Primary Hyperparathyroidism: A Case Series, Patient-Centered Approach to Diagnosis and Management Review

Ann. Ital. Chir., 2025 96, 7: 878–893
https://doi.org/10.62713/aic.3939

Adriana Gioia[1,2], Clemente Junior Nappi[1,2], Martina Socin[3], Giulia Vallon[1,2], Samuele Naviglio[4], Stella Bernardi[1,5], Alessandro Boscarelli[6], Chiara Dobrinja[1,2]

[1]Department of Medicine, Surgery and Health Sciences, University of Trieste, 34149 Trieste, Italy
[2]UCO Clinica Chirurgica, ASUGI (Azienda Sanitaria Universitaria Giuliano Isontina), Cattinara Teaching Hospital, 34149 Trieste, Italy
[3]Anestesia, Rianimazione, Terapia Intensiva e del dolore, Policlinico Umberto I, Sapienza University, 00161 Rome, Italy
[4]Institute for Maternal and Child Health IRCCS "Burlo Garofolo", 34137 Trieste, Italy
[5]SS Endocrinology, ASUGI (Azienda Sanitaria Universitaria Giuliano Isontina), Cattinara Teaching Hospital, 34149 Trieste, Italy
[6]Department of Pediatric Surgery and Urology, Institute for Maternal and Child Health IRCCS "Burlo Garofolo", 34137 Trieste, Italy

Primary hyperparathyroidism (pHPT) is a prevalent disorder of dysregulated calcium homeostasis, marked by excessive secretion of parathyroid hormone (PTH), which results in alterated calcemia and renal and/or skeletal complications. Most patients are diagnosed before experiencing overt clinical symptoms, often as a result of blood tests performed for other disorders. When symptoms do manifest, they are associated with dysfunction of the parathyroid glands. Surgical treatment is considered the first choice and the only curative treatment for pHPT, offering advantages for both symptomatic and asymptomatic patients. The aim of this study is to report our experience in the management of 6 selected complex cases, which often require a multidisciplinary approach due to the lack of established diagnostic and therapeutic algorithms and the variability of clinical presentation and atypical parathyroid adenoma location. We present a series of cases examining the various treatment approaches in six distinct patients: one patient with parathyroid carcinoma with concomitant parathyroid adenoma, a case involving mediastinal parathyroidectomy, a case with an intrathymic parathyroid adenoma, two cases of recurrent pHPT, and one case of hereditary pHPT in Multiple Endocrine Neoplasia (MEN) 1 syndrome. The combination of parathyroid ultrasound and Tc-99m sestamibi scintigraphy is effective for localizing parathyroid adenomas in most patients. Additional imaging, such as single photon emission computed tomography/computed tomography (SPECT/CT) or 18F-Fluorocholine positron emission tomography/computed tomography (18F-FCH PET/CT), may be necessary in other cases. Intraoperative parathyroid hormone monitoring is valuable for detecting double adenomas in patients affected by hereditary familial hyperparathyroidism from MEN 1. Several studies highlight that the surgeon's expertise is the most critical determinant of a safe and successful surgical outcome.

Keywords: primary hyperparathyroidism; parathyroid carcinoma; hereditary primary hyperparathyroidism; recurrent hyperparathyroidism; ectopic parathyroid adenoma; intraoperative PTH monitoring; multidisciplinary approach

Introduction

Primary hyperparathyroidism (pHPT) is one of the most prevalent endocrine disorders, causing disruptions in metabolic processes due to the autonomous overproduction and secretion of parathyroid hormone (PTH) by the parathyroid glands [1,2].

This excessive secretion leads to significantly elevated serum PTH levels, typically resulting in hypophosphatemia, hypocalciuria, and hypophosphaturia.

The prevalence of pHPT ranges from 0.1% to 1.0%, ranking it as one of the most frequent endocrine diseases, following diabetes and thyroid disorders [1,2]. It disproportionately affects women compared to men [3].

The incidence is approximately one case per 1000 men per year over 60 years old and two cases per 1000 women in the same age group [1,2]. pHPT is the leading cause of hypercalcemia and is often diagnosed in its asymptomatic phase as mild hypercalcemia, typically identified during routine biochemical screenings.

There are several aetiologies of pHPT: many cases (95%) seem to be sporadic, and the most common underlying cause is the presence of an adenoma. Adenomas could be single, representing about 84% of cases [1,3]. In rare cases, adenomas may be found in more than one gland. About 0.5–5% of cases of pHPT are represented by parathyroid carcinoma [3,4].

Submitted: 30 December 2024 Revised: 22 January 2025 Accepted: 20 February 2025 Published: 10 July 2025
Correspondence to: Chiara Dobrinja, Department of Medicine, Surgery and Health Sciences, University of Trieste, 34149 Trieste, Italy; UCO Clinica Chirurgica, ASUGI (Azienda Sanitaria Universitaria Giuliano Isontina), Cattinara Teaching Hospital, 34149 Trieste, Italy (e-mail: chiara.dobrinja@units.it).

Patients are generally diagnosed before the onset of clinically significant symptoms through blood tests conducted for other conditions. When symptoms do emerge, major manifestations include nephrolithiasis, peptic ulcers, and increased bone resorption, which heightens the risk of fractures. Additional clinical presentations may involve osteolysis, bone cysts, chronic kidney disease (CKD), nausea, vomiting, constipation, and an increased risk of cardiovascular complications such as hypertension, atherosclerosis, ventricular dysfunction, valvular calcifications, and conduction abnormalities [5,6].

Although parathyroid adenomas are the most common cause of pHPT, distinguishing them from hyperplasia can be challenging. Parathyroid carcinoma, although rare (0.5%–5% of cases) [3,4], requires surgical resection of the affected gland with ipsilateral thyroid lobe and central compartment lymph node dissection. Early diagnosis significantly enhances the likelihood of long-term, recurrence-free survival, although some aggressive carcinomas may metastasize to the lungs, liver, or bones. Despite advancements in diagnostic techniques, the management of primary hyperparathyroidism (pHPT) continues to face considerable challenges. One of the primary issues lies in distinguishing parathyroid adenomas from hyperplasia or carcinoma during imaging or surgical procedures, underscoring the importance of accurate preoperative diagnosis to prevent unnecessary or suboptimal interventions. Surgical decision-making for asymptomatic patients remains complex and is influenced by factors such as patient age, bone density, calcium levels and pathological parathyroid localization.

An additional challenge is the risk of disease recurrence following parathyroidectomy, which necessitates long-term monitoring and may require further surgical interventions, often associated with an increased risk of complications. Ongoing research aims to identify predictors of recurrence and develop effective preventive strategies.

Technological advancements in imaging techniques have significantly improved the preoperative evaluation of pHPT. High-resolution imaging modalities, including four-dimensional computed tomography (4D-CT), sestamibi scintigraphy, and 18F-Fluorocholine positron emission tomography/computed tomography (18F-FCH PET/CT), have enhanced lesion localization.

In surgical practice, focused parathyroidectomy has become the preferred approach for many patients due to its advantages in terms of postoperative pain, lower complication rates, and better cosmetic results. Intraoperative parathyroid hormone (ioPTH) further improves success rates by confirming the complete removal of hyperfunctioning tissue.

The adoption of personalized follow-up protocols and the use of calcimimetics for patients who are not surgical candidates are contributing to better clinical outcomes. Early diagnosis and individualized treatment strategies remain essential for optimizing long-term prognosis. These advancements highlight the evolving landscape of pHPT management and the ongoing need for research and innovation in this field.

The aim of our study was to report our experience in the management of 6 selected complex cases, which often require a multidisciplinary approach due to the lack of established diagnostic and therapeutic algorithms and variability of clinical presentation and atypical parathyroid location. This article discusses the rarity of parathyroid carcinoma, the discovery of ectopic adenomas, the management of recurrent pHPT, and the treatment of pHPT in Multiple Endocrine Neoplasia (MEN) 1 syndrome. It particularly emphasizes the importance of preoperative localization, the value of ioPTH measurement, and the impact of the surgeon's experience on surgical outcome.

Perioperative Management in Prymary Hyperparathyroidism—Review Section

Diagnosis of Primary Hyperparathyroidism

The initial step in differential diagnosis involves obtaining a detailed family history to exclude hereditary forms such as MEN types 1 and 2. The differential diagnosis must also distinguish pHPT from conditions such as lithium therapy-related hyperparathyroidism, malignancy-associated hypercalcemia, excessive calcium intake or reduced excretion, vitamin D toxicity, prolonged immobilization, hyperthyroidism, multiple myeloma, familial isolated hyperparathyroidism (FIHPT), asymptomatic pHPT, normocalcemic primary hyperparathyroidism (NPHPT), and severe forms like atypical parathyroid adenoma and parathyroid carcinoma [4–8].

Normocalcemic hyperparathyroidism poses a diagnostic challenge as serum calcium levels remain normal despite elevated PTH levels. It may overlap with primary or secondary hyperparathyroidism, necessitating a comprehensive evaluation to differentiate between these conditions. Diagnosis requires exclusion of secondary causes of elevated PTH through detailed medical history, physical examination, and targeted laboratory tests [7].

Biochemical Testing

Elevated blood calcium levels are associated with increased PTH secretion [9]. Under normal physiological conditions, hypercalcemia triggers negative feedback on the parathyroid glands, suppressing PTH release. In pHPT, this regulatory mechanism is impaired. Although low serum phosphate levels are often observed, they are less diagnostically significant than hypercalcemia, as phosphate levels can be influenced by diet and renal function. Severe hypercalcemia, however, may result in reduced serum phosphate concentrations.

pHPT is commonly identified through routine blood tests measuring PTH, calcium, and related minerals. Additional

Table 1. Pre-operative localization methods—imaging techniques in primary hyperparathyroidism for preoperative localization [4].

• First tier assessments
– serum calcium (total or ionized calcium)
– serum phosphorus
– serum creatinine
– intact PTH (1–84) (second or third generation assay)
– 25-hydroxy-Vitamin D
• Second tier assessments
– 24 h calciuria and phosphaturia
– Creatinine clearance

PTH, parathyroid hormone.

assessments, such as 24-hour urine collection, can evaluate calcium excretion rates (Table 1, Ref. [4]).

Imaging prior to surgery is considered the gold standard for identifying hyperfunctioning parathyroid glands, facilitating optimal surgical planning [10]. However, several unresolved questions remain in the domain of primary hyperparathyroidism (pHPT), particularly the need for standardizing and improving imaging algorithms for preoperative localization.

Today, various imaging techniques are employed in the pre-operative evaluation, including neck ultrasound (US), 99mTc-sestamibi (MIBI) scintigraphy, four-dimensional computed tomography (4D-CT), magnetic resonance imaging (MRI), and 18F-FCH PET/CT (Table 2). Neck US and MIBI-scintigraphy are the two conventional imaging methods most frequently used for preoperative parathyroid localization, either individually or in combination.

First-Line Imaging

• **Neck Ultrasound (US)**: This technique is valuable both preoperatively and intraoperatively due to its low cost and good access.

• **Single Photon Emission Computed Tomography (SPECT)**: A study indicated that preoperative parathyroid hormone (PTH) levels and gland size were significant determinants of Tc-99m-sestamibi positivity during early-phase Tc-99m scans, with size also being an independent factor in late-phase Tc-99m scans [11,12]. The combination of neck ultrasound and Tc-99m-sestamibi can enhance specificity and sensitivity, achieving over 90% accuracy [9]. When both methods yield positive results, a precise surgical approach can be determined. Negative results often lead surgeons to consider second-line imaging for gland localization. Ultrasound is used in nearly all cases. Cervical ultrasound plus Tc-99m-sestamibi are the most frequent imaging combination performed.

Second-Line Imaging

• **Magnetic Resonance Imaging (MRI)**

• **Four-dimensional CT (4D-CT) Scan**

• **18F-FCH PET/CT (Positron Emission Tomography Combined With CT Scan)**

MRI and 4D-CT are more advanced and costly [13], yet they are useful in identifying ectopic parathyroid glands. These methods are often employed in re-operative cases [14] and are beneficial for differentiating parathyroid carcinomas from other parathyroid lesions. Recent studies suggest that CT features such as irregular shape, peritumoral infiltration, and calcification could help distinguish parathyroid carcinoma from benign parathyroid hyperplasia [13–15]. 18F-FCH PET/CT, specifically with choline, has demonstrated favorable outcomes in detecting hyperfunctioning parathyroid tissue and may eventually replace traditional Tc-99m-sestamibi scintigraphy, SPECT, or SPECT/CT in preoperative planning for parathyroid surgery [16,17]. 18F-FCH PET/CT can localize single gland adenomas in 80–96% of cases. Table 2 listing the advantages and disadvantages, applicable scenarios, and diagnostic success rates of different imaging methods.

Surgical Treatment

Surgical intervention remains the primary and most effective treatment for pHPT. Conservative treatment is only indicated for patients who are unfit for surgery due to severe comorbidities, advanced age, absence of gland localization, or refusal of surgery.

• **Bilateral Neck Exploration (BNE)**

BNE has been the traditional treatment method for pHPT. It is now typically reserved for cases involving familial syndromes, multiglandular hyperplasia, or when imaging results are unclear. This procedure involves exploring the central part of the neck to identify all parathyroid glands. Once the adenoma is excised, the remaining glands or the ipsilateral gland are examined through biopsy or frozen section analysis. If results are normal, no further action is necessary. In cases of multiglandular hyperplasia, subtotal 3.5 parathyroidectomy is recommended [18]. The main drawbacks of BNE are its extended operative time and prolonged postoperative hospital stay compared to less invasive techniques.

• **Unilateral Neck Exploration or Focused Parathyroidectomy**

This technique is less invasive, offering a shorter operative time and improved preservation of the laryngeal nerve function. Intraoperative parathyroid hormone (ioPTH) assays are useful for confirming surgical success [19], although they have a 30% false positive rate in patients with double adenomas and a 13% false negative rate, which can lead to unnecessarily extended resections when no affected glands are present.

• **Minimally Invasive Parathyroidectomy (MIP)**

MIP aims to minimize surgical impact and improve outcomes. It is applicable to most patients with a single adenoma, which can be effectively identified and localized th-

Table 2. Advantages and disadvantages, applicable scenarios, and diagnostic success rates of different imaging methods.

Imaging technique	Advantages	Disadvantages	Applicable scenarios	Diagnostic success rates
Neck ultrasound (US)	- Non-invasive - Easy to perform - Low cost	- Limited sensitivity for ectopic parathyroid glands - Operator dependent	- First-line examination for the localization of parathyroid adenomas - Patients with adenomas localized in the neck	60–80% in patients with typical parathyroid adenomas
99mTc-sestamibi (MIBI) scintigraphy	- High sensitivity for parathyroid adenomas - Identification of ectopic adenomas	- Not always useful in the presence of malformations or non-functioning adenomas - Radiation exposure	- If there is any doubt about the ultrasound result - Localization of ectopic adenomas or recurrences	80–90% in symptomatic parathyroid adenomas
18F-Fluorocholine positron emission tomography/computed tomography (18F-FCH PET/CT) scan	- High sensitivity in complex cases and for ectopic adenomas - Good sensitivity even in case of recurrence	- More expensive than the other techniques - Not always available	- For ectopic adenomas or cases of difficult localization - Recurrences or complicated cases - Patients with suspicious recurrence or small adenomas	90–95% in complex or ectopic cases
Magnetic resonance imaging (MRI)	- Good for assessing the location and size of tumors - No radiation exposure	- Not always sensitive for small adenomas - Expensive and less common for hyperparathyroidism	- If other tests fail - For the evaluation of recurrences or large adenomas	70–85% in cases with detectable parathyroid adenomas
4D-computed tomography (CT)	- Great for locating deep or ectopic adenomas - Good for assessing the presence of adenomas in the mediastinum	- Radiation exposure - Lower sensitivity than other methods for superficial adenomas	- For ectopic or deep parathyroid adenomas - In case of suspected mediastinal	75–90% in cases with deep or mediastinal adenomas

rough preoperative imaging and intraoperative PTH mea surements. There are several techniques:

○ **Open MIP (OMIP)**: A unilateral approach that requires intraoperative PTH assays (measuring at 0', 5', and 15' post-excision). This technique explores only one side of the neck [20].

○ **Endoscopic MIP (EMIP)**: EMIP is known for its superior cosmetic results and safety when dealing with deep or ectopic glands. It offers excellent magnification and lighting for precise dissection [21–23]. This method can also be used in complicated cases. In addition to the cervical approach, an extra-cervical approach, such as axillary, can be considered. It offers the best cosmetic results but requires more dissection time and poses greater risks.

○ **Minimally Invasive Video-Assisted Parathyroidectomy (MIVAP)**: A gasless procedure performed through a 15–20 mm incision at the suprasternal notch, with partial assistance from an endoscope [24,25]. MIVAP is suitable for most patients with sporadically diagnosed pHPT, provided the following criteria are met:

- No prior neck surgeries
- Absence of thyroiditis
- Clear identification of a single adenoma with concordant ultrasound and sestamibi scintigraphy

The benefit of MIVAP lies in its ability to explore both sides of the neck via central access and to perform thyroid surgery with reduced postoperative pain, better cosmetic outcomes, and shorter hospital stays.

○ **PureEndoscopic Technique [21,22]**: This approach involves continuous gas insufflation and the use of three or four trocars. The procedure is entirely guided by the endoscope, with a midline entry between the strap muscles [23] or alternatively a lateral entry along the anterior edge of the sternocleidomastoid muscle, following the "back route" between the carotid sheath laterally and the strap muscles medially [21]. An extra cervical approach, such as through the axilla or the anterior chest, can also be employed. These approaches leave no visible scars but require more extensive dissection.

The main interest of using an endoscope is not that one can perform a parathyroidectomy through a small incision, but that one can perform a safe parathyroidectomy through a small incision [22]. Superior parathyroid glands are located posteriorly to the thyroid lobe, and they tend to be close to the nerve. The inferior parathyroid glands adenomas are usually located at the posterolateral part of the inferior pole of the thyroid lobe and tend to occupy a paratracheal or a paraesophageal position, becoming intimate with the recurrent laryngeal nerve. Other inferior parathyroid adenomas remain located superficially in the neck or in the superior mediastinum. The advantage of EMIP is wider exposure of cervical structures. In addition, insufflation with carbon dioxide (CO_2) creates a working space. According to JF Henry's study [22] studies, the endoscopic lateral approach seemed to provide the best access to the posterior aspect of the thyroid lobe, allowing a complete exploration of all anatomical elements of the retro-thyroidal area [22].

• **Radioguided Parathyroidectomy (MI-RP)**: Utilizes Tc-99m-sestamibi intraoperatively [26]. The patient is re-injected with the tracer up to 60 minutes before surgery. After the gland is excised, the neck's activity is measured using a gamma probe, which is especially useful for excising ectopic adenomas within the thymus [27].

New Surgical Approaches

• **Transoral Endoscopic Parathyroidectomy**

This scarless approach is performed through the oral vestibule and is suitable for selected patients with pHPT [28]. The procedure involves inserting a trocar through the oral vestibule and creating a working space using CO_2 insufflation. Intraoperative PTH levels and frozen section analysis are performed.

• **Robotic-Assisted Parathyroidectomy via Trans-Axillary Approach**

This technique, which has gained popularity in South Korea, eliminates the need for a neck scar. It requires precise preoperative localization using ultrasound and Tc99m-sestamibi scans. While this method offers enhanced precision due to 3D visualization and greater flexibility in robotic arms [29], it has a longer operative time, higher cost, and requires an experienced surgeon. Additionally, some patients may experience mild post-operative discomfort from the flap [30].

Intraoperative PTH Assay

Introduced in 1996, the intraoperative PTH assay tracks serum PTH levels to verify the efficacy of adenoma removal.

(1) Pre-surgery assay (basal) or right before the adenoma excision

(2) 5 minutes post excision assay

(3) 15 minutes post excision assay

A reduction of $\geq$50% in PTH levels five minutes after excision is indicative of surgical success and appropriate calcium levels [31].

Indocyanine Green (ICG) Fluorescence-Guided Parathyroidectomy

ICG is a non-toxic dye that, when exposed to near-infrared light, emits fluorescence that can be detected in real time, allowing for efficient and safe identification of hypervascularized parathyroid adenomas [32,33].

Intraoperative Autofluorescence

The need to identify the parathyroid glands intraoperatively led to the study of various exogenous contrast agents, such as methyl-ne blue or aminolevulinic acid, which were later abandoned because of their toxicity and adverse reactions. An important discovery was published in 2011 by a team of

biomedical engineers at Vanderbilt University (Nashville, TN, USA), who described for the first time the autofluorescent properties of parathyroid tissue in the near-infrared (NIR) spectrum. Parathyroid tissue, following excitation at the NIR wavelength of 785 nanometers, emits at a wavelength between 820–830 nanometers that can be captured by a camera. Its emission intensity is 2 to 11 times higher than that of surrounding tissues, thus enabling its identification. The endogenous fluorophore responsible is still unknown. Therefore, devices consisting of a laser emitter associated with a camera capable of detecting parathyroid autofluorescence and reproducing it in a black-and-white image have been developed.

Recent advances have shown that parathyroid tissue emits autofluorescence when exposed to near-infrared light, with a specificity of more than 80%. This discovery enables precise intraoperative identification of parathyroid glands based on fluorescence patterns, with adenomas displaying less intense and more heterogeneous autofluorescence than normal tissue [34].

Materials, Methods and Results (Case Series)

All patients give the consent to participate at the study. The images were obtained from the hospital radiologic database, and patient information was retrieved from medical records, with prior acquisition of informed consent for both.

Case 1: Parathyroid Carcinoma With Concomitant Parathyroid Adenoma

Female patient, age 73 comes to endocrinological visit because of hypothyroidism associated with previous renal colic and bone fracture. On vitamin D and calcitriol therapy.

At follow-up, the patient had hypercalcemia values of 11.1 mg/dL (range in our laboratory: 8.5–10.5 mg/dL) associated with hypercalciuria and PTH blood serum levels of 298 pg/mL. The patient performed neck ultrasonography identificating of suspected right inferior parathyroid adenoma in the parahistmic site. Subsequent scintigraphy showed a minimal area of increased uptake in the right parahistmic site with nonspecific significance (Fig. 1).

The clinical and radiological findings gave indication to a surgical approach. Surgery intervention consisted of searching the suspected parathyroid adenoma posteriorly of the right thyroid lodge with consequent excision, but after paratracheal neoformation removal, the intraoperative PTH didn't descend (413 pg/mL). Surgery proceeded with bilateral neck exploration and an enlarged inferior left parathyroid gland which was removed with a consequent ioPTH drop (104.9 pg/mL) was found.

Histological examination showed the presence of a right parathyroid carcinoma and the presence of a left parathyroid adenoma. Given the histological results, it was decided to proceed with a complete cervical lodge revision surgery and total thyroidectomy using an intraoperative Nerve integrity monitoring (NIM) system and central compartment lymphadenectomy.

The final histological specimen demonstrated minimal centers of chronic lymphocytic thyroiditis with a microfollicular adenoma in the right thyroid lobe (Table 3). No metastatic lymph nodes were detected, and at 8 years of follow-up, the patient is well and alive.

Case 2: Difficult Preoperative Localization—High Sensibility of 18F-Fluorocholine PET/CT—Mediastinal Parathyroidectomy

Female patient 61 years old, physiologically menopausal, suffering from severe osteoporosis (DEXA 2021: lumbar T-score: –3.1; femur T-score –1.5). Medical history showed a previous quadrantectomy for breast cancer and subsequent tamoxifen therapy and complementary radiation therapy (RT).

Preoperative examination: Calcium 12.5 mg/dL; PTH 213.9 pg/mL; Phosphorus 3 mg/dL; 24 h Calciuria 34.8 mg/dL. Radiological studies including neck ultrasound, scintigraphy with 99mTc pertechnetate and 99mTc-sestamibi resulted negative, excluding the presence of hyperfunctioning parathyroid tissue either in usual or ectopic sites.

Therefore, in reason of the clinal status and laboratory findings the patient performed PET tomography with 18F-Fluorocholine that documented focal hyperaccumulation of the tracer in the anterior mediastinal location, posterior to the retrosternal manubrium (Fig. 2).

The patient was referred for surgery.

During surgery, the difficulties in approaching the gland correctly because of the anatomical site required the support of the thoracic surgeon. Without performing a sternotomy, the parathyroid tissue was found to be localized in a retrosternal ectopic location. The ectopic abnormal gland was removed. The adequate tissue asportation was confirmed at extemporaneous histological examination.

Intraoperative assay of PTH was also performed, showing a progressive decrease in blood serum after the gland's removal (ioPTH at time 0': 205.9 pg/mL, ioPTH at 5': 366.5 pg/mL, ioPTH at 15': 44.9 pg/mL). The patient was dismissed with regular blood serum values of calcium and decreased PTH (41.1 pg/mL). Histological examination confirmed for adenoma (Table 4).

Case 3: Intrathymic Localization

Female patient, 62 years old, with a medical history of bone fractures, osteoporosis and nephrolithiasis, and subclinical thyroid autoimmune disease. Laboratory findings of hypercalcemia (10.6 mg/dL) and high value of PTH (144 pg/mL) levels. Scintigraphy showed presence of a major tracer fixation on the lower inferior thyroid pole (Figs. 3,4). The patient underwent surgery with intraoperative PTH assay.

At the first exploration of the surgical side, identified preoperatively with scintigraphy, no pathological gland was

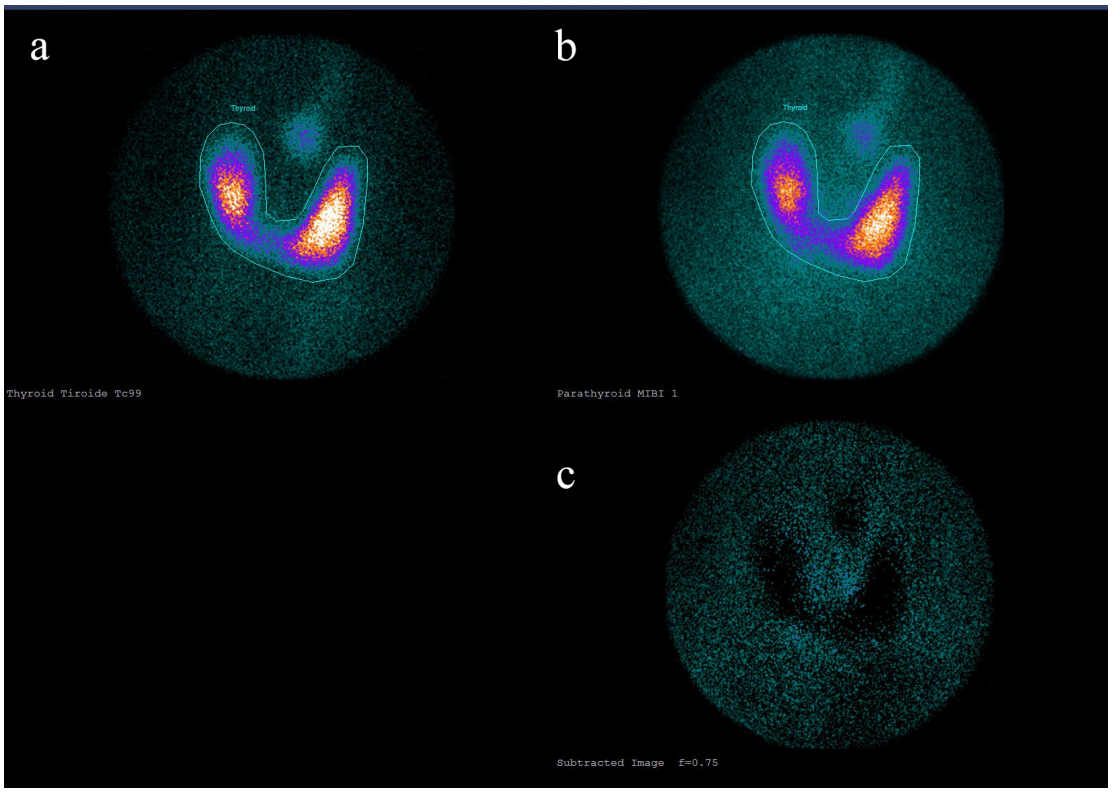

Fig. 1. Dual-phase imaging with Tc-99m-sestamibi localizing parathyroid adenoma on the superior parahistmic right area (a) early phase, (b) delayed phase, (c) subtracted image.

Table 3. Case 1: Parathyroid carcinoma with concomitant parathyroid adenoma—patient's clinical manifestations, laboratory tests, imaging findings, and surgical procedure.

Category	Details
Patient	Female, 73 years old
Clinical manifestations	Hypothyroidism, previous renal colic, bone fractures, hypercalcemia
Laboratory tests	Calcium: 11.1 mg/dL, PTH: 298 pg/mL, hypercalciuria
Imaging	Neck ultrasound: suspected right inferior parathyroid adenoma; Scintigraphy: minimal uptake
Surgical procedure	Right parathyroid adenoma excision; bilateral neck exploration; left inferior parathyroid removal; thyroidectomy
Histology	Right parathyroid carcinoma, left parathyroid adenoma, chronic lymphocytic thyroiditis
Outcome	Complete cervical revision, total thyroidectomy, no metastatic lymph nodes, 8-year follow-up, patient well

found. Some peri-thyroid fat tissue was removed, but the ioPTH showed no decrease after the excision (ioPTH at 0': 110.2 pg/mL, at 5': 107.8 pg/mL, at 10': 151.2 pg/mL). The subsequent exploration of the thymus permitted the discovery of an intrathymic, ectopic, abnormal gland. The ioPTH assay demonstrated the adequate removal (ioPTH 5 minutes after the removal of the intrathymic parathyroid gland: 37.9 pg/mL). The final histological examination confirmed an intrathymic parathyroid adenoma. No vascular, lymphatic or perineural infarction were detected (Table 5).

Case 4: Recurrence of Primary pHPT

87-year-old male patient. In medical history: stroke with right temporal hemianopsia, asthma chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS), adenocarcinoma of prostate radiotherapy and hormone treatment, and monoclonal gammopathy unknown significance (MGUS).

In 2011 the patient underwent right inferior parathyroidectomy surgery for parathyroid adenoma. After 10 years, occasional findings on blood chemistry tests of a higher value of PTH 102.3 ng/L with a normal range of calcium serum levels. Cervical ultrasound was performed with evidence, at the base of the right thyroid lobe, of an 8 mm lesion.

For suspected relapse of primary hyperparathyroidism, a parathyroid scintigraphy with Tc99m-sestamibi was performed and a focal area of radiopharmaceutical hyperaccumulation was appreciated. On SPECT/CT images with low-dose CT this suspected area corresponded to a nodulation located posteriorly to the middle third of the right thyroid lobe. Scintigraphy was compatible with the presence of parathyroid tissue. Re-intervention was planned (Fig. 5).

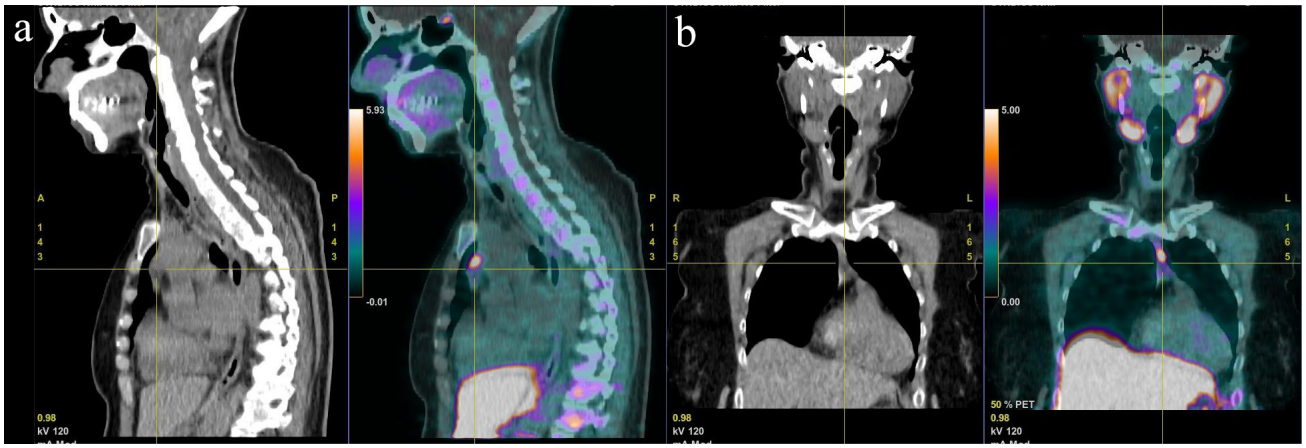

Fig. 2. Case 2: Dual-phase imaging with choline PET/CT localizing parathyroid adenoma on the superior mediastinal left area. (a) Sagittal view of a choline PET/CT scan compared with sestamibi radiotracer imaging. (b) Coronal view of a choline PET/CT scan compared with sestamibi radiotracer imaging.

Table 4. Case 2: Difficult preoperative localization—patient's clinical manifestations, laboratory tests, imaging findings, and surgical procedure.

Category	Details
Patient	Female, 61 years old
Clinical manifestations	Severe osteoporosis, history of breast cancer, osteoporosis
Laboratory tests	Calcium: 12.5 mg/dL, PTH: 213.9 pg/mL, phosphorus: 3 mg/dL, 24 h calciuria: 34.8 mg/dL
Imaging	Negative neck ultrasound, scintigraphy; positive 18F-Fluorocholine PET/CT (mediastinal uptake)
Surgical procedure	Thoracic surgeon support for mediastinal parathyroidectomy; retrosternal parathyroid removal
Histology	Parathyroid adenoma
Outcome	ioPTH reduction post-removal, discharged with normal calcium levels, PTH: 41.1 pg/mL

ioPTH, intraoperative parathyroid hormone.

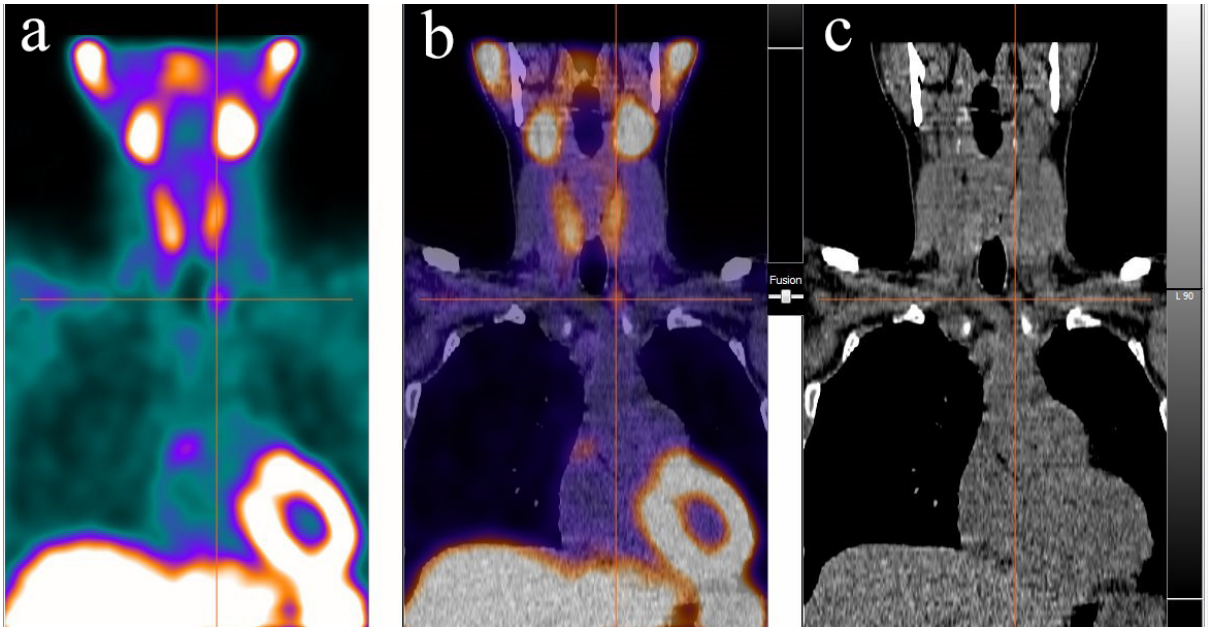

Fig. 3. Case 3: Coronal view: The scintigraphic shows the presence of parathyroid/hyperplastic tissue in the left paratracheal site behind the medial margin of the clavicula. (a) Scintigraphic acquisition phase. (b) Multimodal image fusion. (c) Non-contrast computed tomography phase.

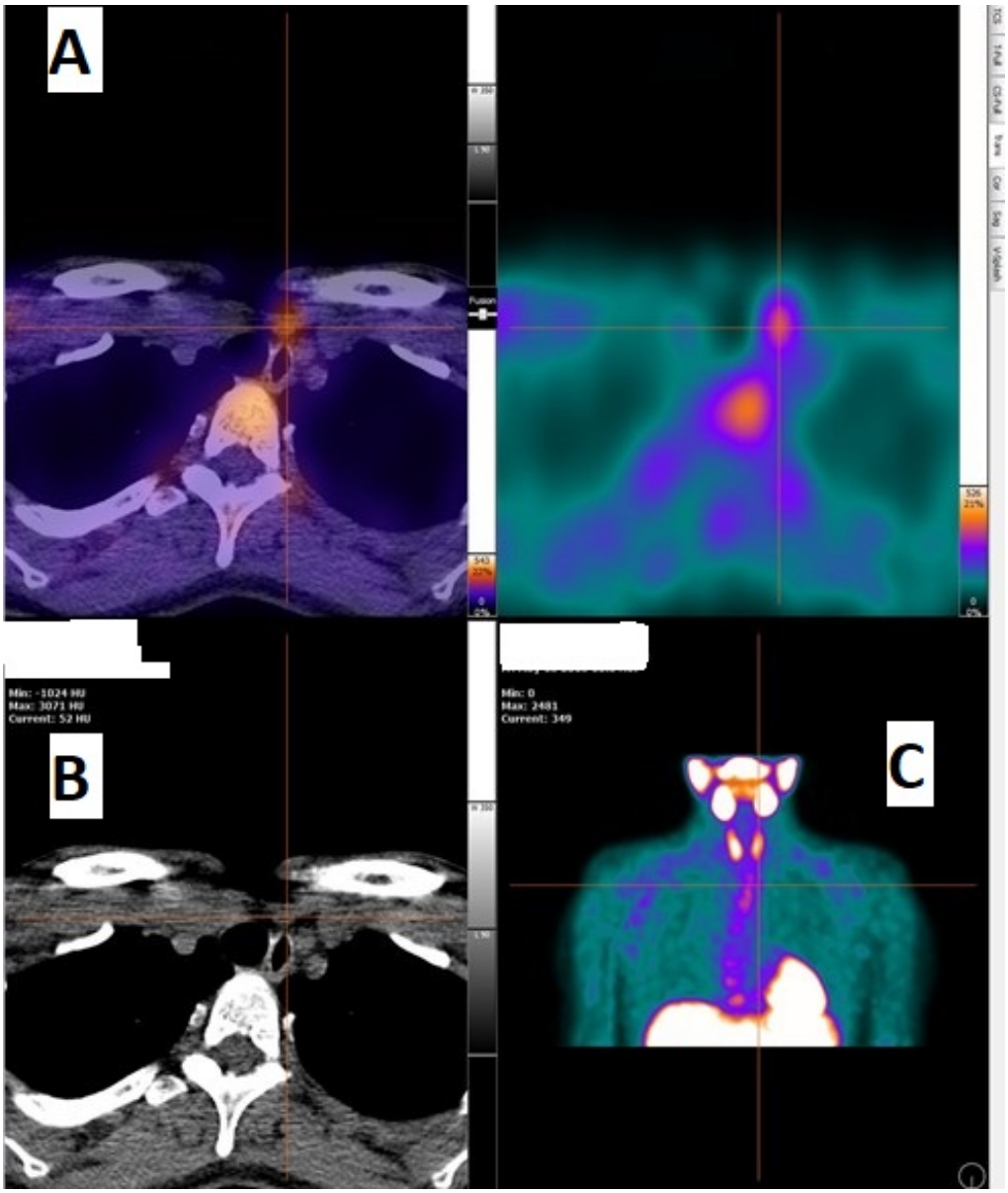

Fig. 4. Case 3: Additional scans that allow better localization of the parathyroid gland relative to the surrounding anatomical structures. (A) Coronal view computed tomography scan with fused imaging of non-contrast CT and Tc-99m sestamibi. (B) Axial view of scintigraphy. (C) Coronal view of scintigraphy with Tc-99m sestamibi.

During preoperatory examination the patient executed a CT chest with i.v. contrast. The patient was diagnosed with a pulmonary neuroendocrine neoplasm and underwent surgery for a right lower lobectomy. The histological results showed pT3 N0G3 lymphovascular invasion (LVI) + IIB Ki67 20%. Due to medical and personal history, it occurs to proceed with a regular follow-up and imaging and laboratory monitoring of recurrent pHPT.

The patient executed an endocrine visit with PTH of 131 pg/mL, calcium of 11 mg/dL, C-terminal telopeptide (CTX) of 0.920 ng/mL, calciuria in normal range, creatinine of 1.26 mg/dL, and Vitamin D 30 ng/mL. The last neck ultrasound performed showed a thyroid with disomogeneous echogenicity due to the presence of multiple nodules; no images referable to enlarged parathyroids were found (Table 6). Considering age and comorbidity it was decided to proceed with medical follow up.

Case 5: Recurrent Primary pHPT

Female patient, 53 years old. Medical history of toxic multinodular goiter (TMNG) and pHPT caused by a left inferior parathyroid adenoma that underwent surgery in 2019. One year after surgery, the patient showed an increased PTH value with regular calcium values with suspected relapsing pHPT due to another adenoma. The patient underwent medical endocrinological follow-up with indication to perform neck scintigraphy.

Table 5. Case 3: Intrathymic localization—patient's clinical manifestations, laboratory tests, imaging findings, and surgical procedure.

Category	Details
Patient	Female, 62 years old
Clinical manifestations	Hypercalcemia (10.6 mg/dL), osteoporosis, nephrolithiasis
Laboratory tests	Calcium: 10.6 mg/dL, PTH: 144 pg/mL
Imaging	Scintigraphy: hyperfixation in lower inferior thyroid pole
Surgical procedure	Exploration of thymus for ectopic parathyroid gland; successful removal
Histology	Intrathymic parathyroid adenoma
Outcome	ioPTH reduction post-removal, no complications, stable condition

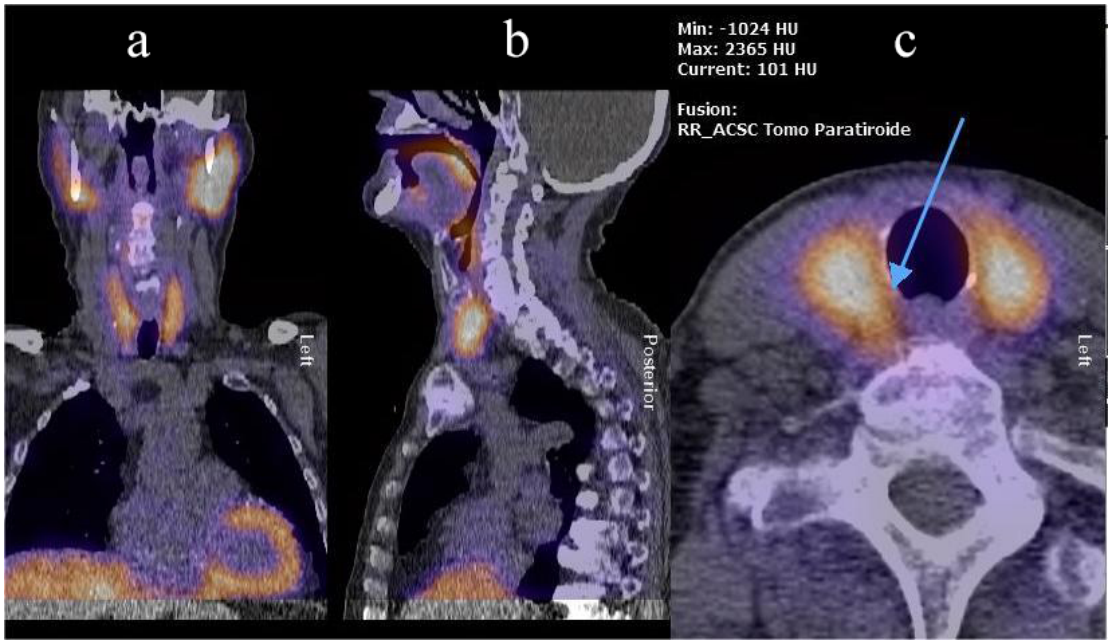

Fig. 5. Case 4: SPECT/CT images with low-dose CT show suspected area corresponding to a nodulation located posteriorly to the middle third of the right thyroid lobe (the blue arrow indicates the location of the suspicious nodular area). (a) Coronal view. (b) Sagittal view. (c) Axial view. SPECT, single photon emission computed tomography; CT, computed tomography.

The imaging confirmed the hyperfixation on the left upper parathyroid, suspected for adenoma (Fig. 6). Occurring with higher levels of calcium serum concentration. The patients continued medical follow up until March 2024 when she underwent surgery. An upper left parathyroidectomy with ioPTH dosage was performed (ioPTH values: at 0': 100.9 pg/mL, at 5': 15.2 pg/mL, at 15': 9.4 pg/mL). The histological examination confirmed the suspected diagnosis of adenoma (Table 7).

Case 6: Primary pHPT in MEN 1

Male patient, E.L, 16 years old. Hypercalcemic primary hyperparathyroidism in patient with MEN 1 (MEN1 mutation c1594_1595). A 68Ga-DOTATOC PET/CT revealed a 9 mm pancreatic neuroendocrine tumours (NET) at the posterior sectors of the pancreatic tail associated with other small formation.

SPECT/CT images with low-dose CT show a suspected an area corresponding to a nodulation located posteriorly of the right thyroid lobe (Fig. 7). Sestamibi focal area SPECT/CT lesion located below the right thyroid lobe, which can be referred to as hyperfunctioning parathyroid (Fig. 8). Echoendoscopy with biopsy confirmed NET G1 for which the patient is currently in follow-up only. The Chromogranin A levels were 37.9 ng/mL. The remaining exams, as pituitary, and hormonal dosage (IGF-1 PRL insulin gastrin) were found to be normal. The patient presented hypercalcemia (11.99 mg/dL) and the PTH levels were 101.7 pg/mL. Cervical ultrasound was negative for parathyroid localization.

Scintigraphy revealed the presence of an uptake area below the right thyroid lobe and a slight hyperfixation of the tracer lower to left thyroid pole (Table 8).

The surgical intervention planned was minimally invasive inferior right parathyroidectomy and possible inferior left parathyroidectomy with intraoperative parathyroid hormone (ioPTH) dosage.

Table 6. Case 4: Recurrence of primary pHPT—patient's clinical manifestations, laboratory tests, imaging findings, and surgical procedure.

Category	Details
Patient	Male, 87 years old
Clinical manifestations	Stroke history, COPD, adenocarcinoma of prostate, monoclonal gammopathy
Laboratory tests	Calcium: 11 mg/dL, PTH: 131 pg/mL, CTX: 0.920 ng/mL
Imaging	SPECT/CT: focal radiopharmaceutical uptake at middle third of right thyroid lobe
Surgical procedure	Right inferior parathyroidectomy, re-intervention for recurrence
Histology	Suspicious for parathyroid tissue (adenoma)
Outcome	Regular follow-up; imaging and laboratory monitoring of pHPT recurrence

pHPT, primary hyperparathyroidism; CTX, C-terminal telopeptide; COPD, chronic obstructive pulmonary disease.

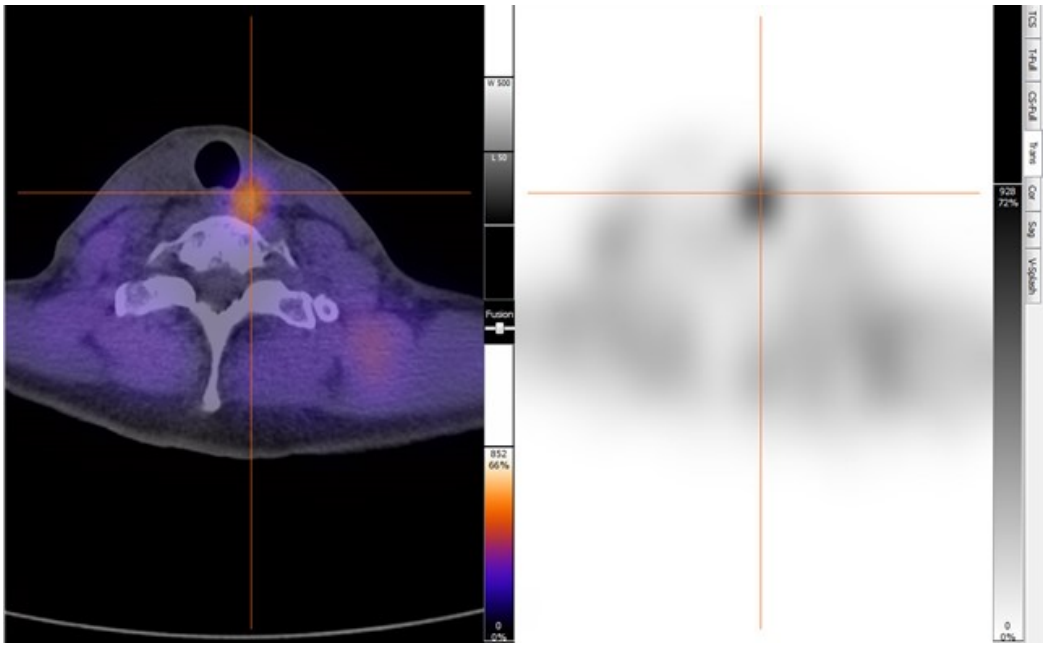

Fig. 6. Case 5: SPECT/CT with low-resolution CT suggesting a left paratracheal inferior parathyroid adenoma. On the left, the fused image of SPECT/CT; on the right, the image derived from SPECT.

The ioPTH demonstrated a very good decrease (Basal PTH: 118.9 pg/mL; PTH 5': 31.9 pg/mL; PTH 10': 29.8 pg/mL after the inferior right parathyroidectomy. The exploration of inferior left parathyroid gland was done but in reason of adequate decrease of ioPTH we performed only del inferior right parathyroidectomy. The postoperative course was regular. Definitive histological examination shows a clear cell parathyroid adenoma. Now, after four months, the patient is in good general condition. The calcium at discharge is 10.37 mg/dL and the PTH 66.1 pg/mL.

Discussion

Case 1: Parathyroid carcinomas are very rare. Carcinomas often present with profound hyperparathyroidism, as most of them are functional. Early metastasis is not uncommon. Imaging is important in their diagnosis, usually a combination of ultrasound and Tc-99m-sestamibi. Parathyroid carcinomas are said to be the rarest of all endocrine malignancies [1–3]. In the USA, estimated incidence is 0.015 per 100,000, with a prevalence of 0.005%. No gender or ethnic bias is known. They are commonly found in those in their late 40s [3,4].

Most parathyroid malignancies are hyperfunctional, with only 10% non-secreting of parathyroid hormone (PTH). Many patients present with symptoms and signs related to profound hyperparathyroidism and metastatic disease at initial presentation is not unusual [3,4]. Most parathyroid malignancies are hyperfunctional, with only 10% non-secreting of parathyroid hormone (PTH). Many patients present with symptoms and signs related to profound hyperparathyroidism and metastatic disease at initial presentation is not unusual. The clinical presentation could be a palpable neck tumour (40–70%) but most of patients presents severe hyperparathyroidism and may present with a hypercalcemic crisis, also known as parathyrotoxicosis. Metastatic adenopathy may be seen in 15–30% at presentation.

Table 7. Case 5: Recurrence of primary pHPT—patient's clinical manifestations, laboratory tests, imaging findings, and surgical procedure.

Category	Details
Patient	Female, 53 years old
Clinical manifestations	Toxic multinodular goiter, history of parathyroid adenoma
Laboratory tests	Calcium: elevated, PTH: increased after initial surgery
Imaging	Scintigraphy: hyperfixation on left upper parathyroid
Surgical procedure	Left upper parathyroidectomy with ioPTH testing
Histology	Parathyroid adenoma
Outcome	ioPTH reduction post-surgery, stable follow-up

Table 8. Case 6: Primary pHPT in MEN 1—patient's clinical manifestations, laboratory tests, imaging findings, and surgical procedure.

Category	Details
Patient	Male, 16 years old, MEN 1 syndrome
Clinical manifestations	Hypercalcemia, family history of MEN 1, pancreatic NET
Laboratory tests	Calcium: 11.99 mg/dL, PTH: 101.7 pg/mL, chromogranin A: 37.9 ng/mL
Imaging	Scintigraphy: uptake in right thyroid lobe, possible left thyroid pole involvement
Surgical procedure	Minimally invasive parathyroidectomy, ioPTH monitoring
Histology	Clear cell parathyroid adenoma
Outcome	Good post-op course, calcium and PTH levels stable, follow-up

PTH, parathyroid hormone; NET, neuroendocrine tumours; MEN, Multiple Endocrine Neoplasia.

The optimal surgical approach for parathyroid carcinoma is resection of the affected gland, including the ipsilateral thyroid lobe and central compartment lymphadenectomy. If the diagnosis is performed early, long-term survival without recurrence is highly likely; however, there are still cases of relapse. Some carcinomas may, otherwise, be aggressive and form lung, liver, and bone metastases.

In our case, the gland wasn't visible at the cervical US, and the preoperative PTH wasn't very high, and probably for this reason, there wasn't a suspicion of parathyroid carcinoma.

Case 2–3: Ectopic adenomas finding occurs in 3–4% of all parathyroid adenoma cases [35]. The surgical treatment for pathological parathyroid glands localised in the superior part of the mediastinum is usually persecuted by a cervical incision. Although in some cases the difficulty in finding those glands, whether they are localised in the upper mediastinum or in the posterior mediastinum or among adipose tissue close to the diaphragm, leads to the necessity of using new way of surgical access to the mediastinum such as median sternotomy or thoracotomy. One of the most alternative approaches to sternotomy may be represented by the use of video-assisted thoracoscopic surgery (VATS) either for detection and removal of affected glands, when it is not possible to perform surgery with the classic neck incision. Video-assisted thoracoscopic surgery may be performed with subxiphoid and lateral thoracic approach. The post-thoracotomy pain syndrome is limited, and the aesthetic outcomes are protreptic [36]. In preparation for VATS, it is worth performing Tc-99-sestamibi scintigraphy and endobronchial ultrasound biopsy. Because Tc-99m-sestamibi reveals the localization of an intense intake, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can be essential for diagnosis confirmation [37].

Cases 4–5: Persistence or recurrence of primary hyperparathyroidism (pHPT) still occurs in 2.5–5% of cases of pHPT [5,38]. Persistent primary hyperparathyroidism is defined as an increase in blood serum of calcium within 6 months after successful surgery, recurrent hyperparathyroidism (RHPT) occurs much later than 6 months. A single adenoma is found in 68% of cases, multinodular disease in 28% and parathyroid carcinoma in 3% [39]. Predictive factors of persistent or recurrent hyperparathyroidism include age >70 years, obesity, American Society of Anesthesiologists Score 3 (ASA3), low hospital volume (<50 surgery cases per year), low surgeon experience, equivocal Tc-99m sestamibi results, initial pathology, surgical strategy [40]. Indeed, it has been reported the 2–10% of surgical failures could be attributed to an incorrect diagnosis [41]. There still is no consensus on the approach for patients with RHPT/pHPT whether the decision orientate for a medical follow up with calcium and PTH levels monitoring.

The presence of severe symptoms or high or increasing levels of blood calcium after parathyroidectomy may be indications to re-surgery. The new surgical intervention should take in consideration the fibrosis and the changes in the neck anatomy after the previous surgery. This requires a new evaluation of the previous surgical and histological data to a proper pre-operatory diagnosis, even to identify the presence of ectopic tissue or the presence of unknown glands.

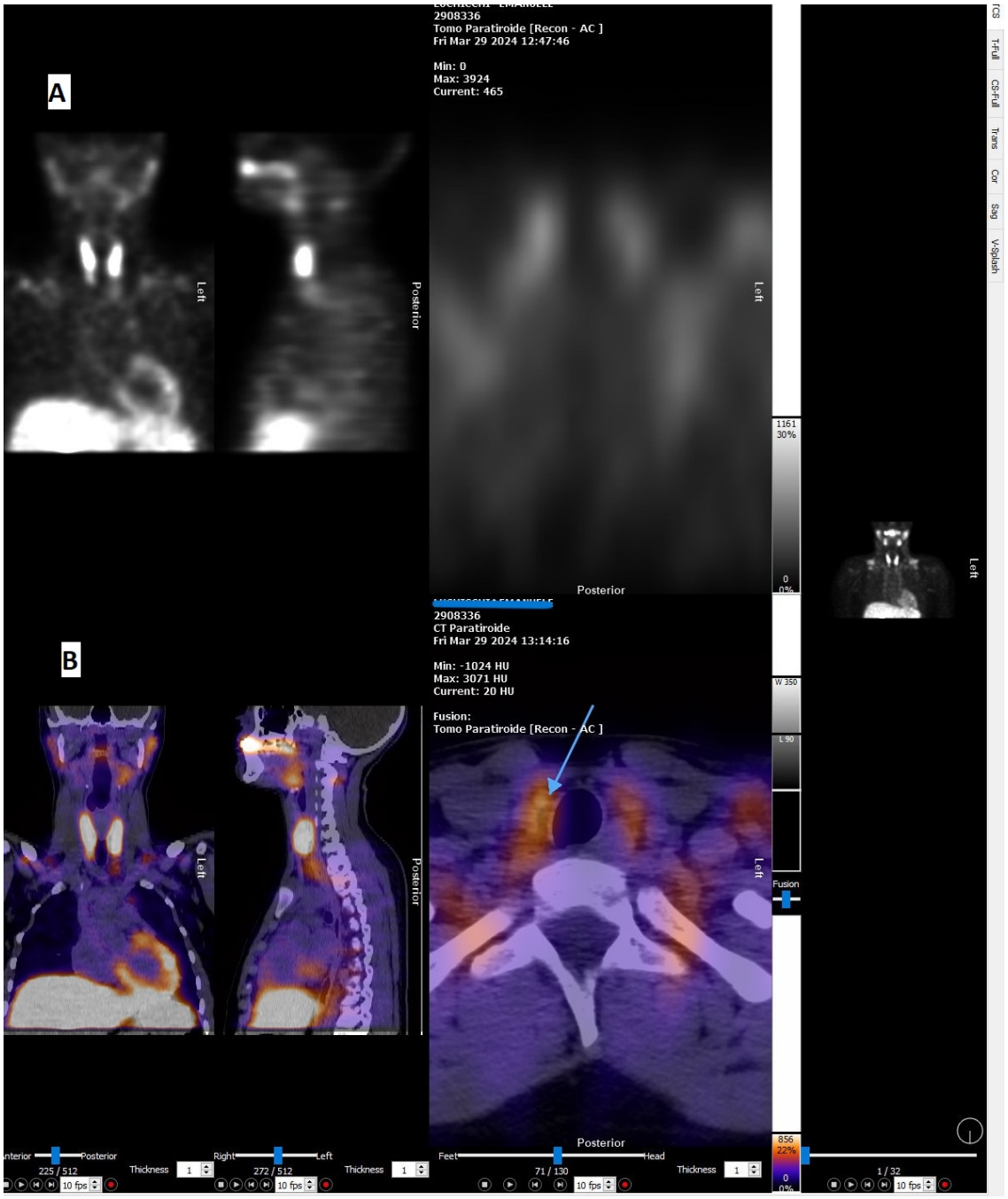

Fig. 7. Case 6: SPECT/CT images with low-dose CT show a suspected area corresponding to a nodulation located posteriorly of the right thyroid lobe (the blue arrow indicates the location of the suspicious nodular area). (A) SPECT images. (B) SPECT/CT fused images.

Case 6: Primary hyperparathyroidism is the most common manifestation of MEN 1 syndrome. The management of these patients is complex due to the underlying disease process, which predisposes patients to persistent and recurrent disease. The surgical treatment of patients with MEN 1 and hyperparathyroidism can therefore be considered to be palliative in nature. The basic principles of surgery include (1) obtaining and maintaining normocalcaemia for the longest time possible, avoiding persistent/recurrent hypercalcaemia, (2) avoiding surgically induced hypocalcaemia, and (3) facilitating future surgery for recurrent disease. Two approaches have been described as the best practice for patients with hyperparathyroidism in MEN 1: subtotal parathyroidectomy, leaving a remnant of no more than 60 mg in the neck, and total parathyroidectomy with immediate autotransplantation of 10–20 mm pieces of parathyroid tissue [40]. Both approaches should be combined with efforts to exclude supernumerary glands and ectopic parathyroid tissue by including resection of fatty tissue from the central neck compartment and thymectomy in all patients.

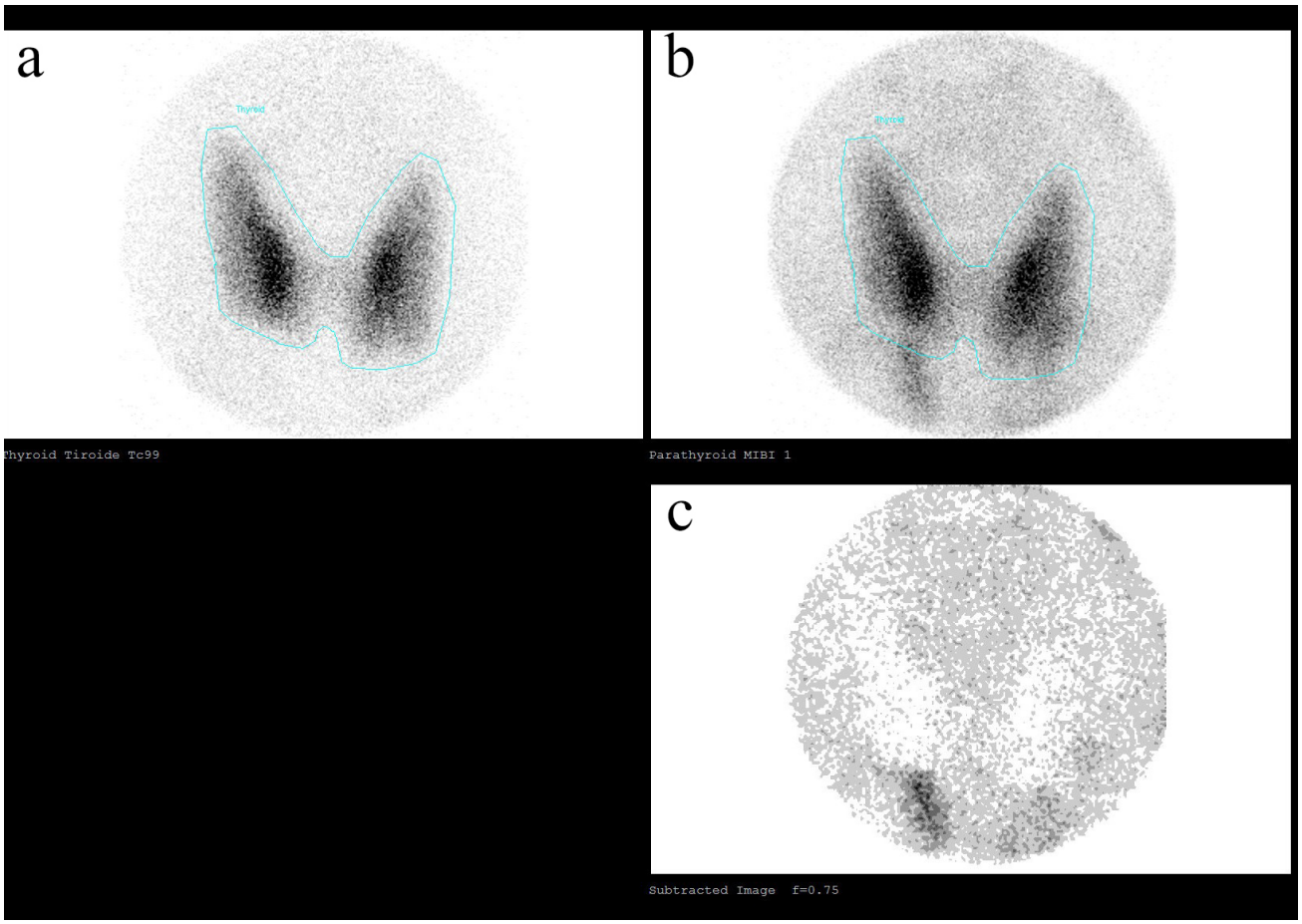

Fig. 8. Case 6: sestamibi focal area SPECT/CT lesion located below the right thyroid lobe, which can be referred to as hyperfunctioning parathyroid. (a) Thyroid parenchyma visualized following Tc-99m administration in SPECT. (b) Parathyroid and Thyroid parenchyma after MIBI administration. (c) Subtracted imaging (only parathyroid parenchyma).

Cryopreservation of parathyroid tissue should be performed whenever facilities are available. In patients with persistent or recurrent disease, an attempt to obtain total elimination of cervical parathyroid tissue is justified, combined with cryopreservation of parathyroid tissue. As radical as surgery is for hyperparathyroidism in MEN 1, the surgeon must take steps to avoid permanent hypoparathyroidism, which in young patients may be worse than the disease itself [40,41].

In our case, the patient was young, and our aim was obtaining and maintain normocalcaemia for the longest time possible avoiding persistent/recurrent hypercalcaemia and avoiding surgically induced hypocalcaemia.

Aim of the study was to analyze selected cases from our surgical series of patients operated for primary hyperparathyroidism and evaluate these cases, trying to analyze what were the peculiar aspects of each individual case. In fact, parathyroidectomy could be the easiest surgical intervention for the endocrine surgeon, but also, at the same time, the most difficult in his life.

The second case shows how actually, in recent years 18F-FCH PET/CT has become very important in visualizing very small adenomas or adenomas in ectopic sites. In the case described (Case 2), only a 18F-FCH PET/CT identified a mediastinal parathyroid gland. In the literature, it has been shown that 18F-FCH PET/CT is more sensible if compared to ultrasound or scintigraphy in the visualization of the parathyroid gland but sometimes identifies very small parathyroid glands. In Case 3, we want to emphasize that even when we have preoperative imaging showing a precise site of the parathyroid gland, after exploration in the inferior and posterior side of the thyroid gland or in the paratracheal area and/or in the prevertebral area and the parathyroid adenoma it is not found, it is very important to suspect that the parathyroid could by intrathymic. In the last case, we treated a very young patient who had familial hyperparathyroidism, and the message that the authors want to give is that it is necessary to focus on the surgical treatment considering the patient in front of you. In this case, the consequence of an aggressive treatment could be definitive hypoparathyroidism. Probably, the more conservative treatment resulted in correct, even also with the risk of possible reintervention in the future.

Conclusions

Combined ultrasound parathyroid and Tc-99m-sestamibi scan are useful in localization of parathyroid adenoma in most patients. Other patients would need further investigation with SPECT/CT or 18F-FCH PET/CT. Ectopic adenomas occur in 3–4% of all parathyroid adenoma cases, and a multidisciplinary approach is recommended. In recurrent primary hyperparathyroidism cases, is very important the right preoperative localization of parathyroid adenoma. Intraoperative parathyroid hormone measurement is useful for evaluating a double adenoma and in patients affected by hereditary familial hyperparathyroidism from MEN 1.

In conclusion, the authors want to stress how important is the surgeon's experience in parathyroid surgery when there is negative preoperative imaging or when the preoperative imaging shows the parathyroid gland in a different site than the one found at the time of surgery. Again, the experience of a surgeon who is able to recognize a parathyroid carcinoma intraoperatively or choose the correct treatment for a young patient with primary hereditary hyperparathyroidism is very important.

Several studies have shown that the surgeon's experience is the most important factor in ensuring the safest and most successful operation possible.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

AG and CJN participated in conception, design, and execution of the study; also participated substantially in the drafting and editing of the manuscript. MS, SN, AB, and SB participated in design, and the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript. GV: participated in the analysis of data. CD: participated in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

Chiara Dobrinja is serving as one of the Editorial Board members of this journal. We declare that Chiara Dobrinja had no involvement in the peer review of this article and has no access to information regarding its peer review. Other authors declare no conflict of interest.

References

[1] Walker MD, Silverberg SJ. Primary hyperparathyroidism. Nature Reviews. Endocrinology. 2018; 14: 115–125. https://doi.org/10.1038/nrendo.2017.104.

[2] Kim SJ, Shoback DM. Sporadic Primary Hyperparathyroidism. Endocrinology and Metabolism Clinics of North America. 2021; 50: 609–628. https://doi.org/10.1016/j.ecl.2021.07.006.

[3] Gurrado A, Pasculli A, Avenia N, Bellantone R, Boniardi M, Merante Boschin I, *et al*. Parathyroid Retrospective Analysis of Neoplasms Incidence (pTRANI Study): An Italian Multicenter Study on Parathyroid Carcinoma and Atypical Parathyroid Tumour. Journal of Clinical Medicine. 2023; 12: 6297. https://doi.org/10.3390/jcm12196297.

[4] Del Rio P, Boniardi M, De Pasquale L, Docimo G, Iacobone M, Materazzi G, *et al*. Management of surgical diseases of Primary Hyperparathyroidism: indications of the United Italian Society of Endocrine Surgery (SIUEC). Updates in Surgery. 2024; 76: 743–755. https://doi.org/10.1007/s13304-024-01796-5.

[5] Masi L. Primary Hyperparathyroidism. Frontiers of Hormone Research. 2019; 51: 1–12. https://doi.org/10.1159/000491034.

[6] Walker MD, Silverberg SJ. Primary hyperparathyroidism. Nature Reviews. Endocrinology. 2018; 14: 115–125. https://doi.org/10.1038/nrendo.2017.104.

[7] Cusano NE, Cetani F. Normocalcemic primary hyperparathyroidism. Archives of Endocrinology and Metabolism. 2022; 66: 666–677. https://doi.org/10.20945/2359-3997000000556.

[8] Cironi KA, Issa PP, Albuck AL, McCarthy C, Rezvani L, Hussein M, *et al*. Comparison of Medical Management versus Parathyroidectomy in Patients with Mild Primary Hyperparathyroidism: A Meta-Analysis. Cancers. 2023; 15: 3085. https://doi.org/10.3390/cancers15123085.

[9] Zhu CY, Sturgeon C, Yeh MW. Diagnosis and Management of Primary Hyperparathyroidism. JAMA. 2020; 323: 1186–1187. https://doi.org/10.1001/jama.2020.0538.

[10] Kowalski GJ, Bednarczyk A, Buła G, Gawrychowska A, Gawrychowski J. Parathyroid carcinoma - a study of 29 cases. Endokrynologia Polska. 2022; 73: 56–63. https://doi.org/10.5603/EP.a2022.0003.

[11] Kushchayeva YS, Tella SH, Kushchayev SV, Van Nostrand D, Kulkarni K. Comparison of hyperparathyroidism types and utility of dual radiopharmaceutical acquisition with Tc99m sestamibi and ^{123}I for localization of rapid washout parathyroid adenomas. Osteoporosis International. 2019; 30: 1051–1057. https://doi.org/10.1007/s00198-019-04846-6.

[12] Paillahueque G, Massardo T, Barberán M, Ocares G, Gallegos I, Toro L, *et al*. False negative spect parathyroid scintigraphy with sestamibi in patients with primary hyperparathyroidism. Revista Medica De Chile. 2017; 145: 1021–1027. https://doi.org/10.4067/s0034-98872017000801021.

[13] Kuo LE, Bird SH, Lubitz CC, Pandian TK, Parangi S, Stephen AE. Four-dimensional computed tomography (4D-CT) for preoperative parathyroid localization: A good study but are we using it? Amer-

ican Journal of Surgery. 2022; 223: 694–698. https://doi.org/10.1016/j.amjsurg.2021.09.015.

[14] Baj J, Sitarz R, Łokaj M, Forma A, Czeczelewski M, Maani A, *et al*. Preoperative and Intraoperative Methods of Parathyroid Gland Localization and the Diagnosis of Parathyroid Adenomas. Molecules. 2020; 25: 1724. https://doi.org/10.3390/molecules25071724.

[15] Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, *et al*. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surgery. 2016; 151: 959–968. https://doi.org/10.1001/jamasurg.2016.2310.

[16] Broos WAM, van der Zant FM, Knol RJJ, Wondergem M. Choline PET/CT in parathyroid imaging: a systematic review. Nuclear Medicine Communications. 2019; 40: 96–105. https://doi.org/10.1097/MNM.0000000000000952.

[17] Gawrychowski J, Buła G. Imaging diagnostics for primary hyperparathyroidism. Endokrynologia Polska. 2013; 64: 404–408. https://doi.org/10.5603/EP.2013.0024.

[18] Tay D, Das JP, Yeh R. Preoperative Localization for Primary Hyperparathyroidism: A Clinical Review. Biomedicines. 2021; 9: 390. https://doi.org/10.3390/biomedicines9040390.

[19] Inabnet WB, 3rd, Dakin GF, Haber RS, Rubino F, Diamond EJ, Gagner M. Targeted parathyroidectomy in the era of intraoperative parathormone monitoring. World Journal of Surgery. 2002; 26: 921–925. https://doi.org/10.1007/s00268-002-6619-7.

[20] Dobrinja C, Santandrea G, Giacca M, Stenner E, Ruscio M, de Manzini N. Effectiveness of Intraoperative Parathyroid Monitoring (ioPTH) in predicting a multiglandular or malignant parathyroid disease. International Journal of Surgery. 2017; 41: S26–S33. https://doi.org/10.1016/j.ijsu.2017.02.063.

[21] Gagner M, Rubino F. Endoscopic parathyroidectomy. In Schwartz AE, Pertsemlidis D, Gagner M (eds.) Endocrine surgery (pp. 289–296). Marcel Dekker: New York. 2004.

[22] Henry JF, Sebag F, Cherenko M, Ippolito G, Taieb D, Vaillant J. Endoscopic parathyroidectomy: why and when? World Journal of Surgery. 2008; 32: 2509–2515. https://doi.org/10.1007/s00268-008-9709-3.

[23] Miccoli P, Bendinelli C, Conte M, Pinchera A, Marcocci C. Endoscopic parathyroidectomy by a gasless approach. Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A. 1998; 8: 189–194. https://doi.org/10.1089/lap.1998.8.189.

[24] Miccoli P, Berti P, Materazzi G, Donatini G. Minimally invasive video assisted parathyroidectomy (MIVAP). European Journal of Surgical Oncology. 2003; 29: 188–190. https://doi.org/10.1053/ejso.2002.1313.

[25] Barczyński M, Papier A, Kenig J, Nawrot I. A retrospective case-controlled study of video-assisted versus open minimally invasive parathyroidectomy. Videosurgery and other Miniinvasive Techniques. 2014; 9: 537–547. https://doi.org/10.5114/wiitm.2014.45087.

[26] Kitada M, Yasuda S, Nana T, Ishibashi K, Hayashi S, Okazaki S. Surgical treatment for mediastinal parathyroid adenoma causing primary hyperparathyroidism. Journal of Cardiothoracic Surgery. 2016; 11: 44. https://doi.org/10.1186/s13019-016-0461-8.

[27] Daliakopoulos SI, Chatzoulis G, Lampridis S, Pantelidou V, Zografos O, Ioannidis K, *et al*. Gamma probe-assisted excision of an ectopic parathyroid adenoma located within the thymus: case report and review of the literature. Journal of Cardiothoracic Surgery. 2014; 9: 62. https://doi.org/10.1186/1749-8090-9-62.

[28] Grogan RH, Khafif AK, Nidal A, Anuwong A, Shaear M, Razavi CR, *et al*. One hundred and one consecutive transoral endoscopic parathyroidectomies via the vestibular approach for PHPTH: a worldwide multi-institutional experience. Surgical Endoscopy. 2022; 36: 4821–4827. https://doi.org/10.1007/s00464-021-08826-y.

[29] Kandil E, Hadedeya D, Shalaby M, Toraih E, Aparício D, Garstka M, *et al*. Robotic-assisted parathyroidectomy via transaxillary approach: feasibility and learning curves. Gland Surgery. 2021; 10: 953–960. https://doi.org/10.21037/gs-20-761.

[30] Arora A, Garas G, Tolley N. Robotic Parathyroid Surgery: Current Perspectives and Future Considerations. ORL. 2018; 80: 195–203. https://doi.org/10.1159/000488355.

[31] Ahmadieh H, Kreidieh O, Akl EA, El-Hajj Fuleihan G. Minimally invasive parathyroidectomy guided by intraoperative parathyroid hormone monitoring (IOPTH) and preoperative imaging versus bilateral neck exploration for primary hyperparathyroidism in adults. The Cochrane Database of Systematic Reviews. 2020; 10: CD010787. https://doi.org/10.1002/14651858.CD010787.pub2.

[32] Demarchi MS, Karenovics W, Bédat B, Triponez F. Intraoperative Autofluorescence and Indocyanine Green Angiography for the Detection and Preservation of Parathyroid Glands. Journal of Clinical Medicine. 2020; 9: 830. https://doi.org/10.3390/jcm9030830.

[33] Demarchi MS, Karenovics W, Bédat B, Triponez F. Near-infrared fluorescent imaging techniques for the detection and preservation of parathyroid glands during endocrine surgery. Innovative Surgical Sciences. 2021; 7: 87–98. https://doi.org/10.1515/iss-2021-0001.

[34] Pastoricchio M, Bernardi S, Bortul M, de Manzini N, Dobrinja C. Autofluorescence of parathyroid glands during endocrine surgery with minimally invasive technique. Journal of Endocrinological Investigation. 2022; 45: 1393–1403. https://doi.org/10.1007/s40618-022-01774-x.

[35] Panchani R, Varma T, Goyal A, Gupta N, Saini A, Tripathi S. A challenging case of an ectopic parathyroid adenoma. Indian Journal of Endocrinology and Metabolism. 2012; 16: S408–S410. https://doi.org/10.4103/2230-8210.104110.

[36] Nagano H, Suda T, Ishizawa H, Negi T, Kawai H, Kawakami T, *et al*. Video-assisted thoracoscopic surgery for ectopic mediastinal parathyroid tumor: subxiphoid and lateral thoracic approach. Journal of Thoracic Disease. 2019; 11: 2932–2938. https://doi.org/10.21037/jtd.2019.07.35.

[37] Buderi SI, Saleh HZ, Theologou T, Shackcloth M. Endobronchial ultrasound-guided biopsy to diagnose large posterior mediastinal parathyroid adenoma prior to video-assisted thoracoscopic resection. BMJ Case Reports. 2014; 2014: bcr2013200131. https://doi.org/10.1136/bcr-2013-200131.

[38] Guerin C, Paladino NC, Lowery A, Castinetti F, Taieb D, Sebag F. Persistent and recurrent hyperparathyroidism. Updates in Surgery. 2017; 69: 161–169. https://doi.org/10.1007/s13304-017-0447-7.

[39] Nawrot I, Chudziński W, Ciąćka T, Barczyński M, Szmidt J. Reoperations for persistent or recurrent primary hyperparathyroidism: results of a retrospective cohort study at a tertiary referral center. Medical Science Monitor. 2014; 20: 1604–1612. https://doi.org/10.12659/MSM.890983.

[40] Hubbard JGH, Sebag F, Maweja S, Henry JF. Primary hyperparathyroidism in MEN 1–how radical should surgery be? Langenbeck's Archives of Surgery. 2002; 386: 553–557. https://doi.org/10.1007/s00423-002-0275-0.

[41] Kochman M. Primary hyperparathyroidism: clinical manifestations, diagnosis and evaluation according to the Fifth International Workshop guidelines. Reumatologia. 2023; 61: 256–263. https://doi.org/10.5114/reum/170705.