondyloarthropathy (24) .

- Neurobehavioral

Neuropsychiatric and cognitive symptoms of PHPT include depression, anxiety, irritability, suicidal ideation, altered mental status, sensory cloudiness, psychosis, delirium, hallucinations, personality changes, sleep disturbances, loss of initiative and concentration, cognitive impairment and dementia (13,24).
Most of them are described only in severe PHPT. Its prevalence ranges between 3% and 50% (22).

- Ocular:

Ocular involvement manifests as ***band keratopathy,*** which is characterized by the precipitation of calcium and phosphate crystals in the cornea (21).

- Other manifestations:

These patients are also at high risk of developing ***glucose intolerance*** (40-80% of cases), or even true diabetes mellitus (7-16% of cases).

The pathophysiology of these alterations seems to be due to a state of hyperinsulinism and peripheral insensitivity to insulin, a situation that has been attributed to both, hypercalcemia and increased PTH levels, due to direct stimulation of pancreatic β cells (21).

3.7 DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF PHPT:

The biochemical profile of PHPT is characterized by ***hypercalcemia*** (variable magnitude) and ***elevated or inappropriately normal PTH concentrations*** . Alterations in total calcium concentrations >10,5 mg/dl corrected for albumin *(corrected calcium (mg/dl) = (4.0 − serum albumin [g/dl]) × 0.8 + Total Ca (mg/dl))* are usually detected in asymptomatic patients on a control blood analysis . Because of the alteration, measurement of urinary calcium excretion in 24-hour would be made , if ***calciuria >200-300 mg/day and urine Ca/Cr >0.02*** are suggestive of PHPT (5). The diagnosis is confirmed by the presence of an elevated or inappropriately high level of intact PTH twice at least 2 weeks apart (utilizing either a second or third generation assay) (13,17,20).

*In view of these analytical determinations, a differential diagnosis must be made, which includes **(ANNEX 2):***

- *Familial hypocalciuric hypercalcemia (FHH),*
- *Use of thiazide diuretics and/or lithium,*
- *Ectopic secretion of PTH ,*
- *Tertiary hyperparathyroidism*.

a) PHPT caused by ***FHH***, a genetically heterogeneous disease due to inactivating mutations of the calcium-sensing receptor (CaSR in both the parathyroid gland and kidney), therefore we have hypercalcemia with PTH in the high range of normal or minimally elevated (18).

In this clinical presentation we must ensure correct calcium intake and optimal levels of 25(OH)D3, then measure urinary calcium excretion in urine in 24 hours (which is usually ***<100mg/day).*** In FHH, the ratio between urinary calcium clearance and creatinine is usually ***< 0.01***, whereas in PHPT it is > 0.02. However, about 40% of patients with either disease have

values between 0.01 and 0.02. Additionally, up to 20% of PHPT patients have Ca/Cr ratios < 0.01 and up to 10% of FHH patients have ratios > 0.02.

FHH is a benign disease, usually without organ damage and cases of renal stones are rare. Correct diagnosis is important, as parathyroidectomy does not cure hypercalcemia and is therefore contraindicated.

Genetic testing should be considered in patients: < 30 years of age, with multiglandular disease, with a family history of hypercalcemia and/or syndromes associated with PHPT (13,18,20,25).

b) Both ***thiazides and lithium*** increase renal calcium reabsorption and may be associated with hypercalcemia and increased serum PTH concentration, which may persist after withdrawal of the medication. They should be discontinued 3 months before repeating the laboratory profile and confirming a diagnosis of PHPT (13,17).

c) The existence of autonomous PTH secretion should be ruled out in any situation of hypercalcemia, symptomatic or not.

We must take into account that in ambulatory patients the most common cause of hypercalcemia is PHPT, while in hospitalized patients it is due to neoplasms.
Within ***tumor hypercalcemia***, a significant number of cases (80%) are due to the production by the tumor tissue of PrPTH (humoral tumor hypercalcemia).
Epidermoid carcinomas of various locations and carcinomas of the breast and kidney are the main ones implicated in humoral tumor hypercalcemia.
Other causes of tumor hypercalcemia are due to local osteolysis (bone metastases) or to increased synthesis of 1,25(OH)2D in neoplastic tissue, which occurs in some lymphomas (5).
All of these are characterized by suppression of PTH and are therefore easily distinguished from HPTP. In this case we would have elevated calcium together with low PTH (<20 pg/mL) and elevated PTHrP (5,18).

d) ***Tertiary hyperparathyroidism*** is characterized by excessive secretion of PTH in patients with long-standing secondary hyperparathyroidism (caused, for example, by uncontrolled renal failure or malabsorption syndromes such as active celiac disease, extensive intestinal resection, or gastric bypass surgery), leading to hypercalcemia. It is usually identified by the clinical context (8).

Once a differential diagnosis has been made and PHTP is confirmed, patients should be evaluated with the following tests ***(Table 1***):

TABLE 1 : EVALUATION OF PATIENTS WITH PRIMARY HYPERPARATHYROIDISM (18,20).

Biochemistry	○ Phosphorus (hypophosphatemia 30% of cases) ○ Intact PTH, ○ 25(OH)D ○ Creatinine ○ Chlorine: high range of normal (chlorine/phosphate ratio in blood greater than 33 presents sensitivity >90% for diagnosis) ○ The presence of elevated serum levels of total alkaline phosphatase (>70 UI/L) gives more evidence of PHPT. ○ Ionized calcium if PHPT is considered normocalcemic
Skeletal	○ Three-site dual-energy X-ray absorptiometry (DXA) (lumbar spine, hip, distal 1/3 radius) ○ Imaging for vertebral fractures (vertebral fracture assessment [VFA] or vertebral X-rays) ○ Trabecular bone score (TBS) if available(13,18)
Renal	○ Estimated glomerular filtration rate (eGFR) or, preferably, creatinine clearance, 24-hour urinary calcium and for biochemical risk factors for stones ○ Imaging for nephrolithiasis/nephrocalcinosis
Genetic	○ Genetic evaluation should be considered for patients <30 years old, those with multiglandular disease by history or imaging, and/or those with a family history of hypercalcemia and/or syndromic disease.

3.8 PRE-OPERATIVE IMAGING:

The study to locate adenomas are radiological examinations that can be invasive and non-invasive, and are only performed when we have the biochemical diagnosis of PHPT, they are performed for surgical planning for parathyroidectomy (20,26,27).

With successful preoperative imaging, selective parathyroidectomy achieves high cure rates in the hands of experienced surgeons. Among the advantages, selective localization allows for

shorter surgical intervention time, less scarring, less risk to surrounding structures, and reduced hospital costs (20).

3.8.1 FIRST-LINE IMAGING TESTS:

- **ULTRASONOGRAPHY:**

On ultrasound, parathyroid adenomas appear as well-defined round or oval hypoechoic structures. Doppler imaging can identify the parathyroid feeding vessel and distinguish the parathyroid from the lymph node (28).

Advantages: it is a low-cost technique ,available ,without radiation exposure and also allows the evaluation of the thyroid gland (27). US is useful in the detection of parathyroid adenomas located near the thyroid gland or the upper cervical portion of the thymus (29).

Limitations : operator-dependent results ,low sensitivity for ectopic parathyroid tissue, small parathyroid adenomas, intrathyroidal masses not visible by ultrasound. Patient factors also play a role such as elevated body mass index ,kyphosis or large gland. False-positive results may also occur due to enlarged thyroid nodules and lymph nodes (29).

There is much variability in the literature regarding the diagnostic sensitivity of ultrasound, which ranges from 29- 91.7%, specificity between 28.5-99% and accuracy between 32-82% (9) .But the sensitivity of ultrasound decreases in patients with previous cervical surgery and is between 51-80% (30) .

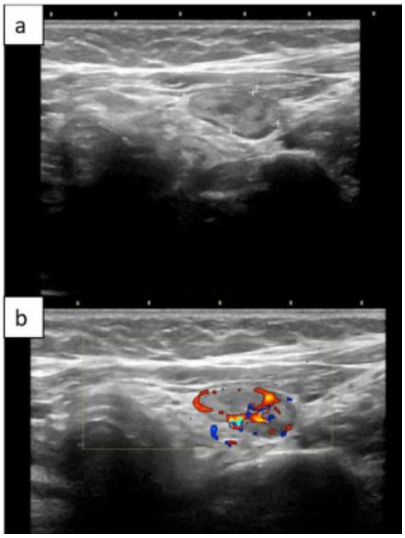


FIGURE 5. LEFT INFERIOR PARATHYROID ADENOMA OBSERVED BY ULTRASOUND. ADAPTED FROM (9).
ULTRASOUND (A) AND DOPPLER (B), IN WHICH A TYPICAL EXAMPLE OF PARATHYROID ADENOMA CAN BE SEEN AS A WELL-DEFINED, HYPOECHOIC AND HYPERVASCULAR MASS IN DOPPLER MODE.

- **99MTC-SESTAMIBI SCINTIGRAPHY**

99mTc-sestamibi (sesta-methoxyisobutylisonitrile) is a lipophilic cationic radiotracer and its uptake depends on plasma and mitochondrial membrane potentials. Because parathyroid tissue has a large number of mitochondria in oxyphilic cells, the uptake of 99mTc-sestamibi is avid and clearance is slow, unlike thyroid tissue is faster (9,28).

Advantages : it is easy to perform, widely available, low cost, allows to detect ectopic lesions more easily and provides functional information in relation to PHPT.

Disadvantages: poor anatomical delimitation and lower spatial resolution (26). Detection of some adenomas may be interfered with by surrounding structures, such as the mediastinum or multinodular thyroid, or by the presence of necrotic or cystic areas within the gland (30). Thyroid nodules, inflammatory thyroiditis, malignancy, brown fat and lymphadenopathy may cause false-positive results. False negative results occur in small sized lesions, multiglandular or ectopic disease, parathyroid hyperplasia (rapid parathyroid washout), few oxyphil cells within an adenoma (4).

Sensitivity decreases (30%-45%) in patients with parathyroid hyperplasia or multiple adenomas. In addition, the detection rate may be limited in cases with low PTH levels or normocalcemic PHPT (29).

Its sensitivity of 49.1-91%, specificity of 33.3-98%, accuracy of 64-76.7% for the detection of parathyroid adenoma, and 44%-78% for multiglandular disease (9,30) .

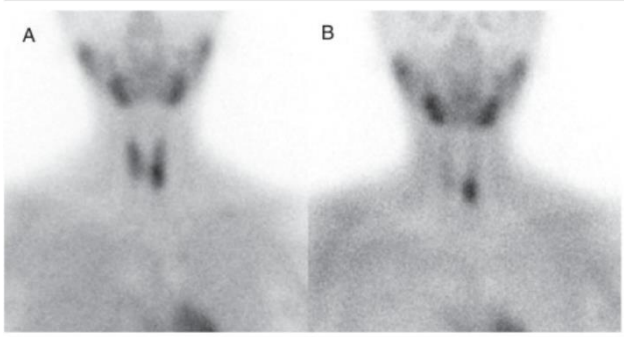


FIGURE 6. DUAL-PHASE PLANAR SCINTIGRAPHY WITH 99MTC-MIBI. ADAPTED FROM (30).
A)99MTC-MIBI SCINTIGRAPHY IN THE EARLY PHASE,
B) PLANAR SCINTIGRAPHY IN THE LATE PHASE

- **SPECT/CT**

SPECT/CT imaging can provide accurate localization of pathological supernumerary glands, it also has a positive impact on the location of ectopic adenomas, being useful in surgical management, especially in adenomas with atypical locations, such as the retrotracheal and

retroesophageal spaces (which would be hidden on planar images) (28). The CT component of SPECT/CT helps to differentiate adenoma from other causes, including lymphadenopathy (4).
Advantages: reduced radiological exposure, as well as the time and cost of the examination (30).
Its sensitivity of 64%-90.6% and a positive predictive value of 83.5%-95% (18).

COMBINATION OF NECK ULTRASOUND AND TC-99M SESTAMIBI COMBINED WITH SPECT/TC.

The usual first-line imaging techniques to reach the diagnosis of PHPT are US and scintigraphy with 99mTc-MIBI combined with SPECT/CT (31).

The combination of 99mTc-sestamibi and SPECT/CT has been described to improve sensitivity, not only providing anatomical information but also differentiating parathyroid lesions from other sources of 99mTc-sestamibi uptake, including thyroid nodules and lymph nodes. Its allows detection of parathyroid glands located in the retroesophageal or posterior retropharyngeal spaces, which would be hidden on plain images (28).

Disadvantages: radiation, longer acquisition ,cannot assess thyroid, reduced detection of oxyphil-poor adenomas and multiglandular disease.

There is much variability in the literature regarding the diagnostic sensitivity of the combination of these two techniques, which ranges from 48.3-96%, specificity between 86-100% and precision between 67-83% (9) . However, its sensitivity is unsatisfactory in specific situations such as multiglandular disease (31%) and 78% in patients with uniglandular disease (29). Sometimes, with these two techniques, the etiological diagnosis of PHPT is not reached and it is necessary to resort to other second-line techniques with lower sensitivity, or PEC/CT choline as described in the following (31).

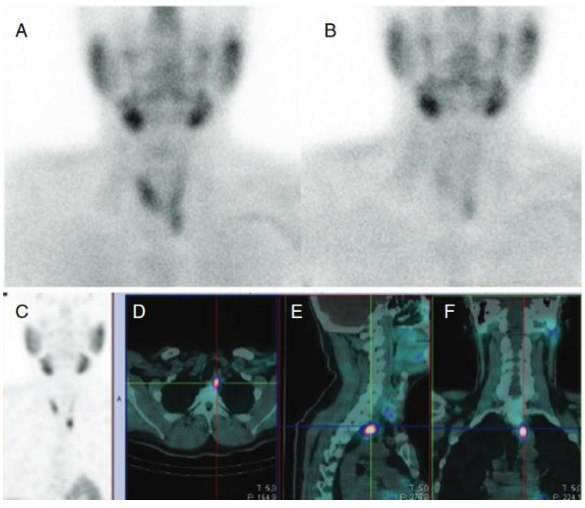


FIGURE 7. COMBINATION OF 99MTC-MIBI AND SPECT/CT. ADAPTED FROM (30).

A: EARLY PHASE; B: LATE PHASE 99MTC-MIBI, OBSERVING A PATHOLOGICAL DEPOSIT OF THE TRACER IN THE LOWER POLE OF THE LEFT THYROID LOBE, WHICH PERSISTS IN THE LATE IMAGE.

EARLY SPECT/CT: MAXIMUM INTENSITY PROJECTION (C) AND AXIAL (D), SAGITTAL (E) AND CORONAL (F) SECTIONS, WHERE A PATHOLOGICAL DEPOSIT OF THE TRACER IS SEEN IN THE LEFT RETROTRACHEAL LOCATION.

3.8.2 OTHER IMAGING TESTS:

In cases of negative first line tests, ectopic location of the adenoma or previous surgeries, other radiological localization techniques can be used.

- **POSITRON EMISSION TOMOGTAPHY (PET)**

PET/CT SCANS WITH 11C-METHIONINE:

11C-methionine accumulates in abnormal parathyroid gland tissue, making it a promising radiopharmaceutical in parathyroid imaging.
Sensitivity was lower in detecting multiglandular disease, and higher in single parathyroid adenoma. Another limitation is the short half-life of 11C, leading to limited availability of the 11C-methionine marker, its high cost, and a substantial workload for its preparation (29).
PET/CT with 11C-methionine presents sensitivity, specificity and precision of 75%, 50% and 71%, respectively (9).

PET/CT CHOLINE:

It is considered ***a first-line alternative imaging method*** in cases of patients with inconclusive or negative results in standard imaging techniques (29,32).
The usefulness of 18F-choline PET/CT in PHPT emerged as an incidental finding in patients with prostate cancer . There are some preliminary studies on the use of 18F-choline PET/CT in patients with PPTH and without prostate cancer that claim that this technique can locate parathyroid adenomas (9).
18F-fluoromethylcholine uptake is increased by choline kinase upregulation, and phospholipid-dependent choline kinase is upregulated where PTH is oversecreted. Based on this, radiolabeled choline PET can be used to detect parathyroid lesions (29). In addiction it has a longer half-life compared to 11-methionine.

Advantages of 18F-choline PET/CT include shorter imaging time, lower radiation exposure compared to 99Tc-MIBI, higher spatial resolution (allows for better identification of small glands, starting at 4mm), the ability to detect multiglandular pathology or parathyroid hyperplasia, as well as adenomas.

Disadvantages include high cost, low availability and exposure to radiation, since it is combined with CT. Uptake by inflammatory lymph nodes and thyroid nodules, malignant

diseases such as differentiated thyroid carcinoma and/or metastatic lymph nodes as a potential source of false positive results (9,32,33).

Numerous publications that state that this technique has a sensitivity of 81-95.8%, a specificity of 12.5-99.7% and an accuracy of 56.8-95.3 (9).

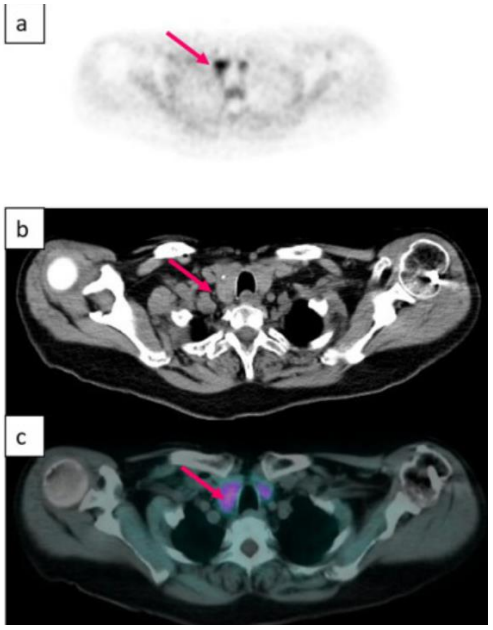


FIGURE 8. RIGHT INFERIOR PARATHYROID ADENOMA DETECTED BY 18F-CHOLINE PET/CT. ADAPTED FROM (9).

A) 18F-CHOLINE PET,
B) CT WITHOUT INTRAVENOUS CONTRAST,
C) 18F-CHOLINE PET/CT.

- **COMPUTERIZED TOMOGRAPHY IN FOUR DIMENSIONS (4D-CT)**

A 4D-CT exam consists of pre-contrast, post-contrast, and delayed phases. On precontract images, parathyroid adenomas have attenuation similar to that of the surrounding muscles and are distinguished from the dense, iodine-rich thyroid gland. On early and late postcontrast images, parathyroid adenomas are seen as hypervascular tissue with variable enhancement and rapid clearing. It has exceptionally high sensitivity and specificity for locating ectopic glands, as well as a negative predictive value of 93.3% (28).

Advantages : 4D-CT had a sensitivity of 88%, higher than that of 99mTc-sestamibi (54%) or ultrasound (21%) in patients undergoing previous neck surgery. In addition, 4D-CT may be useful in patients with multiglandular disease or ectopic glands. Parathyroid adenomas can be diagnosed with a sensitivity ranging from 55 - 89.7%, a specificity of 50 - 94% and a diagnostic accuracy of 86 - 87.1% according to different studies (9).

Disadvantage: high radiation dose received by the patient ,allergy to iodinated contrast, artifacts in the lower neck due to the clavicles and shoulders, as well as motion artifacts due to swallowing, speaking, and coughing during imaging (9). A high rate of false positives, low

ability to detect small adenomas, difficult interpretation, and low availability are also limitations of this modality (29).

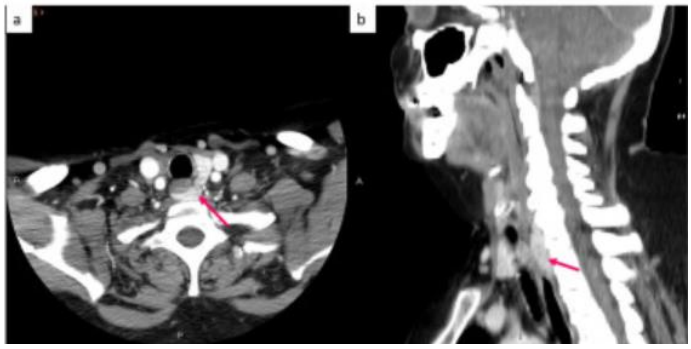


FIGURE 9. CONTRAST-ENHANCED CT OBTAINED 35 S AFTER CONTRAST ADMINISTRATION. ADAPTED FROM (9).

A) AXIAL SECTION,
B) SAGITTAL SECTION, SHOWING A RETROTRACHEAL PARATHYROID ADENOMA.

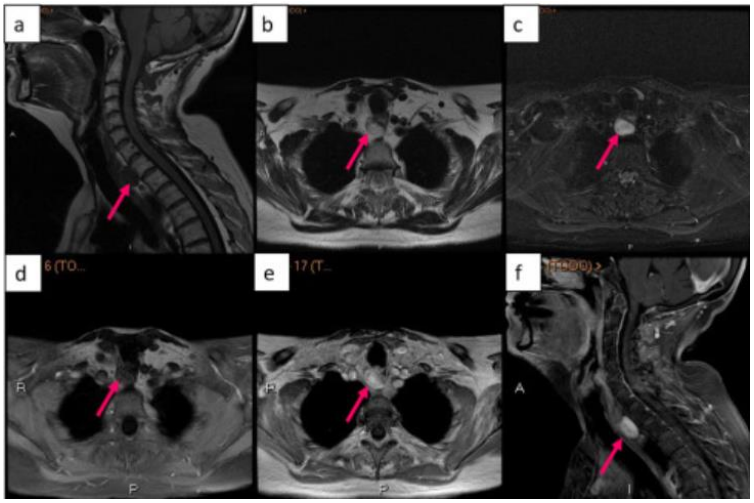
- **MAGNETIC RESONANCE IMAGING (MRI)**

According to the guidelines of the American Association of Endocrine Surgeons , MRI can be considered in cases of reoperation, difficult localization, or contraindication to ionizing radiation (30).

Advantages: no radiation, allows excellent evaluation of the mediastinum and ectopic glands.

Disadvantages: motion artifacts due to respiratory, esophageal and cardiac movements. It takes a long time to acquire the images, high price, lower spatial and temporal resolution (9). It is also limited in patients with renal insufficiency (if contrast medium is used) and implanted medical devices, such as cardiac pacemakers. In addition , it may also be difficult for MRI to differentiate hyperfunctioning parathyroid glands from lymph nodes (32).

The sensitivity for the diagnosis of parathyroid adenoma is similar with both 1.5 Tesla (96.7%) and 3 Tesla (91-92%). However, there are greater differences in specificity, since it has been described as 66.6. % if 1.5 T is used, compared to 95% if 3 T is used (9).



A)

FIGURE 10. RETROTRACHEAL PARATHYROID ADENOMA DETECTED BY MRI. ADAPTED FROM (9).

A)SAGITTAL IMAGE OF T1-WEIGHTED SEQUENCE, B) AXIAL IMAGE OF T2-WEIGHTED SEQUENCE, C) AXIAL IMAGE OF STIR SEQUENCE, D) AXIAL IMAGE OF T1-WEIGHTED SEQUENCE WITH FAT SUPPRESSION AND WITHOUT CONTRAST, E) AXIAL IMAGE OF T1-WEIGHTED SEQUENCE WITH CONTRAST, F) SAGITTAL IMAGE OF T1-WEIGHTED SEQUENCE WITH FAT SUPPRESSION AND CONTRAST.

- **SELECTIVE PATATHYROID VENOUS SAMPLING (PVS)**

Selective parathyroid venous sampling (PVS) can be a useful technique when the localization is inconclusive with the non-invasive tests described above ,when the disease recurs after the first operation or when the location is difficult (9).

The procedure consists of performing venous access through the femoral vein, subsequently, blood samples are obtained from the superior, middle and inferior vena cava, bilateral brachiocephalic, internal jugular, vertebral, thymic and thyroid, and an increase in the PTH level of the vein drainage sites is compared with a peripheral sample(29,32) . A PTH gradient > 1.5-2.0 times the values in peripheral blood is considered positive for adenoma localization (18).

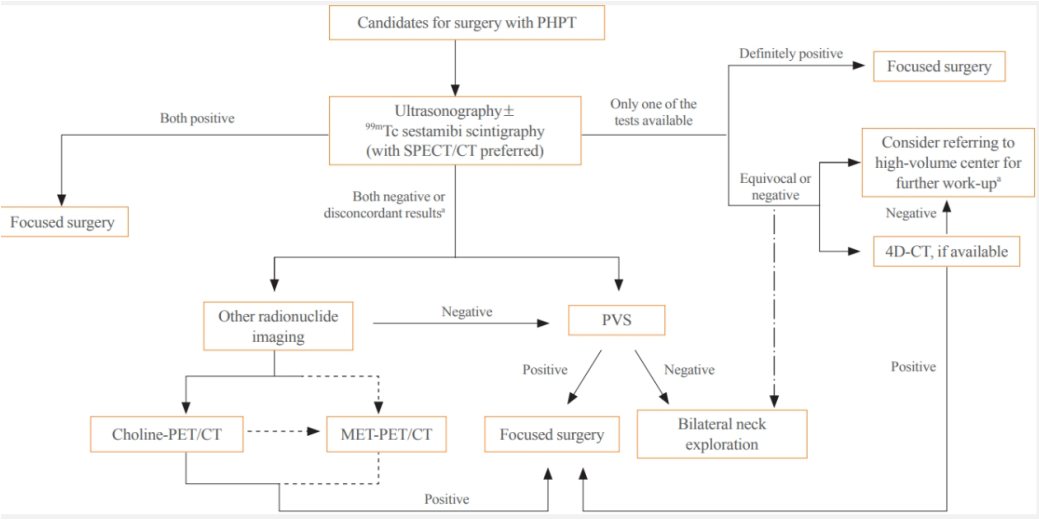
The main ***disadvantages*** are test-related complications : bleeding, infection, arteriovenous fistulas and pseudoaneurysms, although they rarely occur. Radiation exposure during PVS, relatively high cost and the need for experienced radiologists (29).

The sensitivity of PVS ranges from 71% to 90% and specificity of 41% (29,32).

- **SELECTIVE ARTERIOGRAPHY**

Selective arteriography may be useful in patients with poor venous drainage due to previous neck surgery. It is performed by selective transarterial induction of hypocalcemia in combination with nonselective venous sampling. The increase in PTH levels after stimulation is compared to the baseline value. Arteriography has a positive predictive value of 92% in the detection of hyperfunctioning parathyroid gland (32).

FIGURE 11: POSSIBLE PREOPERATIVE LOCALIZATION PROCESS FOR PRIMARY HYPERPARATHYROIDISM .ADAPTED FROM (29).



3.9 TREATMENT:

3.9.1 SURGERY

The only definitive treatment for PHPT is removal of all hyperfunctioning parathyroid tissue , with subsequent quick normalization of calcium levels which remain stable in the long-term. Surgery reduces the risk of nephrolithiasis, bone fracture and increases bone mineral density (27).

Parathyroidectomy is recommended in patients with symptomatic disease, unless there are extenuating medical problems. However, it is also recommended in patients with asymptomatic PHPT, who meet criteria based on the presence of target organ involvement and calcium level ***(table 2)***.

TABLE 2: GUIDELINES FOR SURGERY IN ASYMPTOMATIC PATIENTS WITH PRIMARY HYPERPARATHYROIDISM ACCORDING TO THE FIFTH INTERNATIONAL WORKSHOP (2022) (20).

	CRITERIA FOR SURGICAL TREATMENT OF PATIENTS WITH PHPT (ONE OF FOLLOWING)
SERUM CALCIUM	Total serum calcium adjusted to albumin >1 mg/dL (>0.25 mmol/L) above upper limit of normal
SKELETAL	Vertebral fracture on imaging study Bone mineral density (BMD): T score ≤-2.5 at L1-L4, total hip/neck or radius 33%
RENAL	Creatinine cleanse or eGFR <60ml/min Nephrocalcinosis/nephrolithiasis on imaging study Hypercalciuria 250 mg/day in women; >300 mg/day in men).
AGE	<50years

DEFINITIONS AND DESCRIPTIONS OF DIFFERENT SURGICAL APPROACHES :

- **BILATERAL NECK EXPLORATION:**

Historically the classic approach to PHPT consists of bilateral neck exploration (BNE), but the development of imaging techniques that allow precise preoperative localization, it was replaced my minimally invasive parathyroidectomy. However, BNE is the option for patients whose medical history suggests MGD, and those who need associated thyroid surgery (27,34,35).

Surgically, it requires central access and medial dislocation of both thyroid lobes that allows direct visualization of the parathyroid glands, without compromising their vascularization.

Next, the exploration and identification of all the parathyroid glands is performed with exploration of the expected cervical locations and, if necessary, of the ectopic ones. Subsequently, resection of the macroscopically enlarged glands is performed (35,36).
The possible complications that have been described are hematoma, infection, vocal cord paralysis due to recurrent laryngeal nevus lesion, permanent hypoparathyroidism or hungry bone syndrome (37).

- **MINIMALLY INVASIVE PARATHYROIDECTOMY (MIP):**

Currently, the surgery performed on patients with PHPT is MIP, or focused parathyroidectomy. It is the surgical technique of choice in patients with a single adenoma and is designed to limit the neck dissection to only the area of the parathyroid adenoma (27). This procedure is not recommended for patients at known or suspected risk for multiglandular disease (MGD). If MGD is discovered during the procedure or the abnormal gland is not detected, a bilateral neck exploration (BNE) should be performed (35).
Within group of PMI, open surgery techniques with a minimal central or lateral incision can be included to achieve direct access to the lower glands, video-assisted surgery and endoscopic surgery (36).

Advantage: it offers shorter recovery times, shorter incision length and therefore better aesthetics, shorter operative time and therefore postoperative pain, less occurrence of postoperative complications, as well as days of hospitalization. MIP has high surgical success rates (95%-98%) and low complication rates (1%-3%) (27,36) . It can also be performed under general or regional anesthesia.

The main limitation of this technique lies in the potential poor visualization of the neck structures, due of the small size of the skin incision or, conversely, the need for a larger skin incision compared to video-assisted or endoscopic techniques (38).

To confirm adequate resection, intraoperative cure must be confirmed after resection of the target gland. The indicator of intraoperative biochemical cure is the intraoperative measurement of PTH. A baseline PTH level is determined preoperatively. At the time of target gland resection, additional samples are obtained every 5 minutes. To assess biochemical cure, there are the "Miami" criteria, which suggest cure if a decrease in PTH > 50% of the initial value occurs 10 to 15 minutes after resection of the target gland (27,39). However, with the increasing accuracy of preoperative localization studies there is increasing debate as to

whether ioPTH is necessary in patients with localized single-gland disease (concordant preoperative localization studies) (27,40).

- **RADIOGIDED MINIMALLY INVASIVE PARATHYROIDECTOMY:**

Radioguided minimally invasive parathyroidectomy is an even more effective technique. ***Advantages:*** short surgical times, maintaining a minimal incision and few complications, it allows immediate verification of the excision of the parathyroid lesion and is very useful in patients with ectopic adenomas or a history of cervical surgery. High success rates are described with MIP for intraoperative localization of the adenoma and cure of PHPT (95%-96.9%), MIRP is effective, safe and offers advantages over conventional MIP (15). Some of these techniques are described in the following:

- **RADIOGUIDED PARATHYROIDECTOMY WITH TECHNETIUM-99M (TC-99M) SESTA-MIBI (MIRP-MIBI)**

This isonitrile is administered systemically and is absorbed by the parathyroid lesion as a function of blood flow and mitochondrial activity. On late imaging greater MIBI activity persist in the parathyroid adenoma, while in the thyroid it decreases, allowing the detection of the parathyroid lesion. Prior to MIP, preoperative parathyroid scintigraphy, SPECT or SPECT/CT is necessary for correct identification and anatomical localization, essential before and during surgery, especially in ectopic lesions such as those in the retroesophageal and mediastinal space and complementary preoperative evaluation with US, CT or MRI (15,36).

MIRP-MIBI is usually the most indicated technique in ectopic adenomas and reoperated patients, but its use may be limited in adenomas with low radiotracer uptake in the preoperative diagnostic study, or if thyroid nodule or thyroiditis coexists, since it retains radiotracer longer than normal thyroid tissue (15).

During surgery, the gamma detector probe can be used to better differentiate the adenoma from the surrounding thyroid tissue. Portable gamma camera also used for provide direct images in the same operating field, precisely localizing the adenoma and confirming its removal. Other equipment such as freehand-SPECT also allows determining the depth or distance of the adenoma from the skin surface, very valuable information for surgical access (36).

The indication in multiglandular disease (hyperplasia) or when thyroid pathology coexists is more controversial due to the lower efficacy in localizing multiple lesions and the risk of false positives due to MIBI-positive thyroid nodules (15,36).

- **MINIMALLY INVASIVE RADIOGUIDED PARATHYROIDECTOMY USING THE ROLL TECHNIQUE, GUIDED BY ULTRASOUND (MIRP-MAA (ROLL))**

99mTc-MAA is a radiotracer that is administered to the pathological parathyroid gland under ultrasound guidance. Given its relatively large size (more than 95% of the particles between 10 and 100 micrometers) it remains fixed within the lesion, followed by radioguided excision of the marked lesion with the use of a gamma detector probe or a portable gamma camera (41). To obtain good results, correct pre-surgical localization and concordant functional and morphological test findings are essential (36).

To perform this procedure, the parathyroid adenoma must be solitary, visible and accessible on US. It can also be performed on adenomas that do not capture MIBI, which can occur in up to 40% of cases.

Its usefulness is limited in ectopic cases, small or deep adenomas that are not usually identified by US (15).

- **COMBINED TECHNIQUE [99MTC]TC-MIBI AND FLUORESCENCE.**

The application of fluorescence in radio-guided surgery makes it possible to identify structures invisible to the naked eye, evaluate metabolic processes or tissue perfusion, without increasing surgical time.

The most used substance is ***indocyanine green*** (ICG), which is excited by absorbing light in the near infrared spectrum (NIR) and emits fluorescence at a wavelength of 820 nm. Parathyroid fluorescence is higher than thyroid and the rest of the tissues ,from 30 to 60 seconds to 20 minutes after the infusion, being higher in young age, at high levels of preoperative calcemia and according to glandular size.

Its use is applied both in the identification of parathyroid glands in thyroid surgery and for subtotal parathyroidectomy (36,41).

In 2011, the ***autofluorescence*** of the parathyroid glands after being illuminated with NIR light has been described , clearly superior to that of the thyroid. This technique appears to have a parathyroid identification rate similar to that of ICG, close to 100%, although it decreases in body mass index (BMI) greater than 25 kg/m2, serum calcium > 10.5 mg/dL and vitamin D preoperative < 30 ng/mL (36,41).

- **RADIOGUIDED SURGERY WITH 125I SEEDS.**

The procedure consists of identifying the gland to be treated through ultrasound and placing the 125I seed inside a day or even a week before the intervention. Subsequently, its location can be confirmed through a SPECT-CT study or with external location using a detector probe or gamma camera (41).

During surgery, detection with a gamma probe is essential (another possibility is to use a portable gamma camera). Once the seed has been located and the resection of the parathyroid tissue has been evaluated, it is recovered for subsequent storage in Nuclear Medicine (36).

One of the major complications was hematoma around the 125I seed, which hindered visualization during surgery, and was associated with a higher risk of hemorrhage. Other complications were seed displacement and transient injury to the recurrent laryngeal nerve (36,41).

POST-OPERATIVE AND CONTROL:

It is important to perform an immediate postoperative control to diagnose a possible ***hematoma of the thyroid cell***, which can evolve into a compressive hematoma and require emergency evacuation.

Pulse, blood pressure, respiratory status, pain, agitation and local elements (drains and the anterior cervical region) will also be monitored. The drains are removed on the second postoperative day.

Laboratory monitoring involves a daily determination of ***calcium levels*** during the 2 or 3 days of hospitalization. In case of significant and rapid drop or the appearance of the first clinical manifestations of hypocalcemia (such as tingling of the face and extremities, and Chvostek's sign), calcium supplementation therapy is initiated (42).

3.9.2 NON-SURGICAL MANAGEMENT OF PHPT.

Patients in whom surgery is not indicated or hypercalcemia persists after parathyroidectomy may receive medical treatment (25).

The recommendations for management of PHPT in those not to undergo parathyroid surgery whether or not a pharmacological intervention is implemented (20)*:*

1. Nutritional calcium guidelines: 800 mg/day for women <50 years and men <70 years; 1000 mg/day for women >50 years and men >70 years.

2. Annual measurement of serum calcium and 25-hydroxyvitamin D concentration.
3. BMD every 1 or 2 years.
4. Annual renal function by creatinine clearance or eGFR. If clinically indicated, it is reasonable to perform renal imaging (radiography, ultrasound o computed tomography) or 24-hour calcium.

GENERAL MEASURES:

- All observed patients should be advised not to restrict dietary calcium intake and avoid factors that may aggravate hypercalcemia (thiazides, lithium, volume depletion, prolonged inactivity or bed rest, diet rich in calcium) (25,43) .
- Promote physical activity as a means to minimize bone resorption.
- Ensure adequate hydration (6-8 glasses daily) to minimize the risk of nephrolithiasis (16).
- In patients with PHPT and vitamin D insufficiency (25OH vitamin D <30 ng/mL (75 nmol/L) or deficiency (<12 ng/mL; <30 nmol/L), vitamin D supplementation is suggested, as that its deficiency stimulates PTH production (20). Current guidelines suggest vitamin D supplementation to maintain 25(OH)D concentration > 30 ng/ml and below the laboratory upper limit of normal (usually < 50 ng/ml) (13).

PHARMACOLOGICAL TREATMENT:

- **PATIENTS WITH LOW BMD**

Antiresorptive therapy should be considered in those patients with a T-score at the lumbar spine, hip or distal third of the radius equal to or < -2.5 or who present bone fragility fractures (16).

Oral bisphosphonates (BP) are effective in improving bone mineral density (BMD) at the lumbar spine, femoral neck, and total hip, without altering calcium and PTH concentrations, in both women and men. ***Denosumab***, administered subcutaneously every 6 months, can also increase BMD in these patients (8,11,25).

- **HYPERCALCEMIA:**

Patients with PHPT and serum calcium levels >11.0 mg/dL (>0.25 mmol/L) above the upper limit of normal who do not undergo PTX should be treated with ***Cinacalcet*** (20).
Cinacalcet is a calcimimetic agent that binds to the calcium sensing receptor, mimicking the calcium ion (11).

Cinacalcet effectively reduces serum calcium levels in 70% of patients with PHPT (11). It was approved by the European Medicines Agency in 2008 and by the FDA in 2011 for the treatment of severe hypercalcemia in patients with PHPT who cannot undergo parathyroidectomy. Unfortunately, neither BMD and urinary calcium excretion do not improve with cinacalcet treatment and there are currently no data on the reduction in the risk of nephrolithiasis (8,11).

The drug causes numerous side effects (e.g., anorexia, nausea, vomiting, diarrhea, dizziness) that sometimes lead to its discontinuation (13,25).

- **COMBINATION OF CINACALCET AND DENOSUMAB:**

The different actions of antiresorptive therapy with ***Denosumab*** allows to increase bone density but not to reduce serum calcium, and on the other hand ***Cinacalcet*** allows to reduce serum calcium but not to improve BMD. Due to these conditions, it is possible to try to use both agents in combination, which allows to improve calcium control and to improv bone mass (8,16,20).

- **SECOND LINE PHARMACOLOGICAL TREATMENT:**

-***Hydrochlorothiazide*** was associated with a decrease in urinary calcium excretion, but no changes in serum calcium levels. Thiazide therapy may be indicated in patients at high risk of nephrolithiasis (8).

-Estrogens and selective modulators of estrogen receptors SERMS. Hormone replacement therapy (HRT) has been shown to improve BMD, suppress bone turnover, and reduce calciuria in postmenopausal women with asymptomatic PHPT, however, it does not indicate a reduction in fractures (8,43).

FOLLOW-UP OF MEDICAL TREATMENT:

Patients who do not undergo surgery should be monitored. If any surgical regimen is adhered to during ongoing follow-up, patients should be considered for surgery (11).

TABLE 3. FOLLOW-UP IN PATIENTS WHO DO NOT UNDERGO PARATHYROIDECTOMY (8,20):

Biochemistry	Serum calcium and 25OHD concentrations annually**.** PTH levels may also be measured, as clinically indicated.
Skeletal	DXA at three sites every 1 or 2 years unless BMD is normal. Spinal x-ray, VFA or TBS if clinically indicated.

Kidney	Creatinine clearance (preferably on eGFR), annually. Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated. 24-hour urine for calcium, if clinically indicated.

Parathyroidectomy should be reconsidered in the following cases: serum calcium consistently becomes > 1 mg/dl (> 0.25 mmol/l) above the upper limit of normal, a fracture due to low trauma ,a significant reduction in BMD to a T score ≤ –2.5 at any site, kidney stone, significant reduction in creatinine clearance (> 3 ml/min on average over a period of 1 to 2 years) to < 60 ml/min or if there are other changes indicating progression (13,20).

3.9.3 MANAGEMENT OF PHPT DURING PREGNANCY.

Parathyroid disease is rare in pregnancy, estimated prevalence of 8/100,000 women (23).
The diagnosis of PHPT can be confirmed in the presence of hypercalcemia and a non-suppressed parathyroid hormone (PTH) level (44).
Symptoms that appear are related to calcium levels, especially when calcium is 1 mg/dL above the upper normal limit, and these are: nephrolithiasis, hyperemesis gravidarum and, in severe cases, acute pancreatitis, preeclampsia, spontaneous abortions, intrauterine growth retardation, preterm delivery, polyhydramnios, as well as fetal and maternal mortality (23,44).

Mild cases should be treated by maintaining good hydration and controlling calcium levels, discontinuing of thiazide diuretics, calcium and lithium supplements if possible (44).
Pharmacological options are very limited and there are no safety data with any of the available treatment strategies, so bisphosphonates and denosumab should not be used (20,44).
Consider surgery if it is not contraindicated, in the second trimester patients with serum calcium >11.0 mg/dL and it should be an image-guided localization MIP (20,23,27) .

3.9.4 HYPERCALCEMIC CRISIS.

Parathyroid crisis has a very low incidence, estimated to corresponds to 1.6-6% of cases of primary hyperparathyroidism (45). It is an endocrinological emergency characterized by serum ***calcemia levels >14 mg/dL*** (16).

It is a characterized by severe hypercalcemia causing dehydration, anorexia, constipation, nausea, vomiting, oliguria and acute renal failure, muscle weakness, confusion, lethargy, coma,

QT shortening and arrhythmias (16). Without proper treatment, kidney failure, coma, and death may occur (up to 7%) (5,39).

Initial treatment consists of rapid rehydration with the administration of large volumes of intravenous fluid followed by furosemide to promote renal calcium excretion. If these initial measures fail to control hypercalcemia, treatment with cinacalcet or bisphosphonates may be necessary. Other potentially useful treatments include calcitonin, glucocorticoids (effective in vitamin D intoxication), and dialysis in severe cases with kidney failure (5,39).

Surgery should be performed without delay after medical stabilization. Although there are no strong data, surgery can be performed safely when serum calcium has been reduced to a level of 14 mg/dL (39).

4. JUSTIFICATION:

Primary hyperparathyroidism is an endocrine disease that presents with elevated levels of calcium and parathyroid hormone and affects different organs, especially the skeleton and kidneys, the most frequent cause being a solitary adenoma (80%). Once PHPT is diagnosed, surgical removal of the affected gland is the only curative treatment. A minimally invasive surgical approach has become the standard treatment in selected patients. However, in order to perform targeted approaches, it is necessary to localize all hyperfunctioning glands by nuclear medicine imaging.

The usual first-line imaging techniques to reach the diagnosis of HPTP are ultrasound and Tc99m-sestaMIBI scan combined with SPECT/CT. If the tests are positive and an adenoma is detected, a minimally invasive parathyroidectomy (MIP) is performed.

In some cases, the first-line localization tests are negative or not concordant, in this case the test can be repeated or an imaging technique recently used in HPTP, 18F-Choline PET/CT, can be requested.

Based on multiple articles in recent years it has been shown that 18F-fluoroquine PET has higher uptake rates at the level of hyperfunctioning parathyroid tissue (4 mm or more), allowing the detection of small adenomas and also provides better image resolution compared to SPECT-CT with Tc99m-MIBI (sensitivity of 18F-choline PET/CT and SPECT-CT with 99mTc-sestamibi was 96% and 78%, respectively) (29). Its use in combination with PET/CT imaging techniques allows both anatomical and functional information to be obtained in the same study, allowing patients to benefit from targeted surgery, and is a promising candidate to replace other morphological and functional imaging methods.

Despite its superior diagnostic performance compared to conventional imaging, this method has a major disadvantage due to its high cost and limited availability.

Therefore, we believe that it seems reasonable to propose a randomized clinical trial to evaluate post parathyroidectomy surgical outcomes in patients with topographic diagnosis by 18F-choline PET/CT as a localization imaging test of hyperfunctioning parathyroid tissue, compared to patients undergoing Tc99m-MIBI SPECT/CT.

Thus, this protocol will attempt to demonstrate that, despite the high cost, Choline PET/CT has a very high sensitivity, which would allow avoiding repeat testing and unnecessary re-

interventions. It could also allow a better management of the patient with PTHP, which would translate into better cure rates, shorter surgery time and fewer post-surgical complications. All these factors could lead to reduced clinical costs that would offset the high cost of diagnostic imaging.

If the outcome is favorable, choline PET/CT should become the first-line test in the topographic diagnosis of PHPT.

5. HYPOTESIS:

The hypothesis of this study consists of:

Patients undergoing 18F-Choline PET-CT as a pre-surgical localization test have better anatomical localization of the hyperfunctioning parathyroid tissue and, therefore, shorter operative time, fewer post-surgical complications, fewer days of hospitalization and, therefore, lower hospital costs that offset the high cost of diagnostic imaging, compared to patients undergoing 99mTc-MIBI scintigraphy SPECT/TC as a pre-surgical imaging test.

6. OBJECTIVES:

The objective of this study:

To compare surgical outcomes in post-parathyroidectomy patients with 18F-Choline PET/CT localization imaging test versus Tc99m-MIBI SPECT/CT and to study the impact that all this has on the surgical management of the process, analyzing the benefit/cost ratio.

7. MATERIAL AND METHODOLOGY:

7.1 STUDY DESIGN :

This scientific study is a multicenter, open-label, parallel-group, prospective, randomized, controlled, interventional clinical trial, performed in University Hospital Doctor Josep Trueta and University Hospital Vall d'Hebron, where Hospital Dr. Josep Trueta will be the coordinating center.

The study is designed to compare the surgical outcome obtained by different preoperative localization tests in patients with confirmed PHPT or asymptomatic PHPT but meeting criteria for parathyroidectomy, and will be randomly assigned in a 1:1 ratio to one of the following groups:

A) In the first group, Tc99m MIBI SCPECT/TC will be performed as localization imaging tests.

B) In the second group, 18F-Choline PET-CT will be performed as localization imaging test.

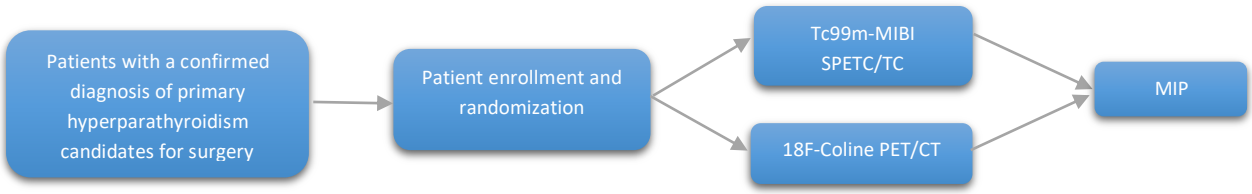


FIGURE 12. STUDY DESIGN.
PET-CT POSITRON EMISSION TOMOGRAPHY AND COMPUTED TOMOGRAPHY SCANS; MIP MINIMALLY INVASIVE PARATHYROIDECTOMY; SPECT/TC SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY/ COMPUTED TOMOGRAPHY

7.2 STUDY SETTING:

This study is designed to be a multicenter study, therefore, it requires the participation of two Catalan hospitals to obtain significant results due to the low incidence of PHPT. A clinical trial is proposed with the participation of two hospitals that are part of the national public health system:

- ***University Hospital Doctor Josep Trueta***, Girona: 800,000 reference inhabitants.

- *University Hospital Vall d'Hebron* , Barcelona: 430,000 reference inhabitants.

The reference center and coordinator of this clinical trial will be the University Hospital Dr. Josep Trueta. An researcher will be assigned as representative and coordinator of the Vall d'Hebron Hospital in order to achieve good communication and coordination between both centers.

7.3 STUDY POPULATION:

The study includes patients diagnosed with symptomatic primary hyperparathyroidism or asymptomatic patients who meet the criteria to be candidates for parathyroidectomy. Candidates who meet the following requirements will be able to enter this study:

7.3.1 INCLUSION CRITERIA:

- Adult male or female patients ≥ 18 year of age.
- Confirmed diagnosis of primary hyperparathyroidism candidates for surgery (symptomatic or asymptomatic patients who meets surgical criteria).
- Patients with confirmation presence of hyperfunctioning parathyroid tissue by preoperative imaging tests.
- Negative pregnancy test at the time of inclusion in women of childbearing age.
- Informed consent accepted and signed.

7.3.2 EXCLUSION CRITERIA:

- Known allergy for Tc99m-MIBI and 18F-Choline or one of its excipients.
- Pregnant or breastfeeding women.
- Any medical conditions or associated psychopathology that may compromise patient's ability to participate in study.
- Patients who do not give informed consent.

7.3.3 WITHDRAWAL CRITERIA :

Participants may withdraw from the study if any of the following situations occur:

- Participants can voluntarily leave the research study at any time by communicating this to the research team by submitting the withdrawal request.
- Patients who at some point in the clinical trial meet an exclusion criterion because it was developed after their inclusion.
- Loss of patient follow-up, if the patient does not show up for any of the scheduled visits after trying to communicate with him/her several times.
- Serious complications during follow-up that do not allow the patient to continue in the study.

All data obtained during the study before withdrawal will be used for the clinical trial results.

7.4 SAMPLING:

7.4.1 SAMPLE SIZE

In a bilateral test, with an alpha risk to 5% and 20% of beta risk , statistical power equal to 80%, 55 individuals will be needed in each group, which in total are 110 patients. However,

assuming a drop-out rate of 10%, the number of subjects required in each group will be 60, with in total are ***120 patients.***

Calculations are performed with Sample Size Calculator.

7.4.2 SAMPLE COLLECTION

A consecutive ***non-probabilistic*** sampling method will be carried out. The Endocrinology Service of each participating hospital will offer to collaborate in the study to all patients with a diagnosis of PHPT who meet the inclusion criteria and none of the exclusion criteria . They will be provided with all the information about the study and they will be given and sign the informed consent form.

Each hospital will be responsible for recruiting and monitoring its own patients.

7.4.3 SAMPLE RECRUITMENT TIME

As previously calculated, 120 patients are needed to carry out the clinical trial. Knowing that the incidence rate of PHPT is 9.95 cases per 100,000 inhabitants/year and taking into account the reference population of the University Hospital Dr. Josep Trueta (Girona) is approximately 800,000 inhabitants, we can assume that there are 79 cases in 1 year.

To reach the estimated sample size and not prolong the study too much, we will need to perform a multicenter study.

University Hospital Vall d'Hebron (Barcelona) has a reference population of approximately 430,000 inhabitants, with these data we can reach the estimated sample size.

The estimated recruitment time to reach the sample size (120) will be approximately ***1 year.***

7.4.4 RANDOMIZATION

Once the Informed Consent is signed, each participant will be randomly assigned in a 1:1 ratio (control or intervention) to the following groups:

- ***Control group (group A):*** in the first group, a Tc99m MIBI SPECT/TC will be performed as a localization imaging test (gold standard).

- ***Intervention group (group B):*** in the second group, 18F-Choline PET/CT will be performed as a localization imaging test.

Randomization will be generated by software and an identification number will be assigned to each patient, to provide the confidentiality of the participant .

7.4.5 MASKING

This study is designed to be open, which means that the physician will know which imaging test will be performed on each patient and the patient will know it as well. Masking this study is impossible, because the nuclear medicine physician will know what type of machine and radiopharmaceutical is used, and the patient will be able to tell by the appearance of the machine.

Therefore, the only possibility to reduce the risk of bias, the statistician who will use the software to separate the two groups of control and intervention, and who will analyze the results, is blinded and does not know the type of imaging performed in each of the groups.

7.5 VARIABLES :

7.5.1 INDEPENDENT VARIABLE:

The independent variable of this study is the type of imaging test being performed. It will be expressed by ***Tc99m-MIBI scintigraphy SPECT/TC*** or ***PET/CT 18F-Choline.***

It is a dichotomous qualitative variable.

7.5.2 DEPENDENT VARIABLE :

Principal outcome:

- **PTH blood levels immediately after surgery :** elevated PTH is considered to be > 80 pg/dL. The determination of PTHio will be performed by extracting a preoperative baseline sample, and after removal of the parathyroid lesion ("time 0") blood samples will be taken at 5, 10 and 15 min. Adequate decrease will be considered when the absolute serum value showed a decrease > 50% with respect to the baseline absolute value at any time (Miami Criteria).

The definitive result will be obtained by PTH levels at 2 hours after surgery. Intraoperative cure is defined if there is a decrease in PTH levels <80 pg/dL or not. It is a dichotomous qualitative variable.

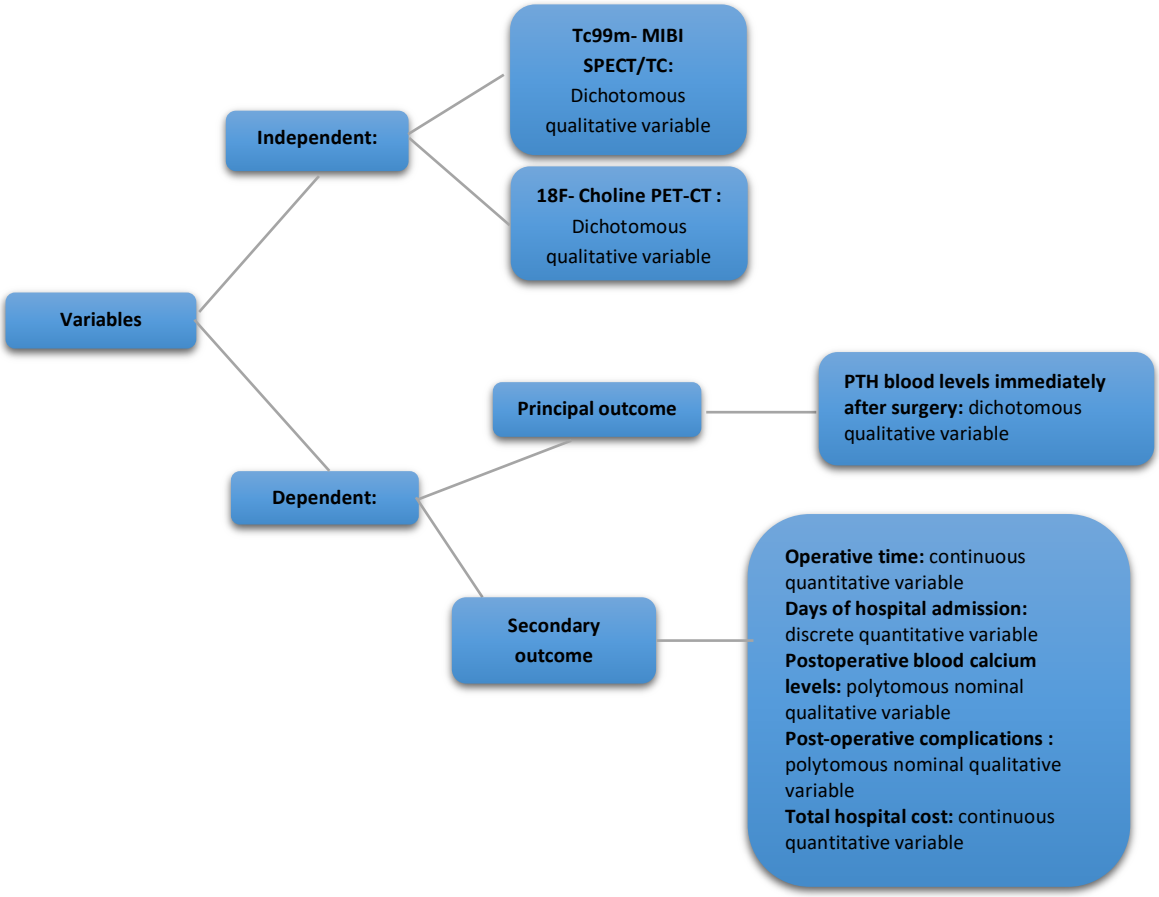
Secondary outcome:

- **Operative time:** at the end of the operation ,the surgeon will report the duration of the operation from the first insertion to the last suture. It is a continuous quantitative variable.
- **Days of hospital admission**: day 0 will be recorded as the day of the operation , and the day on which the patient is discharged from the hospital will be noted. In this way it is possible to calculate the mean number of days of hospital admission for each patient operated . It is a discrete quantitative variable.
- **Postoperative blood calcium levels** : patients will be followed up for 1 and 6 months after surgery with serum calcium determination. Hypocalcemia is determined as serum calcium values < 8.5 mg/dL and hypercalcemia at values > 10.5 mg/dL. Results will be reported:
  - ***Cure*** was considered if the patient had serum calcium within normal limits at least 6 months after surgery.
  - ***Persistence*** was defined as hypercalcemia in the first 6 postoperative months
  - ***Recurrence*** if there was a new elevation of serum calcium 6 months after surgery.

  It is a polytomous nominal qualitative variable.
- **Post-operative complications**: complications such as cervical hematoma, vocal cord paralysis due to recurrent laryngeal nerve injury, hungry bone syndrome (permanent hypoparathyroidism), infection , surgical wound dehiscence will be evaluated and the presence or absence of these complications in each patient, then a percentage estimation of each complications will be made between two groups. It is a polytomous nominal qualitative variable.
- **Total hospital cost**: surgical times, cost of operating room use, average hospital stay per procedure and those derived from the tests performed are calculated and analyzed, and the average cost of each group is calculated. To evaluate the cost of the operating room, we obtain the cost of each hour of use of the operating room and multiply by the total use time for each patient.

The results will be reported in numbers for each intervened group using different localization imaging tests. It is a continuous quantitative variable.

FIGURE 13. VARIABLE TYPE.



7.5.3 COVARIATES:

All possible covariates have been defined to describe patient characteristics. Most of them are evaluated during the patient's first visit to the reference center through anamnesis and diagnostic tests.

- **Age**: at the moment of PHPT diagnosis. It is a discrete quantitative variable. It will be expressed in years.
- **Sex** : male/female. It is a qualitative dichotomous variable.
- **Surgical history**: previous surgeries on thyroid or parathyroid glands. The results will be reported as yes or no. It is a dichotomous qualitative variable.

- **Phenotype of primary hyperparathyroidism** : symptomatic hypercalcemic , asymptomatic hypercalcemic or normocalcemic hyperparathyroidism. It is a polytomous nominal qualitative variable.
- **Preoperative blood calcium and PTH levels**: it is an important parameter to assess the severity of the disease. It is a continuous quantitative variable expressed in mg/dL for serum calcium and pg/dL for parathyroid hormone.
- **Surgical criteria**: the criteria for the surgical decision were based on the guidelines established by Bilezikian (20). For each criterion met, a yes or no result will be reported. It is an nominal polytomous qualitative variable.
    - Age <50 years
    - Hypercalcemia
    - Fractures
    - Osteoporosis
    - Nephrocalcinosis or nephrolithiasis
    - Hypercalciuria
    - Glomerular filtration rate < 60 mL/min
- **Type of lesion**: according to the histopathological result, and will be reported as: adenoma, hyperplasia or carcinoma. This is a polytomous nominal qualitative variable.
- **Location** : upper right, lower right, upper left, lower left, submandibular, mediastinum, bilateral, other, not located. It is a polytomous nominal qualitative variable
- **Measurement of the lesion**: expressed in millimeters. It is a continuous quantitative variable.

FIGURE 14. SUMMARY OF STUDY COVARIATES, MEASUREMENT METHOD AND CATEGORIES.

VARIABLES	DESCRIPTION	MEASURAMENT	CATEGORIES
Age	Discrete quantitative variable	Medical history or anamnesis	
Sex	Dichotomous qualitative variable	Medical history or anamnesis	Male Female
Surgical history	Dichotomous qualitative variable	Medical history or anamnesis	Yes No
Phenotype of PHPT	Polytomous nominal qualitative variable	Clinical and analytical criteria	Symptomatic Asymptomatic Normocalcemic

Preoperative calcium and PTH levels	Continuous qualitative variable	Analytical criteria (mg/dL / pg/dL)	
Surgical criteria	Polytomous nominal qualitative variable	Surgical criteria	Age <50 years Hypercalcemia Fractures Osteoporosis Nephrocalcinosis or nephrolithiasis Hypercalciuria Glomerular filtration rate < 60 mL/min
Type of lesion	Polytomous nominal qualitative variable	Anatomopathological criteria	Adenoma Hyperplasia Carcinoma
Location	Polytomous nominal qualitative variable	Image study, surgical intervention report	Upper right Lower right Upper left Lower left Submandibular Mediastinum Bilateral Other Not located
Measurement of the lesion	Continuous qualitative variable	Anatomopathological criteria	

7.6 INTERVENTION AND DATA COLLECTION:

To ensure proper data collection during the study, a computer database will be created for the clinical trial. Patient names and all clinical information will be coded with an identification number, thus ensuring confidentiality and anonymity of the information.

All data will be collected on the registration sheet ***(ANNEX 6)*** after patient recruitment ,and will be completed when the follow-up of each patient has been completed.

7.6.1 FIRST VISIT:

At the first visit, all patients clinically and biochemically diagnosed with PHPT (PTH >80 pg/mL and/or Ca >10.5 mg/mL without hypocalcemic treatment) will be informed of the diagnosis. If

the patient meets all the inclusion criteria and none of the exclusion criteria, the patient will be informed of the characteristics and objectives of the study, and will be invited to participate.

At the next visit, the patient will communicate her/his decision.

7.6.2 SECOND VISIT:

If patients agree to participate in the study, they will be given the Participation Information Sheet ***(ANNEX 3)*** and the Informed Consent Document ***(ANNEX 4)*** to participate in the research study and perform imaging tests, which they have to sign if they agree.

The second visit will consist of the following procedures that will allow the collection of all data related to the study ***covariates*** :

- Review of the electronic medical record or performance of a directed anamnesis to collect the patient's personal data, age, sex, symptoms if present and history of fractures, osteoporosis, renal lithiasis or previous thyroid or parathyroid surgery.
- Biological examination including blood tests with determination: blood levels of intact PTH, serum calcium, chlorine, phosphorus, albumin, vitamin D and creatinine as well as urinary calcium excretion. Pregnancy test will be performed one week prior to imaging in women of childbearing age.
- Measure bone mineral density (BMD) of the lumbar spine, hip and 1/3 distal radius and vertebral X-rays.
- Perform renal ultrasound to evaluate for possible renal lithiasis.
- A standard neck ultrasound will also be performed prior to computer-generated randomization.

All these data will be collected in the Data Collection Form ***(ANNEX 6)*** at the beginning of the clinical trial.

7.6.3 RANDOMIZATION:

Once the study has been explained and the informed consent for the procedures has been signed, patients will be randomly assigned to two groups:

- Control group (A): performance of Tc99m-sestaMIBI SPECT/CT

- Intervention group (B): performance of 18F-Cholina PET/CT.

7.6.4 INTERVENTION:

Before performing the minimally invasive parathyroidectomy, the localization imaging test 18F-Choline PET/CT or Tc99m- MIBI SPECT/TC is performed, depending on whether the patient belongs to the control or intervention group.

- **INTERVENTION GROUP: PET-CT CHOLINE.**

18F-Choline PET/CT is obtained with patients fasting for 4 hours. A physical will administer 3 MBq/kg of Fluoromethylcholine Chloride (F-18) to the patient and the patient will rest for 15 minutes, and then undergo the PET/CT scan and perform an early cervicomediastinal study according to pre-established acquisition protocols. Subsequently, the patient will return to the injection/repos box to wait until 60 minutes post-injection, at which time the patient will return to the CT scanner to obtain the late cervicomediastinal study, also according to pre-established acquisition protocols (31).

The images obtained will be reviewed in three planes (transaxial, coronal and sagittal) by Nuclear Medicine specialists. Positive results were characterized by localized uptake in the neck or mediastinum superior than adjacent background activity and coincident with a nodular lesion on CT.

- **CONTROL GROUP: TC99M- MIBI SPECT/TC**

Dual-phase scintigraphy involves the use of Tc99m-MIBI as the sole tracer. After the intravenous injection of approximately 740 MBq of Tc99m-MIBI, 2 cervical and mediastinal planar scintigraphy scans were obtained in anterior projection, at 10 minutes (early) and at 2-3 hours (late), followed by SPECT/CT acquisition.

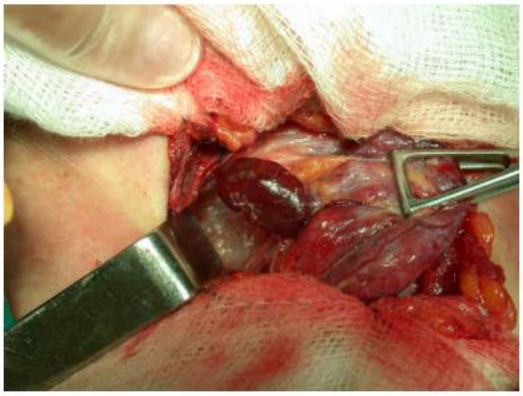
Planar images and SPECT/CT data were reviewed for parathyroid visualization by an experienced Nuclear Medicine physician, and positive result was defined

as a tracer accumulation in the thyroid or mediastinal region that is permanent or increases in intensity on the late image, negative result was defined as the absence of focal uptake on early or late images. An inconclusive result was defined as vague uptake in soft tissue adjacent to the thyroid, or uptake possibly associated with thyroid nodules (30).

7.6.5 SURGERY:

Pre-intervention evaluation: before undergoing a minimally invasive parathyroidectomy (MIP), an imaging test is performed to locate hyperfunctioning parathyroid tissue. Subsequently, a visit is scheduled with the Endocrine Surgeon who will explain the procedure and the patient must sign the Informed Consent Form in order to perform the parathyroidectomy. A visit with the anesthesia team will also be scheduled to proceed with the preoperative study.

Surgical intervention: all patients will undergo selective minimally invasive parathyroidectomy (MIP) under general anesthesia within 8 weeks of imaging .



A transverse neck incision approximately 3 to 4 cm in length was made to evaluate for abnormal parathyroid glands. At the time of surgery, the surgeon will have the results of the imaging modalities to better guide the surgical procedure. The success of the surgery will be verified by a measurement of blood PTH levels and subsequent perioperative decrease of ≥50%. These data will be recorded and will allow the analysis of the ***dependent variable of PTH blood levels immediately after surgery.***

Surgeons will note the exact location of each resected adenoma , along with the total surgery time and surgical complications, if any. This information will be used to analyze the ***dependent variable of complications and operative time***, and the ***co-variable of anatomical location of lesion.***

The surgical specimen will be sent to the pathology laboratory according to the usual protocol and respecting the established coding ***(ANNEX 5).***

The Pathological Anatomy Service will analyze the surgical specimen and prepare a report with the histological findings, which will define the definitive cause of the PHPT, allowing the

analysis of the ***co-variable of type and measurement of the lesion*** and its registration in the Data Collection Sheet ***(ANNEX 6).***

7.6.6 HOSPITAL ADMISSION :

Once the procedure is completed, a possible hematoma of the thyroid cell will be assessed in the immediate postoperative control, which may evolve into a compressive hematoma and require emergency evacuation. The patient will be asked to speak to assess possible lesions of the recurrent laryngeal nerve, if there is vocal cord involvement, laryngoscopy will be performed for evaluation. Subsequently, patients will be transferred to the post-surgical resuscitation area where they will remain for 1-2 hours, and then be transferred to conventional hospitalization.

During admission, heparin will be administered in prophylactic doses to minimize thromboembolic complications and analgesics to control pain. Pulse, blood pressure, respiratory status, pain, agitation and local elements (drainage and anterior cervical region) will be monitored, and during the first 24 hours after surgery the temperature will be determined every 6 hours. Drains are removed on the second postoperative day.

Laboratory monitoring involves daily determination of calcium levels during the 2 to 3 days of hospitalization. In case of significant and rapid decrease or appearance of the first clinical manifestations of hypocalcemia (such as tingling in the face and extremities and Chvostek's sign), therapy with calcium supplements is initiated.

All possible complications allow us to analyze the ***dependent variable*** , such as: ***cervical hematoma, vocal cord paralysis due to recurrent laryngeal nerve injury, hungry bone syndrome (permanent hypoparathyroidism), infection and surgical wound dehiscence***. If any of the other acute complications mentioned occur, they will be noted.

The data will also be analyzed as ***days of hospitalization for the dependent variable***.

7.6.7 FOLLOW UP:

One week after the operation, the Endocrine Surgery team will schedule a visit with the patient for postoperative follow-up including exploration of the surgical wound, pain, complications, etc. Histological results will also be communicated and provided to patients.

One and 6 month after the operation, a visit is scheduled with the Endocrinology Service to evaluate the cure of the PHPT, otherwise evaluate the pharmacological treatment.

The follow-up consist of biological testing with determination calcium and PTH levels. Cure is defined as normalization of serum calcium and PTH levels at 1 month and 6 months after surgery. During follow-up we can evaluate the ***dependent variable of postoperative blood calcium and PTH levels.***

At this point the patient's participation in the study ends. The research team will proceed to analyze the results obtained and perform the statistical analysis.

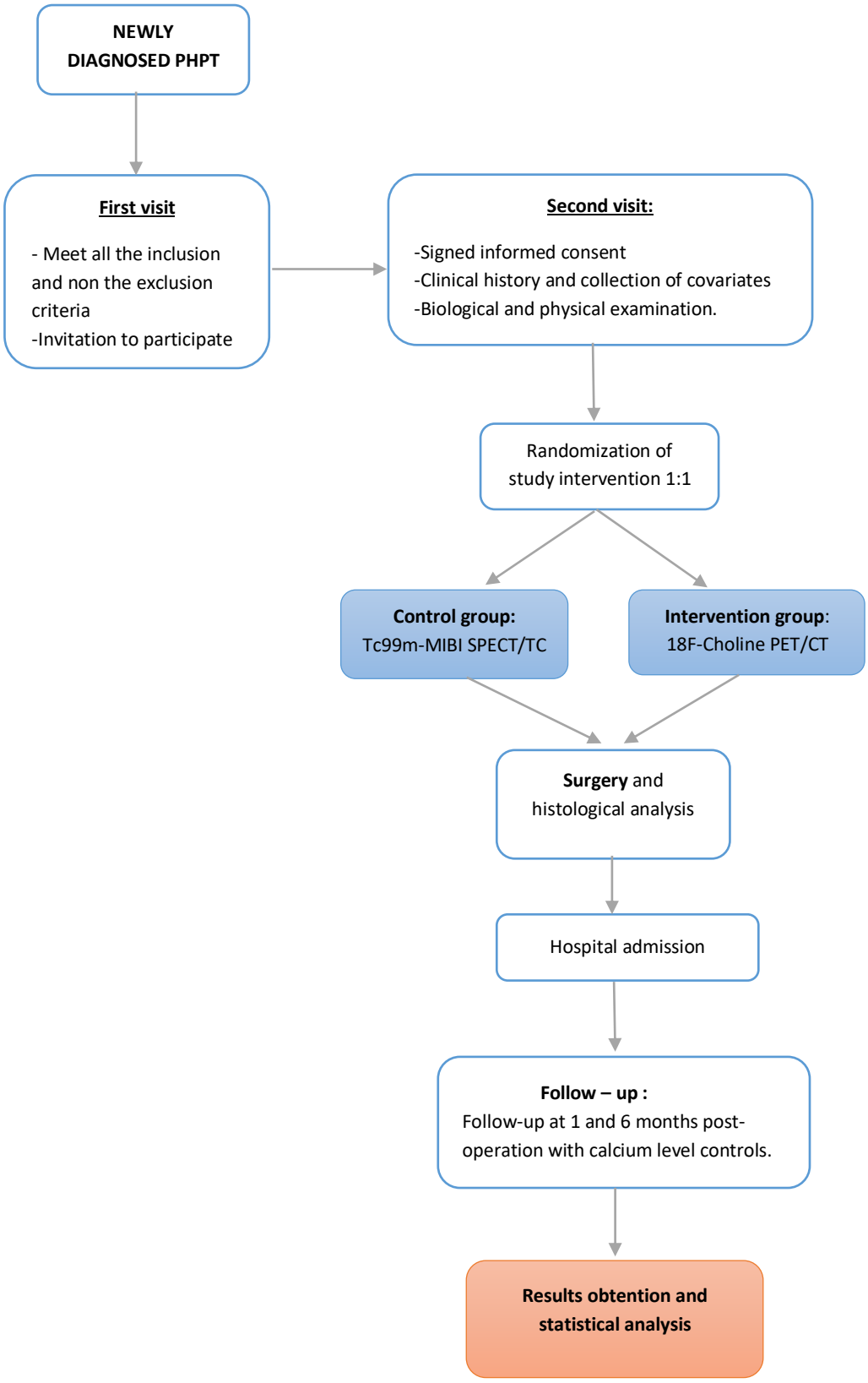
7.7 SAFETY:

The 18F-Choline PET/CT intervention proposed in this study has been previously applied in numerous studies and has demonstrated an acceptable safety profile. As with any diagnostic test using ***radiotracers*** , we must assume that these particles are radioactive. Radiation exposure always carries a potential risk, in this case negligible (given the low radiation doses) compared to the benefits of the test and there is no evidence of harmful effects of low doses of radiation in these types of tests. Some of the possible adverse effects are described in the following:

- There may be allergic reactions, usually mild, to radiotracers. In any case, if a patient has any type of allergy, he/she should inform the doctor before undergoing the test.
- The radiotracer injection may cause mild pain or redness, which resolves quickly.

If there is any possibility that you are pregnant or breastfeeding , you should notify your physician and the radiologist.

FIGURE 15. FLOW CHART.



8. STATISTICAL ANALYSIS :

The statistical analysis will be performed by a ***blinded statistician***, using the Statistical Package for Social Sciences (SPSS Windows®). For all results, we will consider the statistical significance at a value of p<0,05, defining a confidence interval 95%.

8.1 DESCRIPTIVE ANALYSIS :

In the univariate analysis, the ***qualitative variables*** (PTH blood levels immediately after surgery, postoperative blood calcium levels (we understand them as a qualitative variable), postoperative complications) will be expressed in ***proportions, percentages or frequencies.***

To describe the ***quantitative variable*** such as days of hospitalization, we will use ***mean +/- standard derivation*** (when following a symmetric distribution) or ***median and interquartile range*** (when following an asymmetric distribution).

Covariates will be summarized in proportions (qualitative variables), means and standard deviations (continuous variables), and medians and interquartile range (discrete variables), stratifying by the groups of intervention.

8.2 BIVARIATE INFERENCE :

The difference in the proportions of the ***qualitative variables*** between the intervention and control groups will be tested using the ***Chi-square test or Fisher's exact test***, if the expected number of cases in a cell will be less than 5.

The difference in the medians of the ***quantitative variables*** between the intervention and control groups will be carried out using ***Student-t test*** for quantitative variables with a symmetric distribution, ***Mann-Whitney U*** for quantitative variables with an asymmetric distribution. These analyzes will be stratified by covariates.

8.3 MULTIVARIATE ANALYSIS:

To evaluate the association between the independent and dependent variables, a multivariate analysis will be performed using ***logistic regression***, controlling for covariates that may interfere in the results and to avoid possible confounding factors.

9. ETHICAL AND LEGAL CONSIDERATIONS:

The clinical trial will be carried out in accordance with the medical ethics requirements defined in the Helsinki Declaration of "***Ethical Principles for Medical Research Involving Human Subjects*** " signed by the World Health Association in October 2013. It will also respect the ***Principles of Ethics Biomedical from Beauchamp and Childress*** from 1970 and revised in 2009, which includes respect to autonomy, non-maleficence, beneficence and justice.

This protocol has been developed and will also comply with the standards established in ***Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos ; Real Decreto Legislativo 1/2015, del 24 de Julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitario and Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios.*** Furthermore, this essay will take into account ***Ley 14/2007 de 3 de julio, de investigación biomédica***, which regulates biomedical research with human beings and invasive procedures.

Before carrying out this study, the protocol will be presented to the CEIC (Clinical Research Ethics Committee) of the main center, the University Hospital Dr Josep Trueta, for evaluation and approval of the protocol. In case the CEIC has objections, all suggestions will be considered and modifications will be made to the protocol to meet their conditions.

Once approval by the ethics committee, the protocol will be sent to the University Hospital Vall d'Hebron participating in the research to obtain their approval and confirm their participation. This study can only begin after receiving approval from the two hospitals.

In addition, we will request the participation of the Department of General and Digestive Surgery, Endocrinology and Nuclear Medicine to guarantee their involvement in the surgical and interventional procedures of the clinical trial.

Before the start of the clinical trial study, all patients will be provided with an information form, which contains all the information about the clinical trial, whose language and terms are easily understandable. If the participants agree to participate in the study, they must read and sign an informed consent evaluated by the CEIC of the two participating centers, respecting ***Ley 41/2002, de 14 de Noviembre, Básica reguladora de la autonomia del paciente y de derechos y obligaciones en materia de información y documentación clínica.***

To maintain confidentiality, patient data will be recorded using a numerical code assigned to each patient at the start of the study. Personal data such as all personal medical information will be completely confidential and only the researchers will have access to this information, solely for scientific purposes related to this study.

The confidentiality of all participating patients will be respected in accordance with the ***Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales*** , and all personal information required in this study, its transfer and confidentiality will be respected and will complied in accordance with the ***Regulation (EU) 2016/679 of the European Parliament and of the Council, of 27 April 2016, on the protection of natural persons with regarding the processing of personal data and the free movement of such data.***

Access to patient data will be available only to the research team, the Ethics and Clinical Research Committee, the relevant health authorities and those responsible for data analysis. All data will be published transparently. Unfavorable developments or events will not be excluded.

The researchers in charge of this study declare that they have no conflict of interest.

10 WORKING PLAN :

10.1 RESEARCH TEAM:

This study will be carried out by a research team consisting of the following:

- **Study coordinator**: responsible for monitoring the study and coordinating the research team of the participating centers.
- **Principal Investigator**: responsible for the elaboration of the protocol and will direct the execution of the project, supervise correct application of the protocol and correct storage of the data. In addition, will participate in the discussion of the results, prepare the final report containing the conclusions and its subsequent dissemination through the publication of the results.

- **Co-investigator**: in University Hospital Vall d'Hebron will be a co-investigator responsible for coordinating and supervising its team, to ensure compliance with the protocol within its center.
- **Data manager**: responsible for applying randomization, collecting all data and creating a database.
- **Statistical analyst**: responsible for the statistical analysis of the study.
- **Collaborators**: all healthcare personnel in order to carry out this clinical trial, including nursing staff, endocrinology team, endocrine surgery team, nuclear medicine team, laboratory and pathology team .

Virtual training meetings and workshops will be held prior the start of the intervention to ensure maximum uniformity during the research study.

10.2 STUDY STAGES :

STAGE 0: STUDY DESIGN (SEPTEMBER 2023-NOVEMBER 2023)

- **1st step (September 2023):** First meeting between the study coordinator and the principal investigator. An agreement was reached to conduct this study.
- **2nd step (September 2023-November 2023):** Bibliographic research on primary hyperparathyroidism, epidemiology, symptoms, diagnosis and treatment.
- **3rd step (September 2023-November 2023):** Preparation of the protocol and limitation of the objectives, hypotheses, variables and methodology.

During this period, the University Hospital Vall d'Hebron will be contacted to propose participation in the study. After acceptance to participate, the following stages will continue.

STAGE 1: ETHICAL EVALUATION AND APPROVAL OF THE STUDY (DECEMBER 2023 - FEBRUARY 2024):

- **4th step (December 2023 - February 2024**): Presentation of the protocol to the CEIC of the Doctor Josep Trueta University Hospital for approval, any proposed suggestion will be considered and added to the study development plan. Once approved, the protocol must be accepted by the CEIC of the Hospital Vall d'Hebron.
- **5th step (December 2023 - February 2024):** Civil liability insurance will be contracted.

STAGE 2: COORDINATION AND TRAINING (MARCH 2024 - APRIL 2024)

- **6th step (March 2024 - April 2024):** The first meeting will be organized with the principal investigator, the study coordinator and the co-investigator of the Vall d'Hebron University Hospital to clarify the work plan, the different phases of the trial, distribute and organize tasks.
- **7th step (March 2024 - April 2024**): Virtual training workshops will be held for the physician and Nuclear Medicine technicians from both centers responsible for performing 18F-Choline PET-CT and 99mTc-MIBI SPECT/CT. The physicians and technicians will attend a practical workshop at the HUJT. The main objective is to ensure maximum uniformity of imaging techniques in both centers in order to obtain representative results.

STAGE 3: RECRUITMENT, INTERVENTION, HOSPITAL ADMISSION , MONITORING AND DATA COLLECTION (MAY 2024 - FEBRUARY 2026).

- **8th step (May 2024-April 2025):** A non-probability consecutive sampling method will be used to recruit 120 patients needed for the study in 1 year. Patients will only be accepted into the clinical trial if they meet all the inclusion criteria and none of the exclusion criteria, and must have read and signed the Informed Consent Form. Subsequently, they will be randomly assigned into two groups depending on whether they undergo the 18F-Choline PET-CT imaging test or 99mTc-MIBI SPECT/CT.
- **9th step (May 2024- Juny 2025)**: Imaging tests are performed, then in the first 8 weeks the minimally invasive parathyroidectomy is performed and the patients are hospitalized. Data are collected on the duration of the procedure, complications, blood PTH levels immediately after surgery, days of hospitalization and total hospital cost for each patient.
- **10th step (May 2024-December 2025)**: Patient follow-up will be carried out 1 week after surgery to assess possible post-parathyroidectomy complications. During subsequent follow-up visits, clinical evaluations and blood tests will be performed at 1 and 6 months.
- **11th step (May 2024- February 2026)**: The data analyst will record all data in a database.

During this entire stage, once every 3 months the study coordinator, the principal investigator and the co-investigator will meet telemetrically to evaluate whether the protocol is being complied with and communicate the progress in carrying out the clinical trial.

STAGE 4. STATISTICAL ANALYSIS AND INTERPRETATION (MARCH 2026 – JUNY 2026).

- **12th step (March 2026 – April 2026):** The statistical analysis of all the information collected will be carried out by the statistician who will be masked for intervention groups.
- **13th step (May 2026 - Juny 2026)**: The final statistical analysis will be interpretated by the main investigator and the coordinators of the two participating hospital. Then, discussion and conclusions from the previous analyses will be elaborated.

STAGE 5: PUBLICATION AND DISSEMINATION OF RESEARCH RESULTS (JULY 2026 – OCTOBER 2026).

- **14th step (July 2026 - October 2026)** : Presentation of the study result to the National Congress of General and Digestive Surgery and European Academy of General and Digestive Surgery. Publication of the results in scientific journals.

FIGURE 16. CHRONOGRAM .

	2023				2024							2025							2026			
	Sep	Oct	Nov	Dec	Jan	Feb	Mar-Apr	May-Jun	Jul-Aug	Sep-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun	Jul - Aug	Set-Oct	Nov	Dec	Jan-Fab	Mar-Apr	May-Jun	Jul-Oct
Stage 0																						
1: First meeting																						
2:Bibliographic research																						
3:Protocol elaboration																						
Stage 1																						
4: CEIC																						
5:Insurance																						
Stage 2																						
6: First meeting of the research team																						
7: Training workshop																						
Stage 3																						
8: Recruitment																						
9: Intervention																						
10: Follow-up																						
11: All data collection																						
Stage 4																						
12: Statistical analysis																						
13: Data interpretation																						
Stage 5																						
14: Report publication and congress presentation																						

11.BUDGET:

11.1 PERSONNEL EXPENSES :

The budget does not include the cost of the main research team, made up of physician belonging to the study hospitals. Therefore, no additional cost will be required.

A data manager will be hired to collect data and create a database. The approximate salary will be 30€/hour with a total cost of 2,100€ for 70 hours.

An independent statistician will also be hired to randomize and code patients, as well as perform the final statistical analysis from the data collected. The salary will be 40€/hour, for approximately 60 hours, and this will cost 2,400€.

11.2 INSURANCE POLICY:

Given that the study will require an injection of radiopharmaceuticals used in Nuclear Medicine to obtain the images, it is likely that the CEIC will consider this project as an invasive clinical trial. Therefore, it will be necessary to take out civil liability insurance that covers possible adverse events that may arise from the intervention of the procedure. The estimated cost is 40,000€.

11.3 EXECUTION EXPENSES :

The material for bibliographic research did not represented an additional expense.

Patients must be diagnosed by the Endocrinologist team, regardless of whether they enter the study or not, so the expense related to blood tests, ultrasound, densitometry will not be included in the budget. As the preoperative localization test, localization imaging tests such as 18F-Choline PET-CT and 99mTc-MIBI SPECT/TC will be performed, which will increase the budget. The price of PET-CT 18F-Choline is 800€, taking into account that it will be performed on 60 patients, the total would be 48,000 €. And the price of the Tc99m-MIBI SPECT/TC is 380 € , which will be applied to another 60 patients, the total price will be 22,800 €.

Subsequently, patients will undergo surgery and will be hospitalized, regardless of whether they will be included in the study or not, for this reason the costs related to the

parathyroidectomy and hospital stay are not included in the budget of this study. As during follow-up, blood test costs will not be included either.

The expense that we must include is the printing of the protocol, study information sheet, the informed consents and data collection sheets for each participant. The printing cost is 0.05 € per page.

11.4 TRAVEL AND COORDINATION EXPENSES:

For the proper functioning of the study, on-line meetings are planned every 3 months between the study coordinator, the principal investigator and the co-investigator. Its cost is not included in the budget.

At the beginning and at the end of the clinical trial at HUDJT, a meeting will be organized between the principal investigator and the co-investigators from the Vall d'Hebron Hospital. In the first meeting the study will be organized and, in the last meeting, the results obtained will be discussed to draw conclusions. Therefore, the person in charge of the Vall d'Hebron Hospital will have to travel to Girona. The average cost for both stays will be 460 €, including travel expenses, accommodation and meals.

11.5 PUBLICATION AND DISSEMINATION EXPENSES:

To disseminate the results of our clinical trial to the scientific community, we will attend national and international conferences. The study coordinator and the principal investigator will participate in the national conference with the final statistical analyzes and discussion. Its entry price is estimated at 500 € per person. Accommodation and meals are estimated at 500 € per person. Therefore, we estimate an approximate cost of 2,000 €.

The study coordinator and the principal investigator will also present our results and discussion at the international conference. Their entrance fee is estimated at 700 € per person and travel, accommodation and subsistence cost at 500 € per person. Thus, we are approaching a cost of 2,400€.

Once our study is completed and the results have been extracted and interpreted, it will be published as a journal article. We will need an English correction (500 €) and we must prepare Open Access (1,800 €), which represents a total expense of 2,300 €.

TABLE 5. APPROXIMATE BUDGET FOR THE CLINICAL TRIAL.

EXPENSES	COST PER UNIT	NUMBER OF UNITS	SUBTOTAL
Personnel expenses			
Investigators	-	-	0 €
Data manager	30€/hour	70 hours	2,100 €
Statistical analysis	40€/hour	60 hours	2,400 €
Insurance policy			
Trial policy	40,000€/trial	1	40,000€
Material and execution			
PET-CT 18F-Choline	800€	60	48,000 €
99mTc-MIBI scintigraphy SPECT/CT	380€	60	22,800 €
Printing cost	0,05€ /page	2,700 pages	135€
Travel and coordination			
Meetings	460 €	2	920€
Dissemination and Publication			
National congress	1,000€	2	2,000€
International congress	1,200€	2	2,400€
Article translation	500€	1	500€
Article publishing fees	1,800€	1	1,800€

TOTAL: 123,055€

12 LIMITATIONS:

During the design process of this clinical trial protocol, several limitations were identified that should be taken into account when performing statistical analyses.

- This study is **open-label** and cannot be blinded to patients or radiologists, which may lead to **detection bias.** To minimize this potential bias, the statistician evaluating the final results will be masked.

- This is a multicenter trial, first of all there is a probability that Hospital Vall d'Hebron will refuse to participate in the study, which will reduce the sample size. In addition, the intervention is an operator-dependent imaging test and there is the possibility of inter and intravariability not only between hospitals but also between professionals in the same hospital. To avoid this possible **variability,** all Nuclear Medicine physicians and technician will receive a telematic workshop to unify their techniques and discuss their different approaches. In addition, the two hospitals selected to participate in this study have similar capabilities and resources to obtain common results.
  In addition, being a multicenter study improves its **external validity.**

- Since the sampling method will be **non-probability consecutive**, there is a risk of selecting a non-representative sample, giving rise to **selection bias**. The consecutive method was chosen because it is one of the non-probability methods that induces less bias.
  To minimize selection bias, the inclusion and exclusion criteria were carefully selected and randomization will also be performed to distribute the patients in a 1:1 ratio.

- Due to the prospective format of the clinical trial, there is a risk of **withdrawals** during the 6-month follow-up period. This risk was assessed with a 10% dropout rate when determining the sample size. Therefore, the sample size has been increased to cover those who might drop out of the clinical trial. To avoid dropouts, the research team will make calls to patients if they are absent at follow-up visits and encourage them to continue with the study.

- This clinical trial will **cost** a total of 123,055 €, due to the use of imaging techniques that have high costs. We are aware that this is a costly study, but we believe that the impact of this study on the public health system can be so significant that the cost is fully justified. In addition, it may provide better quality of life for patients during and after surgery.

- It is important to note possible **confounding bias**. In order to minimize it, adequate randomization will be performed, in addition, we will perform stratified analysis for each subgroup and multivariate analysis to minimize the presence of confounding factors. In addition, the sample will be limited by exclusion criteria that will eliminate some of the confounding.

- Both arms of the study involve invasive interventions, although they have minimal **adverse effects and complications**, patients should be warned of the possible harms derived from the intervention so that if they perceive any, they should go immediately to the hospital.

13 FEASIBILITY:

We consider this clinical trial feasible taking into account the following points.

This trial will be carried out in two Catalan hospitals, the **Dr. Josep Trueta University Hospital** and the **Vall d'Hebron University Hospital**, both of which have the necessary resources and the appropriate Nuclear Medicine machines to perform the imaging tests necessary for this study.

We do not expect to have any problems when requesting the necessary imaging tests to perform the trial, as this is a standard procedure in both hospitals.

The project will be carried out in the **Endocrine Surgery Unit**, a multidisciplinary team made up of Endocrinologists, General Surgeons, Nuclear Medicine physician, nursing staff and pathologists. All professionals have sufficient experience to meet the needs of patients and carry out the study procedures.

A sample of 120 patients was estimated to carry out the study. A multicenter study will be carried out so as not to extend the estimated recruitment time more than 1 year. This is a reasonable period from a logistical point of view. The total duration of the study will be approximately 3 years and 2 month with the possibility of financing, because the price of the study is high.

Coordination of both centers will be done through telematic meetings once every 3 months. It will be necessary to hire a data manager to collect data and create a database, and a statistician to analyze the results.

We believe that the main obstacle in the execution of this protocol is its **cost,** but we have no doubt that we will obtain the necessary financing to carry it out.

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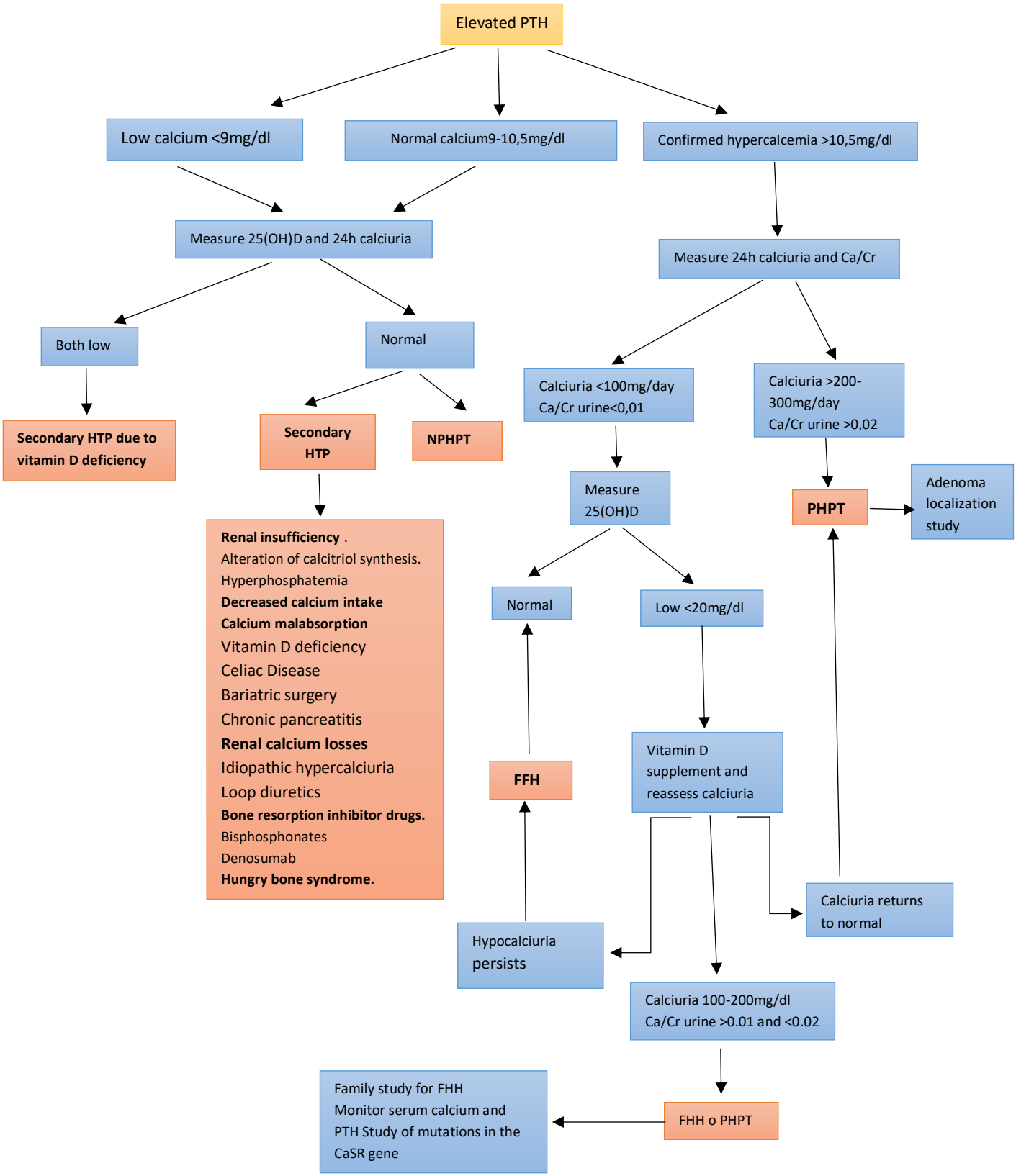
15 ANNEXES:

ANNEX 1. THE MAIN GERMLINE MUTATIONS AND/OR MOLECULAR MECHANISMS RELATED TO PHPT (6,14,16,18).

Hereditary disorder and inheritance	Gene (protein)	Gene location	Mechanism	Clinical Features
MEN 1 (AD)	MEN 1 (Gene encoding menin, a protein involved in cell cycle control)	11q13	Tumor suppressor gene; loss of function	PHPT (95%); pancreatic islet tumors (40%); anterior pituitary adenomas (30%); additional features: adrenocorticoid or carcinoid tumors, lipomas, cutaneous angiofibroma and collagenomas.
MEN 2 (AD)	RET (proto-oncogene c-Ret, gene encoding a receptor tyrosine kinase involved in cell proliferation)	10q11.21	Proto-oncogene ; gain of function	PHPT (20%); Medullary thyroid carcinomas (99%); pheochromocytomas (50%)
MEN 4 (AD)	CDKN1B (gene encoding p27)	12p13.1	Tumor suppressor; loss of function	PHPT (~80%), anterior pituitary tumors (~40%), pancreatic neuroendocrine tumors; other features: adrenal, thyroid, gonadal and renal tumors,
Hyperparathyroid–Jaw Tumor Syndrome (HPT-JT) (AD)	CDC73 (also known as HRPT2; gene encoding parafibromin, a protein that regulates histone methylation.)	1q31.2	Tumor suppressor ;loss of function	PHPT with a high prevalence of parathyroid carcinomas (15%) and adenomas 80%; ossifying fibromas of the mandible and maxilla; renal and uterine tumors including adenomyosis and leiomyoma
Familial isolated hyperparathyroidism (FIHP) (AD)	MEN1 (menin) CASR (CASR) GCM2 (GCM motif protein 2, also known as hGCMb) CDKN1B HRPT2	6p24.2	Proto-oncogene; gain of function	PHTP (100% exclusive form) Isolated PHTP, multiglandular hyperparathyroidism
Neonatal Severe Primary Hyperparathyroidism (NSHPT) (AD or AR)	CASR	3q13.3-q21.1	Impaired calcium sensing or signal transduction; loss of function	Severe hypercalcemia at birth with associated bone demineralization and failure to thrive (associated with bi-allelic loss of function of CASR), hypotonia, respiratory distress
Familial Hypocalciuric Hypercalcemia (FHH) **-FHH type 1** **-FHH type 2** **-FHH type 3** (AD)	 CASR GNA11 AP2S1	 3q13.3-q21-1 19p13.3 19q12.32	Impaired calcium sensing or signal transduction	Lifelong elevation of serum calcium with inappropriately low urinary calcium excretion (Ca/Cr <0.01) and normal or mildly elevated PHT
GCM2 (AD?)	GCM2	6p24.2	Proto-oncogene; gain of function	Multiglandular hyperparathyroidism (enriched in Ashkenazy Jewish populations)
AIP (AD)	AIP (aryl hydrocarbon receptor modulating protein)	11q13.2	Tumor suppresser	Its germline mutation has been related to the appearance of pituitary adenomas (Familial Isolated Pituitary Adenoma [FIPA]).

ANNEX 2: DIAGNOSTIC ALGORITHM FOR HYPERPARATHYROIDISM (18,25).



*PHPT: Primary Hyperparathyroidism ; FHH Familial Hypocalciuric Hypercalcemia; NPHPT: Normocalcemic hyperparathyroidism; Ca: calcium; Cr: creatinine

ANNEX 3: PROTOCOL INFORMATION SHEET.

HOJA DE INFORMACIÓN PARA EL PACIENTE SOBRE EL ENSAYO CLÍNICO

NOMBRE DE ESTUDIO:

INVESTIGADOR PRINCIPAL:

CENTRO DE REFERENCIA:

Bienvenido/a,

Nos dirigimos a usted para invitar-lo/la a participar en un estudio de investigación médica que se está llevando a cabo por el Servicio de Cirugía General y Digestiva del Hospital Universitario Dr. Josep Trueta de Girona y Hospital Universitario Vall d'Hebron de Barcelona.

Este estudio ha sido aprobado por el Comité de Ética de investigación clínica de los dos hospitales que participan, y por la Agencia Española del Medicamento y Producto sanitario.

El objetivo de este documento es proporcionar toda la información relacionado con el estudio para que pueda decidir voluntariamente si quiere participar. Por este motivo le pedimos que lea atentamente todos los apartados y no dude en ponerse en contacto con nosotros si tiene alguna pregunta o necesita alguna aclaración.

DESCRIPCION Y OBJETIVO DEL TRABAJO:

Este estudio se centra en las persona recientemente diagnosticados del Hiperparatiroidismo Primario, que consiste en un trastorno endocrino caracterizado por una secreción excesiva de hormona paratiroidea , que provoca hipercalcemia y diversas manifestaciones clínicas. En un 80% de los casos la causa es un adenoma paratiroideo único.

Para su tratamiento existen dos opciones:

- Tratamiento quirúrgico: consiste en extirpación del tejido paratiroideo hiperactivo, es el único método probado para el tratamiento definitivo y potencialmente curativo del hiperparatiroidismo primario.

- Tratamiento farmacológico: permite reducir hipercalcemia y controlar resorción ósea, pero no puede proporcionar la curación de la enfermedad. Este tratamiento está indicado en pacientes que no son aptos para el tratamiento quirúrgico o rechazan la intervención.

Antes de realizar el procedimiento quirúrgico , se realizan la pruebas de imagen para localizar el tejido paratiroideo a extirpar, lo que permite al cirujano identificarlo más fácilmente durante el procedimiento.

Las pruebas de imagen que se utilizaran para localizar el tejido hiperfuncionante en este estudio serian: la gammagrafía con Tc99m- sestaMIBI en combinación con SPECT/CT que se realiza como prueba de primera línea y se utiliza de forma habitual , permitiendo localizar el tejido hiperactivo en mayoría de los casos y la segunda prueba utilizada en este estudio es 18F-Colina PET/CT, esta prueba normalmente se utiliza en casos si las pruebas de primera línea son negativas o no concordantes.

Durante los últimos años ,en base de diferentes estudios, se ha visto que la prueba PET-CT 18F-Colina proporciona mejores resultados en localización de tejido paratiroideo patológico, en comparación de las pruebas convencionales ,y tiene un perfil de seguridad adecuado.

El propósito de este ensayo clínico es comparar los resultados quirúrgicos en pacientes sometidos a PET-CT 18F-Colina preoperatoria en un grupo de pacientes , y otro grupo de pacientes sometidos a gammagrafía con 99mTc-MIBI . Además se analizaran y se compararán posibles complicaciones, curación postoperatoria , estancia hospitalaria y coste hospitalario entre ambos grupos.

METODOLOGIA Y INTERVENCION:

En este estudio participaran un total de 120 pacientes, los cuales serán distribuidos de forma aleatoria en 2 grupos de igual tamaño:

- Grupo A: a los pacientes de grupo A se realizara la prueba de imagen estándar que es gammagrafía con Tc99m- sestaMIBI SPECT/TC.
- Grupo B: a los pacientes de grupo B se realizara la prueba de imagen PET-CT 18F-Colina.

Una vez realizadas las pruebas de imagen , independientemente en que grupo se encuentren los pacientes, se realizara paratiroidectomía mínimamente invasiva. Los datos obtenidos durante el procedimiento quirúrgico, hospitalización y las visitas de seguimiento se quedaran registrados en la base de datos para su posterior análisis de forma totalmente anónima.

Tras el alta hospitalaria, el paciente será seguido por el departamento de Cirugía General y Digestiva y profesionales de servicio de Endocrinología y Nutrición de cada hospital.

BENEFICIOS Y RIESGOS DEL ESTUDIO:

El principal beneficio esperado en este estudio, es mejorar resultados quirúrgicos después de paratiroidectomía ,aumentar la tasa de curación y disminuir las estadas hospitalarias post-intervención en pacientes a los que se realiza prueba de imagen de localización 18F-Colina PET/CT.

Estudios anteriores no han informado sobre efectos adversos significativos relacionados con la proba PET-CT F18-Colina. Sin embargo hay que mencionar que, es una prueba que utiliza radiotrazador, es decir , unas pequeñas partículas radioactivas , lo que conlleva un riesgo insignificante debido a baja dosis de radiación. También pueden experimentar reacciones alérgicas leves a radiotrazador y un ligero dolor o enrojecimiento leve a la zona de inyección de radiosonda.

Además, para garantizar no perjudicar la salud de los pacientes, seleccionamos a las personas que participan en el estudio con criterios específicos.

ALTERNATIVAS AL PROCEDIMIENTO:

En caso si el paciente decide no participar en el estudio, se le realizaran las pruebas de imagen convenciones preoperatorias y se realizara procedimiento quirúrgico. Recibirán la misma atención y visitas de seguimiento igual que los pacientes que deciden participar en el ensayo clínico.

CONFIDENCIALIDAD:

Toda la información médica y personal proporcionada durante el estudio será tratada con la máxima confidencialidad de acuerdo con la Ley 3/2018, de 5 de Diciembre , de protección de datos personales y garantía de los derechos digitales .

Debemos destacar que en caso si los resultados se publicaran en congresos o publicaciones científicas , siempre serán anónimos y globales, ninguna información personal será publicada.

PARTICIPACIÓN Y COMPENSACIÓN ECONÓMICA:

Su participación es estrictamente voluntaria y no recibirá ninguna compensación por participar en este estudio, pero tampoco le supondrá ningún gasto. Los investigadores y coautores de este estudio tampoco recibirán compensación por su participación.

Si elige participar , debe firmar un formulario de consentimiento, que será entregado después de que haya leído documento de información del paciente y desee participar en este estudio. También tiene su derecho de salir del estudio durante el transcurso del mismo si asi lo desea, aunque le pedimos que previamente lo comunique al equipo investigador.

RESPONSABILIDAD Y SEGURO:

Los patrocinadores de este estudio tienen contratada una póliza de seguro para poder realizar este ensayo clínico, de acuerdo con los requisitos legales. Recibirá una indemnización en caso de perjuicio o deterioro de la salud como resultado de su participación en el estudio.

CONTACTO:

Si tiene alguna duda en relación a este estudio o necesita más información , puede contactarnos en cualquier momento mediante:

Investigador principal: Dr/Dra:_____

Teléfono: _____

Correo electrónico:_____

Gracias por su atención**.**

ANNEX 4 : STUDY INFORMED CONSENT:

DOCUMENTO DE CONSENTIMIENTO INFORMADO:

Yo,_____ ,con DNI/NIF_____
acepto voluntariamente participar en este estudio y manifiesto:

- He estado debidamente informado/a por el Dr./Dra. _____ i he recibido una copia de la hoja de información para el paciente.
- He leído y he entendido todo el contenido que aparece en la hoja de información para el paciente.
- He podido plantear todas las dudas que me han surgido , y me las han resuelto adecuadamente.
- Estoy de acuerdo con la cantidad de información proporcionada.
- Comprendo los riesgos y beneficios que comporta participar en este estudio.
- Comprendo que puedo negarme a participar en este estudio sin la necesidad de dar explicaciones y sin que ello afecte mi trato médico.
- Comprendo que mis datos se utilizaran únicamente con finalidad de investigación médica, y serán completamente confidenciales .
- Comprendo que mi participación es totalmente voluntaria y que podre revocar el consentimiento previamente firmado en cualquier momento .

Firma del paciente: **Firma del responsable/ investigador:**

Lugar y fecha: _____, _____ de _____ del 20_____.

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO:

Yo,_____ revoco el consentimiento informado previamente firmado para participación en este estudio especificado en mismo documento.

Firma del paciente: **Firma del responsable/ investigador**

Lugar y fecha:_____, _____ de _____ del 20_____.

ANNEX 5 : PATHOLOGY REPORT.

DATOS DEL PACIENTE:

Número de identificación:

Sexo:

Edad:

SOLICITUD ESTUDIO DE ANATOMÍA PATOLÓGICA:

Centro peticionario:

Servicio remitente:

Tipo de paciente:

Prioridad: Fecha de solicitud:

Tipo de muestra :

Órgano:

Datos clínicos:

Numero de muestras:

Datos adicionales:

Firma:

ANNEX 6 : DATA COLLECTION FORM.

Investigador: _____

Centro: _____

DATOS DE INDENTIFICACIÓN:

Número de Identificación:_____

DATOS GENERALES:

Fecha de Nacimiento:___/___/_____

Sexo:

☐ M ☐ F

ANTECEDENTES:

Antecedentes de cirugía tiroidea o paratiroidea:

Sí ☐

No ☐

Fenotipo de Hiperparatiroidismo primario:

☐ Clásico o sintomático

☐ Asintomático

☐ Normocalcemico

Niveles sanguíneos de calcio y PTH:

Calcio :_____mg/dL

PTH: _____pg/dL

Criterio quirúrgico:

☐ Edad <50 años
☐ Hipercalcemia
☐ Fracturas
☐ Hipercalciuria
☐ Osteoporosis
☐ Nefrocalcinosis o nefrolitiasis
☐ Filtrado glomerular < 60 mL/min

DATOS ANATOMOPATOLÓGICOS:

Tipo de lesión:

☐ Adenoma

☐ Hiperplasia

☐ Carcinoma

Localización:

☐ Superior derecha
☐ Inferior derecha
☐ Superior izquierda
☐ Bilateral
☐ No localizado
☐ Inferior izquierda
☐ Submandibular
☐ Mediastino
☐ Otro

Mida:

_____mm

INTERVENCIÓN QUIRÚRGICA:

Data intervención : ___/____/____

Duración: _____

Niveles sanguíneos de PHT postoperatorios:_____pg/dL

Complicaciones:

☐ Hematoma cervical

☐ Lesión del nervio laríngeo recurrente

☐ Hipoparatiroidismo permanente

☐ Infección

☐ Dehiscencia de la herida quirúrgica

Nº días de hospitalización: _____ días

Coste total:_____ €

SEGUIMIENTO:

Niveles sanguíneos de Calcio_____ mg/dL y **PTH**_____pg/dL