PERFORMANCE OF PREOPERATIVE IMAGING IN PRIMARY HYPERPARATHYROIDISM

PERFORMANCE DE L'IMAGERIE PRÉOPÉRATOIRE DANS L'HYPERPARATHYROÏDIE PRIMAIRE

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ABSTRACT:

Objectives: Primary hyperparathyroidism (PHPT) is one of the most common endocrine diseases and has parathyroidectomy (PTHx) as its sole curative treatment. The aim of this study was to evaluate the value of 99m Tc-sestaMIBI scintigraphy (99mTc-MIBI) and single-photon emission computed tomography with computed tomography (SPECT/CT), along with ultrasound (US) and to correlate surgical outcomes with pre-operative localization.

Material and methods: This retrospective and monocentric study comprised 79 patients diagnosed with primary hyperparathyroidism undergoing parathyroidectomy between 2011 and 2022 in ear nose and throat (ENT) department and endocrinology department. US, 99mTc-MIBI, and SPECT-CT were performed and their imaging data have been quantified. The diagnostic performance of imaging methods was evaluated using preoperative findings as the gold standard.

Results: Sensitivity was 74.68% for US, 87.5% for 99mTc-MIBI, 88.14 for SPECT-CT and 86.9% for associated ultrasound-scintigraphy. The sensitivity of both US and MIBI correlates with the number of pathological parathyroids. Additionally, the size of the parathyroid gland and the PTH level are positively correlated. The surgical success rate was 96.2%. There were 2 cases of persistence primary hyperparathyroidism and one case of recurrence.

Conclusion: The combination of ultrasound-99mTc-sestamibi-scintigraphy provided a higher sensitivity and specificity.

Key words: primary hyperparathyroidism, imaging, ultrasound, sestamibi, concordance, parathyroidectomy

RÉSUMÉ

Objectif: L'hyperparathyroïdie primaire (HPTP) est l'une des maladies endocriniennes les plus courantes pour laquelle la parathyroïdectomie (PTHx) est le seul traitement curatif. L'objectif de cette étude était d›évaluer l'importance de la scintigraphie au 99m Tc-sestaMIBI (99mTc-MIBI) et de la tomographie par émission monophotonique couplée à la tomodensitométrie (SPECT/CT), ainsi que de l'échographie et de corréler les résultats chirurgicaux avec la localisation préopératoire.

Matériel et méthodes: Cette étude rétrospective et monocentrique a inclus 79 patients diagnostiqués avec une hyperparathyroïdie primaire ayant subi une parathyroïdectomie entre 2011 et 2022 dans le service d'oto-rhino-laryngologie (ORL) et le service d'endocrinologie. L'échographie, le 99mTc-MIBI, et le SPECT-CT ont été réalisés et les données d'imagerie ont été quantifiées. La performance diagnostique des méthodes d'imagerie a été évaluée en utilisant les résultats préopératoires comme référence.

Résultats: La sensibilité était de 74,68 % pour l'échographie, 87,5 % pour le 99mTc-MIBI, 88,14 % pour le SPECT-CT, et 86,9 % pour l'association échographie-scintigraphie. La sensibilité de l'échographie et celle du 99mTc-MIBI sont corrélées avec le nombre de parathyroïdes pathologiques. De plus, la taille de la glande parathyroïde et le niveau de PTH sont positivement corrélés. Le taux de réussite chirurgicale était de 96,2 %, avec deux cas d'hyperparathyroïdie primaire persistante et un cas de récidive.

Conclusion: L'association échographie-scintigraphie au 99mTc-sestamibi a offert une meilleure sensibilité et spécificité.

Key words: hyperpathyroidie primaire, imagerie, échographie, sintigraphie au MIBI-Tc99m, concordance, parathyroidectomie

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 DOI:10.71705/jtorlccfi52p4

INTRODUCTION

Primary hyperparathyroidism (PHPT) is the most common cause of ambulatory hypercalcemia (1), and the third most frequent endocrine disease with an estimated incidence of 45 cases per 100,000 person-years (2,3). PHPT is caused by a parathyroid adenoma in 85% of the cases, followed by multiple adenomas (15-20%), parathyroid hyperplasia (less than 15%), and parathyroid carcinoma (<1%) (2,4,5).

Parathyroidectomy (PTHx) is the only available curative treatment (3,5–7). Minimally invasive surgery became the standard surgical attitude and its success relies on precise preoperative localization, emphasizing the necessity for pre-operative imaging (6,7). The most commonly used procedures are ultrasound (US) and 99m Tc-sestaMIBI scintigraphy (99mTc-MIBI) associated or no single-photon emission computed tomography (SPECT-CT). They have already been identified in the literature as a front-line preoperative localization strategy (1). Preoperative imaging may not always be precise, as demonstrated by cases where surgical exploration identifies enlarged parathyroid glands that were not successfully localized beforehand as well as cases of HPTP recurrence or persistence where imaging did not identify all pathological glands.

There is a necessity to evaluate the role of preoperative imaging in topographic diagnosis and in improving surgical outcomes as well as to define their limitations and the place of each exploration technique.

MATERIAL AND METHODS

We performed a retrospective study that included all patients diagnosed with PHPT who underwent PTHx in our ear nose and throat (ENT) department and endocrinology department, in the period 2011 and 2022. We included all patients with primary hyperparathyroidism who were either clinically symptomatic or who met one of the criteria in the 4th International Guidelines for the management of asymptomatic PHPT (8) (Age < 50 years, Serum calcium > 1 mg/dL or >0.25 mmol/L of the upper limit of the reference interval for total calcium and >0.12 mmol/L for Ca2+, Bone Mineral Density (BMD) T-score ≤–2.5, a prevalent low-energy fracture, a glomerular filtration rate (GFR) of <60 ml/min, stone(s), nephrocalcinosis, or high stone risk) with at least 6 months of post-operative follow-up. A review of the patient's chart was conducted to evaluate epidemiologic, clinical, biological, imaging, and surgical data.

We excluded patients with primary hyperparathyroidism not indicated for surgery, patients with secondary or tertiary hyperparathyroidism, hyperparathyroidism secondary to hypovitaminosis D (25-OH vitamin D < 20 nmol/l), patients without a follow up after surgery and patients with an incomplete data.

Before surgery, all patients underwent US and 99mTc-MIBI. Second-line localization methods, computed tomography (CT) and magnetic resonance imaging (MRI), were performed when US or 99mTc-MIBI failed to localize the abnormal parathyroid gland. First-line MRI was indicated in case of CT's contradiction such as pregnancy and kidney failure. The Gamma-Probe guided surgery was indicated in cases of not concordant imaging or surgical resumption.

Surgery was carried out PTHx under general anesthesia by experienced ENT surgeons. All the patients underwent a minimally invasive procedure with a basal anterior cervicotomy when the preoperative localization imaging were concordant. A bilateral surgical exploration was carried out when preoperative localization imaging or a multiglandular disease were suspected. The surgeon indicates the exact location and the number of enlarged parathyroid glands discovered in the surgical field. The excised parathyroid tissue underwent both an extemporaneous histological examination and a definitive histological examination to confirm the diagnosis of parathyroid hyperplasia/adenoma or carcinoma.

Surgical success was defined as a normalization of PTH and calcium levels six months after surgery. HPTP persistence was defined by the persistence of abnormal PTH and calcium levels within 6 months after the surgery. HPTP recidivism or recurrence was defined by the reappearance of high levels of PTH and/or calcium 6 months after the surgery.

STATISTICAL ANALYSIS

The diagnostic performance of the different imaging methods (sensitivity, specificity, positive predictive value (PPV), negative predictive values (NPV)) was determined through statistical software (SPSS version 25), using intraoperative findings as a gold standard then they were compared to each other.

The findings were categorized as true positive, false positive, true negative or false negative regarding their ability to predict the exact location of abnormal glands in the right quadrant, as confirmed through the intraoperative findings.

In our study, were considered true positive pathological parathyroids properly localized and excised, false negative pathological parathyroids not localized and yet removed, false positive locations indicated but not corresponding to the time of operation to any pathological parathyroid, true negative localization sites not mentioned in the report and resulting surgical disease free. In patients affected by multiglandular disease, each gland was evaluated separately.

RESULTS

Of the total study group, 79 patients had PHPT with a median age of 59 years old [IQ 51-69] and a sex-ratio F/H 5:1.

Of our patients, 55 patients (69.9%) were exhibiting symptoms and the rest were completely asymptomatic. Hence, the discovery of diagnosis was fortuities following a regular biological test. The patients' medical history and clinical data was summarised in table 1.

Table 1: Patients' demographics and clinical data

Factor	Statistics
Total number of patients	79
Sex Male Female H/F	 12 (15.2%) 67 (84.8%) 1/5
Age	59 [IQ*: 51-69]
Patients' history High blood pressure Diabetes Cardiac disease PTHx** Total or partial thyroidectomy	 38 (48.1%) 28 (35.4%) 6 (7.6%) 1 (1.3%) 2 (2.5%)
Asymptomatic patients	24 (30.4%)
Symptomatic patients	55 (69.6%)
Bone symptoms Osteoporosis Pathological fracture	 40 (50.6%) 4 (5.1%)
Renal symptoms Nephrolithiasis Renal failure	 16 (20.3%) 7 (8.9%)
General symptoms	20 (25.3%)

IQ*: interquartile range
PTHx**: Parathyroidectomy

In the biological chart, a classic profile was observed in 87% of the patients, 12.3% of patients had a normocalcemia. The mean preoperative corrected serum calcium was 2,59 mmol/l ± 0,167, the median preoperative sPTH was 228 pg/ml [IQ 165,5-735,5], the median preoperative phosphorus was 0.73 mmol/l [IQ 0,7-0,94] and the median preoperative vitamin D was 17.9 ng/l [IQ 7,9-26,2].

All patients had a preoperative neck ultrasound. Regarding the parathyroid gland, inferior glands were affected in 75,9% and upper glands in 22,8%. The left side was concerned at 51.9% and the right side at 46.9%. An ectopic intrathyroidal localization was suspected in one patient (1,3%). The involvement was multinodular in 12 patients **(Table 2)**.

The ultrasound features of the adenoma were those of a hypoechoic nodule compared to thyroid tissue, well restricted, and vascularized to Doppler. The midsize of the pathological parathyroid gland was 12mm [IQ 8-16.75]. Co-existing nodular thyroid was observed in 32 patients (39.5%), ipsilateral in 19 patients and bilateral in 13 patients.

Table 2: Gland involvement from US

Parathyroid location		Statistics
Single nodule (N=67)	Right upper gland	6 (7.6%)
	Right lower gland	24 (30.4%)
	Left upper gland	7 (8.9%)
	Left lower gland	29 (36.7%)
	Ectopic nodule (Intrathyroidal)	1 (1.3%)
Double nodules (N = 12)	Right upper gland	3 (3.8%)
	Right lower gland	4 (5.1%)
	Left upper gland	2 (2.5%)
	Left lower gland	3 (3.8%)

All patients underwent 99mTc-MIBI with double tracer subtraction technique and 60 patients underwent SPECT-CT (74.7%) (**Table 3**). The midsize of the pathological parathyroid gland was 15mm [IQ 10-21]. CT was used in only 9 patients, and MRI in one patient.

Table 3: Gland involvement from 99mTc-MIBI

Parathyroid location			Statistics
99mTc-MIBI			
Single nodule (N= 63) Right lower gland Left upper gland Left lower gland Ectopic nodule (intrathymic)		Right upper gland	3 (3.8%)
		25 (31.6%)	
		8 (10.1%)	
		24 (30.4%)	
		3 (3.8%)	
Multiples nodules (N = 16)	Double nodule (N = 14)	Right upper gland	3 (3.8%)
		Right lower gland	10 (12.7%)
		Left upper gland	4 (5%)
		Left lower gland	14 (17.7%)
	Triple nodule (N = 2)	Right upper gland	2 (2.5%)
		Right lower gland	2 (2.5%)
		Left upper gland	1 (1.3%)
		Left lower gland	1 (1.3%)
SPECT-CT			
Single nodule (N= 47) Right lower gland Left upper gland Left lower gland Ectopic nodule		Right upper gland	3 (3.8%)
		15 (18.9%)	
		5 (6.3%)	
		21 (26.6%)	
		3 (3.8%)	
Multiples nodules (N = 13)	Double nodule (N = 12)	Right upper gland	4 (5%)
		Right lower gland	6 (7.6%)
		Left upper gland	6 (7.6%)
		Left lower gland	8 (10.1%)
	Triple nodule (N = 1)	Right upper gland	1 (1.3%)
		Right lower gland	1 (1.3%)
		Left upper gland	1 (1.3%)
		Left lower gland	0

All of our patients had a PTHx. Fifty-three of the patients (67,1%) underwent minimally invasive surgery, 22 patients (27.8%) had 2/4 parathyroidectomy, 3 patients (3.8%) had ¾ parathyroidectomy, and one patient (1.3%) had a subtotal parathyroidectomy 7/8. Parathyroidectomy was associated with a lobo-isthmectomy in 24.7% and a total thyroidectomy in 11.1% for concomitant thyroid pathology. One patient (1.3%) presented with an intrathyroidal localization of the pathological parathyroid and underwent an ipsilateral lobectomy combined with bilateral central neck dissection.

The patient who underwent a subtotal parathyroidectomy (7/8) had three foci on the imagery.

Extemporaneous histological examination showed parathyroid tissue in 93.7%. In 5 patients (6.3%), the pathological parathyroid gland couldn't be isolated on both sides of the thyroid gland and was not revealed by extemporaneous histological examination, necessitating bilateral central neck dissection. In 2 patients (2.5%), preoperative findings suggested a potential parathyroid carcinoma, so an ipsilateral central neck dissection was performed. In 3 patients (3.8%) extemporaneous histological examination identified a thyroid papillary carcinoma leading to bilateral central neck dissection. The Gamma-Probe guided surgery was completed in 3.8% of the surgeries in cases of not concordant imaging or surgical resumption.

The imaging results were compared and correlated with preoperative findings as a gold standard **(table 4)** and the diagnostic performance indices were computed for the US, the 99mTc-MIBI and SPECT-CT **(table 5).** In our study, the SPECT-CT had the highest sensitivity, specificity, PPV and NPV **(table 5)**. The US has the lowest sensitivity, specificity, PPV and NPV **(table 5)**.

Table 4: Concordance of imaging modality with surgery finding

Imaging modality	Statistics
US	79 (100%)
Concordant	56 (70.9%)
Not concordant	23 (29.1%)
99mTc-MIBI	79 (100%)
Concordant	65 (82%)
Not concordant	14 (18%)
SPECT-CT	60 (75.9%)
Concordant	50 (83.9%)
Not concordant	9 (16.1%)
US - 99mTC-MIBI	79 (100%)
Concordant	53 (67%)
Not concordant	26 (33%)

Table 5: The diagnostic performance of US, 99mTc-MIBI and SPECT-CT

	US	99mTc-MIBI	SPECT-CT	Couple US -99mTc-MIBI
Sensibility	74.68%	87.5%	88.14%	86.9%
Specificity	86.67%	88.52%	92.86%	95.5%
PPV	87.5%	90%	92.86%	96.4%
NPV	74.29%	85.71%	88.13%	84%

To evaluate the efficacy of both diagnostic methods, US and 99mTc-MIBI in preoperative prediction of the presence of a pathologic parathyroid gland, we calculated the concordance between US and 99mTc-MIBI according to the preoperative findings. Fifty-three (67%) of patients had concordant results in both tests (US and 99mTc-MIBI). The combination of US and 99mTC-MIBI had a higher sensitivity compared to US alone (86.9% vs 74.68%) and showed comparable sensitivity to 99mTC-MIBI (86.9% vs 87.5%). The specificity of the couple US-99mTC-MIBI is higher compared to each modality individually.

US sensibility is related to the number of pathologic parathyroids that vary in the same direction, as well as 99mTc-MIBI's sensitivity (Pearson coefficient: US 0.464 – 99mTc-MIBI: 0.519). US sensibility is not correlated to the size of the parathyroid gland, the preoperative sPTH and the number of pathologic parathyroids (p=0.269 – p: 0.394 – 0,464 respectively). Also, 99mTc-MIBI's sensitivity is not associated with the size of the parathyroid gland, the preoperative sPTH and the number of pathologic parathyroids (p= 0.474 – p: 0.053 – p: 0,519 respectively). The size of the parathyroid node and the PTH level are correlated and both variables vary in the same direction (Pearson Test).

Histological examination showed that 61 patients had an adenoma (77,2%), with 75% of single adenoma and 25% of multiple adenomas. Four patients had glandular hyperplasia (5.1%) and there were 4 cases of parathyroid carcinoma. The midsize of the pathological parathyroid gland was 20mm [IQ 12-25]. The median postoperative calcemia on the third day was 2.27 mmol/l [IQ 2.16-2.39] and the median postoperative sPTH was 88 pg/ml.

After a median follow-up of 12 months, the surgical success rate was 96.2% (76 patients). We documented HPTP persistence, with persistent hypercalcemia lasting over 6 months, in 2 patients (2.5%). There was one case of recurrence where a decrease in calcemia and sPTH wasn't observed.

In the two cases of HPTP persistence, the final pathological examination showed a parathyroid adenoma in 2 patients. Preoperative imaging consisted of US and 99mTc-MIBI for the two patients. US and 99mTc-MIBI were concordant and revealed a parathyroid nodule in both patients. These patients underwent a surgical resumption. The first patient underwent a parathyroidectomy of the lower right nodule. The other underwent a parathyroidectomy of

the lower left nodule associated with ipsilateral central neck dissection

In the one case of recurrence, the final pathological examination showed a parathyroid adenoma. Preoperative imaging revealed a parathyroid nodule located on the lower right pole of the thyroid, as observed in US, 99mTc-MIBI, SPECT-CT and CT. The patient underwent a surgical resumption with a parathyroidectomy for a lower right nodule. The final pathological examination confirmed the diagnosis of parathyroid adenoma. Following a median follow up of 6 months, no recurrence was observed.

DISCUSSION

Our study demonstrated that both US and 99mTc-MIBI are sensitive and specific in for locating pathologic parathyroid glands. 99mTc-MIBI demonstrates higher sensitivity compared to US. The combination of both methods demonstrated increased sensitivity compared to US alone and a comparable showed equivalent sensitivity to 99mTc-MIBI. The sensitivity of both US and MIBI correlates with the number of pathological parathyroids, (Pearson coefficient: US 0.464 – MIBI: 0.519). Additionally, the size of the parathyroid gland and the PTH level are positively correlated. The sensibility of US and 99mTc-MIBI's are not associated with the size of the parathyroid gland and the preoperative serum PTH. The cure rate was 96.2%.

PTHP is an endocrine disease that is caused in 85% by a unique parathyroid adenoma (2). Surgery is the baseline and curative treatment (3–5.7). Accurate preoperative localization is critical for performing targeted or minimally invasive surgery (3,8). That's how, imaging is now a standard preoperative procedure for locating the abnormal parathyroid tissue(5). Thus, imaging is recommended unless surgery is planned (5). The American Head and Neck Society (AHNS) Endocrine Section highlighted the need for precision preoperative localization to prevent unnecessary repetitive operations and identify a concomitant thyroid condition that could be treated in the same procedure (4). The most commonly used imaging techniques include US, 99mTc-MIBI, and SPECT-CT. The US is a simple method, inexpensive, harmless and operator-dependent (2,5). Vitteta et al, reported that the diagnostic performance of the US, is significantly improved when performed by more experienced operators (2). As well, it is very helpful in identifying parathyroid adenoma near the thyroid gland or upper cervical area and can identify concomitant thyroid nodules (5,9). Yet, the US is less useful in identifying parathyroid adenomas located behind the trachea or esophagus or ectopic glands in the mediastinum and it has a low sensitivity for small parathyroid glands (5) (10). It has been reported that US has a sensitivity of 76–87 % with a PPV of 93–97 %(5). In our study, US had a lower sensitivity at 74.68% with a lower PPV of 87.5% which seems related to operator dependence. The American Association of Endocrine Surgeons guidelines recommended that the US must be carried out by an experienced parathyroid sonographer (8). While a study of 1485 cases, elaborated by Broom et al, did not report a statistically significant difference between surgeon performed US, and radiology-performed US (1). US is sensitive enough that it can be used in the first-line investigation, instead, it is limited in patients with an elevated body mass index and the ectopic glands, especially those located in the mediastinum(11). Consequently, US is typically used in combination with a different imaging modality, most commonly 99mTc MIBI (11). When ultrasound is associated with SPECT, the localization precision of an adenoma increases to about 90% (12).

99mTc-MIBI is relatively inexpensive and implies low radiation exposure (9). In this study, it had a sensitivity of 87.5% with a PPV of 90%, which was higher than that reported in the literature of 78.9% sensitivity and 90.7% for PPV (5). Furthermore, 99mTc-MIBI is not dependent upon the operator as is the case in US(9). The 99mTc-MIBI in combination with SPECT is now carried out preventively in developed countries with a sensitivity of 79% and a positive predictive value of 91% (5). In our case, SPECT/CT had a sensitivity of 84.1%. 99mTc-sestamibi is a lipophilic cation that accumulates in the mitochondria rich oxyphil cells of abnormal parathyroid tissue and various metabolically active tissues (10,11).

The two most widely used protocols for parathyroid scintigraphy are based on two techniques: single-tracer double phase and dual-tracer single phase (8,11). The 99mTc-MIBI can detect ectopic lesions, in particular, mediastinum lesions and this gives MIBI an advantage over US (11). Furthermore, SPECT offers the benefit of 3 dimensions (11). Nowadays, SPECT has been merged with CT, which is more responsive and accurate (11). A meta-analysis comparing SPECT/CT, SPECT and planar images concluded that SPECT/CT was superior to SPECT with a common overall sensitivity and PPV of 84% and 95%, respectively, compared to 66% and 82% for SPECT (11).

CT and IMR are used in second-line investigations. Even though CT failed to provide satisfactory results in parathyroid imaging with a sensitivity of around 40% to 70% , 4D-CT gives excellent results for locating adenomas as well as detecting ectopic lesions (11). 4D-CT is more susceptible than US and sestamibi-SPECT to detect adenomas with a sensitivity of 88% compared to 65% (12,13). MRI is reserved for problem solving and reoperative cases (10). It has a sensitivity of 43%-94% (10). Parathyroid adenomas usually appear hypo-intense in T1-weighted and hyper-intense T2-weighted sequences.

In same challenging cases, fine needle aspiration-PTH (FNA-PTH) is sometimes necessary (10). Based on the American Association of Endocrine Surgeons, FNA should only be considered in patients eligible for surgery and the localization of pre-operative imaging must be not conclusive (8). However, the main restriction of

FNA-PTH, is that it can lead to malignant or benign dissemination (14). Several other complications were reported, such as hemorrhage, abscess, inflammation, and fibrosis (14).

Parathyroidectomy is the only definitive treatment for this pathology (5,8). All of our patients underwent surgery. The approach of parathyroidectomy has developed, from the conventional parathyroidectomy that envisages the exploration of the 4 parathyroid glands to the minimally invasive parathyroidectomy (MIP) aimed at removing preoperatively localized abnormal parathyroid gland. In MIP, the dissection is limited to the anatomically located site (12). The success of the surgical procedure is confirmed biochemically by the intra-operative monitoring of PTH (IOPTH) when it drops by at least 50% of the highest pre-excision level and into the normal PTH range (12). The bilateral neck exploration (BNE) is a conventional parathyroidectomy where the surgeon has to identify the parathyroid glands in their intended anatomical position and their ectopic locations (thymus, anterior mediastinum, tracheoesophageal groove and retroesophageal space, posterior mediastinum, carotid sheaths, thyroid gland). Without reliable and accurate preoperative localization, BNE is usually necessary (15). BNE is also indicated in multiple endocrine neoplasia (MEN) types 1 and 2a, familial hyperparathyroidism and lithium-induced hyperparathyroidism (12). These two techniques are equally efficient and associated with good results. Overall, the rates of complications are similar (12) (16).

CONCLUSION:

Preoperative imaging plays a crucial role in optimizing both preoperative and intraoperative topographic diagnosis. In our study, SPECT-CT exhibited the highest sensitivity, specificity, PPV and NPV. Our findings indicate that combining preoperative ultrasound with 99mTc-MIBI significantly improves both sensitivity and specificity.

Declaration of interests : The authors declare that they have no conflicts of interest

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