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The Role of Preoperative Ultrasound and Sestamibi Scintigraphy in the Surgical Management of Primary Hyperparathyroidism: A Review of Literature

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Abstract

Background: Primary hyperparathyroidism (pHPT) is one of the most common endocrine diseases and the most common cause of hypercalcemia. Since routine laboratory testing, the prevalence of the disease has increased from 0.1% to 0.4% worldwide. The only curative treatment is parathyroidectomy. Nowadays, preoperative localization studies have become standard before surgical treatment, and the first stage imaging methods are cervical ultrasonography (US) and/or Sestamibi scintigraphy. **Objectives:** To describe the accuracy of US and Sestamibi for detection of hyperfunctioning parathyroid adenomas preoperatively in patients with confirmed pHPT from our medical institution. **Results:** This is a retrospective study from a prospectively kept database that included thirty-one patients with the confirmed diagnosis of pHPT clinically and biochemically. The average age was 57.8 years old. Preoperative US and surgery findings were compared with a sensitivity of 51%. Preoperative Sestamibi and surgery findings were compared resulting in a sensitivity of 71%. Both imaging methods combined, resulted in a sensitivity of 80%. **Conclusion:** In patients with pHPT, Sestamibi is an effective method for localizing parathyroid pathology preoperatively, but the false negative rate can be high. US tends to have a wider range explained by the operator-dependent factor. The combination of US and Sestamibi reduces the rate of false nega-

tives, as reported in international literature. It is important to mention that these studies cannot be used as a confirmatory test for this disease. It should only be used as an adjunct to help plan the operation.

Keywords

Parathyroid Glands, Primary Hyperparathyroidism, Parathyroid Adenoma, Parathyroid Hyperplasia, Parathyroidectomy, Cervical Ultrasound, Sestamibi Scintigraphy, Limited Neck Exploration

1. Introduction

The overproduction of parathyroid hormone (PTH), termed hyperparathyroidism can be categorized as primary, secondary and tertiary hyperparathyroidism. Primary hyperparathyroidism (pHPT) is defined as hypercalcemia or widely fluctuating levels of serum calcium resulting from the inappropriate or autogenous secretion of PTH by one or more parathyroid glands in the absence of a known or recognized stimulus [1] [2] [3] [4] [5].

In the United States, it affects 0.2% to 0.8% of the population, or 65.5 per 100,000 person-years in women and 27.7 per 100,000 person-years in men [6]. Women have consistently made up the preponderance of cases, with a female-to-male ratio of 3 to 4:1 [7].

The principal role of PTH is the maintenance of the concentration of calcium ions in the extracellular fluid (ECF). Two principal sources of the calcium flow into the ECF are the resorption of bone that is released during bone remodeling and the intestinal absorption of calcium ingested as foods and supplements [8]. The homeostatic challenge consists principally in setting the level at which these fluxes occur and in matching the outflows to the inflows.

Hypercalcemia negatively affects patients by causing non-specific symptoms such as fatigue, constipation, decreased cognitive capacity, kidney stones, and skeletal problems. Recently, due to routine laboratory screening, most patients are diagnosed either while asymptomatic or with mild symptoms [3] [4] [5] [9]. Symptomatic disease is the dominant phenotype of pHPT in the United States, contrary to the current thinking of "asymptomatic" disease. pHPT that is truly asymptomatic is a rare occurrence, seen in less than 5% of patients [10] [11]. The most common symptoms are non-specific. Most patients present with fatigue, decrease levels of energy, general malaise, anxiety, irritability leading to decrease social interaction, depression (10% of cases), memory loss, decrease concentration, decrease ability to learn new things, decrease ability to complete daily tasks at home, decrease ability to complete daily tasks at work, decrease social interaction, insomnia, arthralgias (32% of the cases), myalgias (14% to 41% of the cases), bone pain, muscle weakness (specially proximal muscle groups), intermittent headaches, polydipsia, polyuria, nocturia, nausea (24% of the cases), anorexia (15% of the cases), non-specific abdominal pain, heartburn (30% of the

cases), constipation (33% of the cases), palpitations, arrhythmias (usually atrial fibrillation), elevated blood pressure, thinning of the hair (specially in women in the frontal region), and pruritus [3] [4] [5]. As we can determine, many "asymptomatic" patients do not have the classical symptoms of an advanced disease and are automatically classified as "asymptomatic". Skeletal and renal manifestations have declined roughly 17% to 20%.

pHPT is caused by a parathyroid adenoma in approximately 75% to 89% of the cases, multiple adenomas or hyperplasia occurs in 15% to 25% of the cases, and parathyroid carcinoma as the cause of PHPT is extremely rare (~1%) [12] [13] [14]. Ectopic glands can be present (4% to 16% of cases) [3] [4] [5] [15] [16] [17]. The treatment for pHPT is surgery, considered the only curative treatment [8]. Bilateral neck incision (BNE) and exploration was the standard surgical approach with a surgical cure rate of 95% in experienced centers and institutions [18]. It is reported that the only excision of the enlarged gland is sufficient for treatment in most of the cases [19]. This explains the current shift from BNE to minimally invasive parathyroidectomy (MIP).

The parathyroid glands are usually located at the four poles of the thyroid gland; however, they may be difficult to locate. Parathyroid imaging has become an important tool for assessment and preoperative location of the parathyroid glands, not always identifying the affected gland or glands. In the last decades, different imaging methods been used for parathyroid imaging, including USG, Sestamibi, computed tomography and others [20] [21].

2. Methods

We retrospectively evaluated thirty-one patients from our medical institution during a 4-year period (2016-2020) from our prospectively kept database. The inclusion criteria were:

1) Confirmed biochemical and clinical diagnosis of pHPT.

2) Preoperative US and Sestamibi scintigraphy for preoperative localization.

3) Bilateral neck exploration with a minimally invasive parathyroidectomy.

Exclusion criteria were secondary hyperparathyroidism, tertiary hyperparathyroidism, and previous neck surgeries.

When the adenoma was identified in the preoperative scintigraphy, it was evaluated according to the neck side or neck quadrant, and the results were compared with intraoperative localization findings.

For all of the included patients, one hour before the operation 15 millicuries of technetium 99 m were administered to the patient intravenously. The operation was performed through a 2 cm to 2.5 cm incision at the level of the cricoid cartilage with identification of all four parathyroid glands, the enlarged gland was biopsied, and a radioactive count was obtained using a gamma counter. If the count was greater than 20% of the baseline neck count it was considered an adenoma and removed [5]. After finishing the resection of all abnormal parathyroid glands serial rapid PTH levels were obtained at 10, 20 and 30 minutes

after resection and the patient was considered cured if the 10-minute count showed a 50% drop of the PTH levels and were within the normal range (15 to 65 pg/dl).

This Table 1 summarizes the sociodemographic characteristics of the population selected for this study.

Table 1. Sociodemographic characteristics of the population.

Sex	Age	BMI	Ultrasound Results (0: negative findings, 1: positive parathyroid gland pathology)	Sestamibi Results	Pathology Diagnosis (0 - single adenoma, 1 - double adenoma, 2 - triple adenoma, 3 - hyperplasia)	Preoperative Identification of Both (B), only Sestamibi (S), only ultrasound (US), None (N)
F	63	24.3	1	Right inferior parathyroid nodule.	0	B
F	63	27	0	Abnormal left parathyroid gland.	0	S
F	62	26.3	1	No parathyroid glands were identified.	0	US
F	68	32	1	Two right parathyroid adenomas.	1	B
F	77	21.9	0	Abnormal normal left inferior parathyroid gland.	0	S
F	72	22	1	Abnormal normal left superior parathyroid gland.	0	B
F	49	19.1	0	Abnormal normal left inferior parathyroid gland.	3	S
F	45	33.1	1	Abnormal normal left superior parathyroid gland.	0	B
F	66	32	0	No parathyroid glands were identified.	3	N
M	57	22.4	1	No parathyroid glands were identified.	0	US
F	67	25.7	1	Abnormal left parathyroid gland.	0	B
M	44	23.9	0	No parathyroid glands were identified.	3	N
M	44	35.6	1	Abnormal normal right parathyroid gland.	0	B
F	58	20.2	0	Abnormal normal left inferior parathyroid gland.	0	S
F	50	27.9	0	No parathyroid glands were identified.	0	N
M	68	21.1	1	Abnormal left parathyroid gland.	0	B
F	65	25.3	1	Right inferior parathyroid adenoma.	0	B
F	87	18	0	Abnormal normal left inferior parathyroid gland.	0	S
F	62	31.4	0	No parathyroid glands were identified.	0	N
F	57	19.2	0	Abnormal normal right inferior parathyroid gland.	0	S

Continued

F	66	25.8	1	Right inferior parathyroid gland with increased physiological activity, ectopic glands were ruled out.	1	B
F	62	23.7	0	Right parathyroid glands with increased physiological activity, ectopic glands were ruled out.	0	S
F	64	21.9	0	Abnormal normal left parathyroid gland.	0	S
F	55	19.5	0	Abnormal normal left parathyroid gland.	0	S
M	29	32.4	1	No parathyroid glands were identified.	0	US
M	35	22.1	0	No parathyroid glands were identified.	0	N
F	31	33.8	1	Right lower parathyroid gland with increased physiological activity, ectopic glands were ruled out.	0	B
M	59	18.9	1	Abnormal normal right parathyroid gland.	0	B
F	64	21.6	0	Normal parathyroid glands	3	N
F	47	25.1	1	Abnormal normal left inferior parathyroid gland.	0	B
F	61	23.3	1	Abnormal normal left parathyroid gland.	0	B

3. Results

Thirty-one patients with confirmed pHPT after surgery by pathology were evaluated retrospectively from our prospective kept database. There were no surgical complications reported.

Patient Characteristics

The age range was from 29 to 87 years old, with an average age of 57.8 years old. Twenty-four patients were women (77%), and seven patients were men (23%). The BMI average was 25.04 (range from 18 to 35.6). Patient characteristics are summarized in Table 1. There were no differences in age, gender or BMI among groups.

Surgical Data

The preoperative serum calcium average was 10.24 mg/dL (range: 8.8 to 11.9 mg/dL). The average of preoperative parathormone levels was 91.33 pg/mL (range: 29 to 247 pg/mL). The percentage of patients with single adenomas was superior in all groups. No carcinoma was reported. No complications were reported.

US and Sestamibi

The first study was the cervical ultrasound (US) with 16 patients positive for a parathyroid gland pathology, resulting in a sensitivity of 51%, and 15 patients

with normal findings (49%). The US was done by radiologists, technicians and residents.

Next, we had 22 patients with positive preoperative imaging findings by Sestamibi determining a sensitivity of 71%, and 9 patients with negative imaging findings (29%) (Table 2 and Table 3). A positive single focus was identified in 20 patients and a double focus was observed in 2 patients.

All 31 patients had a positive diagnosis of pHPT that was confirmed by pathologic examination. All scans were performed at our institution. In 25 patients, there was a complete correlation between the ultrasound, the Sestamibi and the operative findings resulting in a sensitivity of 80%. There were no false positives in this series; therefore, no specificity. All patients had normal serum calcium and intact PTH six months after surgery.

4. Discussion

Once the pHPT diagnosis is made, the next ideal step for the surgeon is to order imaging studies to help plan the surgical procedure, which could be a limited neck exploration or bilateral neck exploration [22]. The limited neck exploration is performed through a 2 to 3 cm incision, which provides a good exposure of the anatomic structures. The original technique described in 2005 by Norman *et al.* [23]: a biopsy of the four glands is obtained in-vivo and their functionality is measured ex-vivo. Only the metabolically hyperfunctioning gland(s) is/are resected. The goal of preoperative imaging in pHPT is to help plan the operation rather than as a confirmatory test of the diagnosis. The success rate of parathyroidectomy in bilateral neck exploration with preoperative biochemical and clinical diagnosis exceeds 90% in a majority of cases [24]. However, when limited minimally invasive parathyroidectomy is selected as the management modality

Table 2. Number of patients diagnosed by the different imaging tools.

Type of Imaging	Disease +	Disease −
Sestamibi (+)	22	0
Sestamibi (−)	9	0
Ultrasound (+)	16	0
Ultrasound (−)	15	0
Sestamibi + US (+)	25	0
Sestamibi + US (−)	6	0

Table 3. Sensitivity of neck ultrasound, Sestamibi and both studies combined.

Type of Imaging	Sensitivity
Ultrasound	51%
Sestamibi	71%
US + Sestamibi	80%

(a procedure of choice for many surgeons today) can lead to a delay in definitive management when preoperative imaging studies fail to localize the disease [25] [26] [27]. We have to be careful in the management of pHPT patients with negative preoperative studies. The international literature shows 20% to 30% of negative scans in positive pHPT patients, varying upon the chosen image study [24] [28]-[36]. Our study produced 20% to 50% of false negatives depending on the technique. The parathyroid pathologies can be localized by preoperative imaging methods with an adequate sensitivity and specificity that helps the surgeon to do a more specific surgery. It also helps the patient have a faster recovery, a smaller incision and less exposure to complications such as postoperative hypocalcemia [34].

The most commonly used imaging methods for imaging in pHPT are US, Sestamibi, or a combination of these [35]. Although, the sensitivity of our study was below from the data reviewed previously (71% vs. 73% to 83%), it is close to the expected results of Sestamibi as a preoperative imaging. The combination of US and Sestamibi is correlated with the international review. [36] Combining the different attributes of ultrasound and Sestamibi results in increased accuracy of preoperative localization and accordingly, current guidelines recommend dual US and Sestamibi scintigraphy scans [37] [38]. It is important to mention that Sestamibi in the diagnosis of parathyroid hyperplasia drops the sensitivity to 44% [12] [39]. Our database includes four patients (12%) with parathyroid hyperplasia confirmed by pathology. During follow-up, no patient developed a recurrence.

5. Imaging Modalities

Ultrasonography

Ultrasonography of the neck (US) is a common first-line imaging modality for preoperative localization with the lower-cost. US is generally performed with high-frequency linear transducers. The examination includes the anterior cervical region, where pathological parathyroid tissue become visible by its increased size and echogenicity, as shown in **Figure 1** [29] [30]. The normal parathyroid glands are not visible, but an adenoma is described as a well-circumscribed mass with homogenous hypoechogenicity with internal flow on Doppler evaluation, as shown in **Figure 2**. [30] The advantages include assessment for thyroid pathologies, lack of ionizing radiation, low cost, and widespread availability [3]. The disadvantages include operator-dependent effectiveness, inability to assess mediastinal tissue and decreased sensitivity, also seen in persistent and recurrent Phpt [34] [35] [36] [37]. The sensitivity for US alone varies from 47% to 88% [14] [15] [16] [37]. False positive or negative sonographic diagnosis may be secondary to prominent thyroid nodules, prominent blood vessels, cervical lymph nodes, esophagus and longus colli muscle [36].

Sestamibi

99m Tc-methoxy isobutyl isonitrile (MIBI) also known as Sestamibi, is a radioactive diagnostic agent used in the evaluation of pathology within the cardiac,

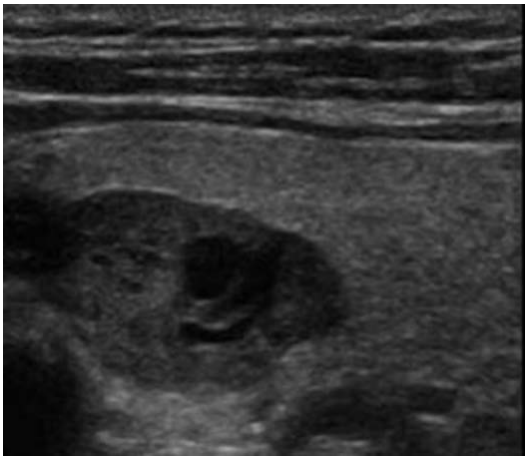

Figure 1. Parathyroid adenoma below the inferior pole of the left lobe of the thyroid.

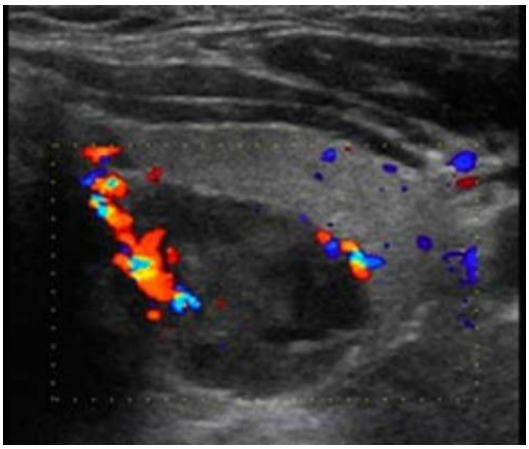

Figure 2. Abundant blood flow signals on color Doppler flow imaging.

breast, and parathyroid tissues. Sestamibi is a radiotracer used as a perfusion agent to observe the blood flow of the heart, left ventricular ejection fraction, also used in thrombolytic therapy. It is lipophilic and cationic having a predilection in tissue with high mitochondrial content and negative plasma membrane potentials, used in the non-invasive intraoperative localization of hyperfunctioning parathyroid tissue, as shown in **Figure 3** and **Figure 4**. Since the 1980's, the use of 99m-technetium was described by Young *et al.* with promising results [6]. The sensitivity and specificity reported is between 73% and 80%, respectively with an increase up to 90% in adenomas bigger than 500 mg. The sensitivity of identifying a single adenoma is similar to double adenomas (75% and 68%). The specificity is higher in double adenomas than in single adenomas (100% and 78%) [40] [41].

Single-Photon Emission Computed Tomography

The main advantage of SPECT/CT is their application for the acquisition of high-precision fusion images, using both CT and SPECT imaging. The images can be used to identify abnormal uptake based on the diminution of scattered radiation [42] [43].

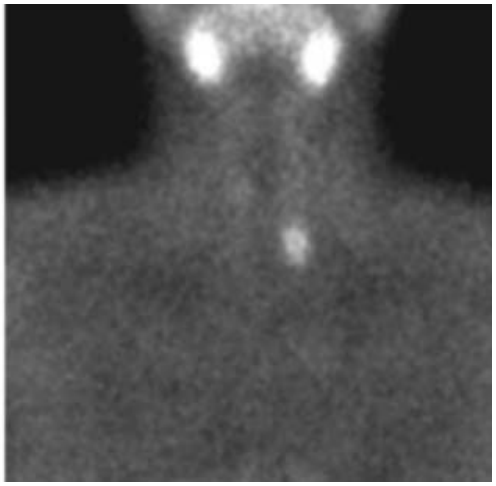

Figure 3. Delayed sestamibi acquisition in a 63 year-old patient confirming a single focus related to the left inferior parathyroid gland. Surgery was performed confirming a parathyroid adenoma.

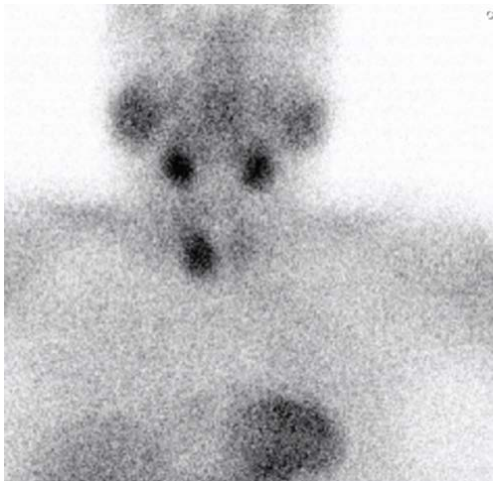

Figure 4. Delayed sestamibi acquisition showing multiple focus related to parathyroid hyperplasia.

4-Dimensional Computed Tomography

The 4-dimensional computed tomography (4D-CT) generates detailed multiplanar images providing anatomical and functional information in a single study, showing to be useful in a variety of clinical scenarios including in patients with and without previous neck surgery, mild hyperparathyroidism, multigland disease, and in patients with Sestamibi and US examinations that are negative for adenoma [44]. This technique relies on the vascularity of the parathyroid glands and their relative enhancement with contrast compared to the surrounding structures. The name 4D is because of addition of changes in the perfusion of contrast over time to the three-dimensional anatomic CT images [45]. They showed an improved sensitivity of 88% for 4D-CT. More recently, Kutler *et al.* using a combination of 4D-CT/US technique reported a sensitivity of 94% and specificity of 96% for lateralizing the hyperfunctioning parathyroid glands and a

sensitivity of 82% for localizing the gland to the correct quadrant [45] [46]. This combination appears to be an ideal preoperative for localization of abnormal parathyroid glands.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is an effective test in the identification of parathyroid gland pathology. It is preferred over CT due to the lack of ionizing radiation and better resolution, but is more expensive, slower and not available in every center. Principally, indicated in recurrent pHPT with previous surgery. The sensitivity of MRI in detecting abnormal parathyroid glands is reported from 69% to 88% with a false positive rate of 1.6% to 10% [47] [48] [50]. Accuracy increased to 92% when MIBI and MRI results were combined [48].

PET-CT

Choline is a precursor for the biosynthesis of phospholipids, which are essential components of the cell membrane. Cells with high proliferation rates have increased demand for choline because of enhanced phospholipid synthesis [49]. Choline-based PET tracers have been introduced into clinical practice and parathyroid adenoma, initially reported by Mapelli *et al.* [50] has shown similar sensitivity and specificity in parathyroid adenomas than Sestamibi, but has better accuracy in patients with hyperplasia and recurrent pHPT. The limiting factors are the number of PET centers, availability of the tracer, and cost-effectiveness [3] [4] [5] [51] [52].

The optimal imaging algorithm has not yet been determined [25] [26], as evidence supports multiple techniques as described in our **Table 4** and **Figure 5**.

Table 4. Preoperative imaging in pHPT, a review of literature.

Diagnostic Tool	Sensitivity	Specificity
USG	47% - 88% [20] [37]	71% - 82%
Sestamibi	73% - 83% [19] [20]	71% - 91% [22]
USG + Sestamibi	80% - 97% [22]	83% [22]
SPECT/CT	86% [21]	87% - 96%
SPECT + Sestamibi	86% - 90% [18] [21]	98% [24]
4D-CT	88%	88% [24]
PET-CT	78%	86% [23]

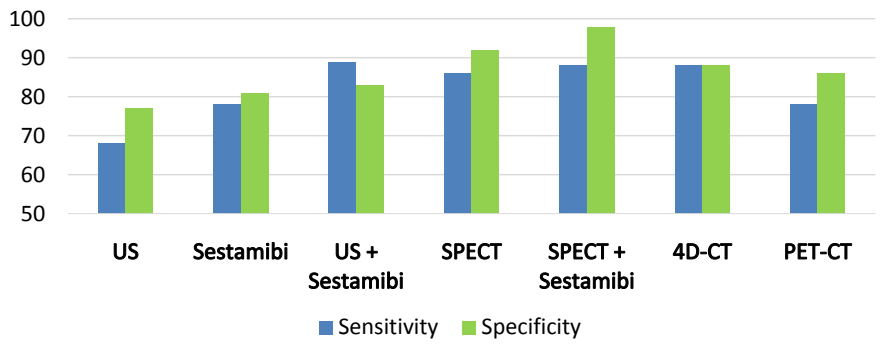

Figure 5. Describing the sensibility and specificity of the diagnostic tools.

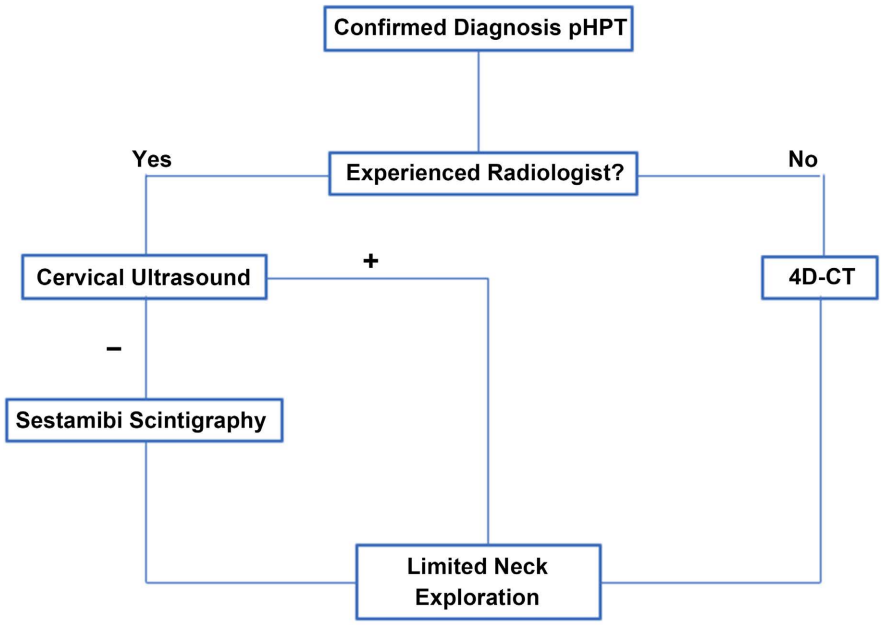

Figure 6. Algorithm for management of pHPT.

The availability, the radiation exposure, the cost, the surgeon's preference, patient specific factors and the radiologist experience are factors that help us decide which imaging modality to use for each patient [27].

We present our practice algorithm (**Figure 6**) based on the most common diagnostic tools available and we hope this algorithm can help less-experienced centers to approach a patient with pHPT in order to adequately plan the surgical intervention more efficiently.

6. Conclusion

The primary treatment of pHPT is surgical, whether it is a BNE or a limited parathyroidectomy. We do not perform MIP because of the percentage of failure. As surgeons, we need to individualize each patient to offer them the best preoperative approach and type of surgery for avoiding recurrent disease. Sestamibi proves to be an efficient, cost-benefit, widespread available preoperative study which improves its outcomes with the combination of another study as ultrasound. We need to achieve effective surgical management of pHPT to resolve it safely and efficiently.

Conflicts of Interest

All the authors involved in the elaboration of this manuscript do not have any disclosures of any commercial interest, financial or material support.

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