

Surgery for Primary Hyperparathyroidism in Patients with Preoperatively Negative Sestamibi Scan and Discordant Imaging Studies: The Usefulness of Intraoperative Parathyroid Hormone Monitoring

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ABSTRACT: The aim of this study was to evaluate the impact of intraoperative parathyroid hormone (PTH) monitoring on surgical strategy, intraoperative findings, and outcome in patients with negative sestamibi scintigraphy and with discordant imaging studies. We divided our 175 patients into 3 groups: group A was methoxyisobutylisonitrile (MIBI)-positive and ultrasonography positive and was concordant (114 patients), group B was MIBI-positive and ultrasonography-negative (50 patients), and group C was MIBI— and ultrasonography-negative (11 patients). The overall operative success was 99.12% in group A, 98% in group B, and 90.91% in group C, with an incidence of multiglandular disease of 3.5% in group A, 12% in group B, and 9.09% in group C. Intraoperative PTH monitoring changed the operative management in 2.63% of patients in group A and 14% in group B. The use of intraoperative PTH achieves to obtain excellent results in the treatment of primary hyperparathyroidism in high-volume centers, even in the most difficult cases, during MIBI-negative and discordant preoperative imaging studies.

KEYWORDS: primary hyperparathyroidism, intraoperative PTH, sestamibi scintigraphy, parathyroidectomy

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Introduction

Primary hyperparathyroidism is a common endocrine disease that affects 1% of the adult population¹; its incidence is increasing, and surgical treatment remains the only curative therapy.^{2,3} Primary hyperparathyroidism is commonly due to a single parathyroid adenoma (80%–87%) followed by multigland disease (5%–15% with asymmetric 4-gland hyperplasia; 2%–12%, multiple adenomas) and, rarely, carcinoma (<1%).^{4–6}

Localizing studies seems to be the key for determining the optimal surgical strategy in patients with sporadic primary hyperparathyroidism.^{7,8} Neck ultrasound and methoxyisobutylisonitrile (MIBI) scan are generally used as the first tool in the diagnostic approach of primary hyperparathyroidism.^{6–8} Neck ultrasound is the least invasive and cheapest method to accurately localize hyperfunctioning parathyroid,

but its efficacy is related to operator experience and may be reduced in the presence of a concomitant nodular goiter.⁸ MIBI scan is able to localize hyperfunctioning parathyroid in primary hyperparathyroidism patients with high sensitivity (68%–95%) and specificity (90%) and, for this reason, it has been used as the technique of choice to guide minimally invasive parathyroidectomy.^{5,6,8,9} However, the small dimension of hyperfunctioning parathyroid, oxyphil cell content, and various degrees of apoptosis or necrosis may reduce MIBI uptake causing false-negative results.^{8,9} The association between thyroid nodules with primary hyperparathyroidism occurs frequently in iodine-deficient areas (Italy or central Europe), where the incidence of nodular goiter varies from 20% to 60%; this has been reported to reduce the diagnostic performance of MIBI scans to 60% to 70%.⁸ In such conditions, the combined



use of MIBI scan and neck ultrasound may also improve the diagnostic efficacy, but a 15% to 20% rate of inaccurate localization still remains.⁸ Some investigators have also suggested that patients with primary hyperparathyroidism who have negative sestamibi scan results are more likely to have ectopic parathyroid glands and warrant referral to a tertiary care center with experienced endocrine surgeons.⁵

For many years, bilateral neck exploration in patients with primary hyperparathyroidism with resection of enlarged parathyroid glands, and without any preoperative localization studies, has resulted in a success rate exceeding 95%, and only minimal morbidity was observed in the hands of an experienced endocrine surgeon.^{1-3,10-13} Recently, it has been shown that limited exploration has its advantages, including shorter hospital stay, less postoperative pain, and fewer complications.¹ In consideration that more than 80% of the patients are cured after removal of a solitary parathyroid adenoma, which is the most common cause of primary hyperparathyroidism,² focused parathyroidectomy is currently the treatment of choice.

Some problems currently affect patients with negative sestamibi scintigraphy or in which imaging studies are discordant. In these cases, bilateral neck exploration is generally recommended, although limited exploration (focused operation or unilateral neck exploration) with the aid of intraoperative parathyroid hormone (PTH) monitoring has been suggested to be an alternative approach.^{10,14}

The aim of this study was to evaluate the impact of intraoperative PTH on surgical strategy, intraoperative findings, and outcome in patients with negative sestamibi scintigraphy, and discordant imaging studies.

Materials and Methods

We conducted a retrospective study of 239 patients who were operated on for primary hyperparathyroidism in our surgical department between May 1, 2003, and December 31, 2012. A total of 202 patients were female, and 37 were male, and the median age was 58 years (range, 19–85 years). Before the operation, hypercalcemia and elevated PTH levels were observed in all patients.

In order to localize hyperfunctioning glands, a technetium (TC) 99m-sestamibi scan (MIBI) was performed in 191 patients (79.9%); pathologic parathyroid was localized in 178 cases (93.2%). All MIBI scans were performed at the same nuclear medicine center. High-resolution ultrasound was performed in 233 patients, and pathologic parathyroid was localized in 146 patients (62.7%). The association of ultrasound and 99m TC-sestamibi scan localized hyperfunctioning parathyroid in 164/175 patients (93.7%). Single-photon emission computed tomography-TC (SPECT-TC) was performed on 140 patients, and hyperfunctioning parathyroid was localized in 134 patients (95.7%). The association of SPECT-TC and ultrasonography localized hyperfunctioning parathyroid in 121/122 patients (99.2%).

We considered only the 175/239 patients that underwent both ultrasound examination and MIBI scan. We divided the patients into 3 groups: group A was MIBI- and ultrasonography-positive and concordant (114 patients), group B was MIBI-positive and ultrasonography-negative (50 patients), and group C was MIBI- and ultrasonography-negative (11 patients).

The patients in groups A and B ($n = 164$) underwent a focused parathyroidectomy; the patients of group C ($n = 11$) were submitted to bilateral cervical exploration. In all 175 patients, rapid intraoperative PTH assay monitoring was performed. All patients had normal renal function (serum creatinine value ranging from 0.7 mg/dL to 1.2 mg/dL), and they all gave informed consent for the procedure. All operations were performed under general anesthesia with endotracheal intubation and by the same team of surgeons, who were highly experienced in parathyroid surgery. Blood samples were collected at the following times: (1) at preincision time, (2) at 10 minutes after gland excision, and (3) at 20 minutes after excision if a sufficient reduction of PTH value was not observed. The STAT-IntraOperative-Intact-PTH chemiluminescence immunoassay semiautomated mobile system (Future Diagnostics, Wjichen, the Netherlands) was used within the surgical suite complex for the intraoperative quantitative determination of PTH levels in ethylenediaminetetraacetic acid plasma.

Ethical approval for our study was obtained from our institutional ethical committee. Informed consent was obtained from patients for their inclusion in our study.

On the bases of the Irvin criterion,^{2,11} an intraoperative PTH drop $>50\%$ from the highest preincision or preexcision level after parathyroid excision was considered a surgical success. A PTH drop of $<50\%$ from the highest basal value within 20 minutes after gland excision was considered predictor of persistent hyperfunctioning parathyroid tissue, and further surgical exploration was required.

Statistical analysis was based on the χ^2 test, the Student t test, or Fisher exact test. A P value < 0.05 was considered significant.

Results

Group A. A $>50\%$ decrease of PTH within 10 minutes compared with the highest preexcision value occurred in 93/114 patients (81.57%). In 18 patients, a $>50\%$ decrease of PTH was obtained after 20 minutes (15.78%) (Table 1). In the remaining 3 patients, the surgical procedure went on, and bilateral neck exploration was performed; an additional pathologic parathyroid gland was removed in all 3 cases. Postoperative normal calcemia and PTH were found in 113 patients, and persistent postoperative hypercalcemia with an increased value of PTH was found in 1 patient. In this case, the histology showed parathyroid hyperplasia. The patient was operated on again, and a further hyperplastic parathyroid gland was removed and was associated with normalization of PTH. The overall operative success was 99.12% with a 3.5% incidence of

**Table 1.** Decrease of intraoperative PTH in the 3 groups.

	GROUP A	GROUP B	GROUP C	TOTAL
PTH decrease >50% at 10 min	93/114	33/50	10/11	136/175
PTH decrease >50% at 20 min	18/114	10/50	1/11	29/175
PTH decrease <50%	3/114	7/50	0/11	10/175
PTH elevated after operation	1/114	1/50	1/11	3/175

Abbreviation: PTH, parathyroid hormone.

multiglandular disease (4 cases) (Table 2). Intraoperative PTH monitoring changed the operative management in 2.63% of patients; the other results are reported in Table 3.

Group B. A >50% decrease of PTH within 10 minutes compared with the highest preexcision value occurred in 33/50 patients (66%). In 10 patients, a >50% decrease of PTH was obtained after 20 minutes (20%) (Table 1). In the remaining 7 patients, the surgical procedure went on, and bilateral neck exploration was performed; an additional pathologic parathyroid gland was removed in 5 cases. In the other 2 cases, no pathological parathyroid glands were found at surgical exploration. Postoperative normal calcemia and PTH were found in 49/50 patients, and persistent postoperative hypercalcemia with an increased value of PTH was found in 1 patient. In this case, histology showed parathyroid hyperplasia, and an additional ectopic mediastinal parathyroid was found at postoperative MIBI (captation was not present preoperatively). The removal of the gland led to a normalization of PTH. The overall operative success was 98%, with a 12% incidence of multiglandular disease (6 cases) (Table 2). Intraoperative PTH monitoring changed the operative management in 14% of patients; the other results are reported in Table 3.

Group C. A >50% decrease of PTH within 10 minutes compared with the highest preexcision value occurred in 10/11 patients (90.9%). In 1 patient, a >50% decrease of PTH was obtained after 20 minutes (9.09%) (Table 1). Postoperative normal calcemia and PTH were found in 10/11 patients, and persistent postoperative hypercalcemia with an increased value of PTH was found in 1 patient. In this case, histology showed parathyroid hyperplasia. The patient was operated on again, and a further hyperplastic parathyroid gland was removed with normalization of PTH. The overall operative success was 90.91% (Table 2). The other results are reported in Table 3.

Results of surgery. The median duration of surgery was 60 minutes (range, 40–80 minutes). Surgical complications were observed in 3 patients: 2 had transient recurrent laryngeal nerve paresis, and 1 had a hematoma necessitating reoperation. Transient hypocalcemia occurred in 24 cases (12.7%) and was treated with calcium and vitamin D per os with resolution within 1 month. No cases of permanent hypocalcemia were observed. There were no wound complications and no perioperative deaths. The median postoperative recovery was 2 days (range: 1–3 days). The overall operative success was 98.2%, with a 6.3% incidence of multiglandular disease (11 cases). Intraoperative PTH monitoring changed the operative management in 5.7% of patients. The total results of the use of PTH are reported in Table 3.

Discussion

Successful preoperative localization of parathyroid pathology is essential for a focal neck exploration.⁷ Neck ultrasound and MIBI scan represent the first diagnostic tools used to correctly plan surgery for hyperparathyroidism in the absence of concomitant cervical masses.⁸ False-negative neck ultrasound results may be rarely found in cases with small and ectopic parathyroids, intrathyroidal parathyroids, and underscent parathyroid situated along the common carotid artery or recurrent laryngeal nerve, while false-negative MIBI scans have been observed in the presence of small size, low oxyphilic cell content, and morphological changes of parathyroids.⁸ However, negative MIBI imaging is uncommon and of low clinical impact (with only 5.7% of operative patients reported in the experience of Dy⁴). In our experience, negative MIBI imaging was found in only 11 patients (6.2%), while discordant preoperative studies were found in 50 patients (28.5%), confirming the results of other studies in the literature.⁴

When the sestamibi scan and neck ultrasound results are negative, the risk of multiglandular disease is reported as

Table 2. Multigland disease and operative success in the 3 groups.

	GROUP A	GROUP B	GROUP C	P
Multigland disease	4/114	6/50	1/11	0.1101
Operative success	113/114 (99.12%)	49/50 (98%)	10/11 (90.91%)	0.1319

**Table 3.** Results of the use of intraoperative PTH in the 3 groups.

	GROUP A	GROUP B	GROUP C	TOTAL
True positives	110	43	10	163
True negatives	3	6	0	9
False positives	1	0	1	2
False negatives	0	1	0	1
Sensibility	100%	97.7%	100%	99.48%
Specificity	75%	100%	–	81.81%
Accuracy	99%	98%	90.9%	98.53%
Positive predictive value	99%	100%	90.9%	98.97%
Negative predictive value	100%	85.71%	–	90%

Abbreviation: PTH, parathyroid hormone.

very high (31.6%–40%).^{5,13,15} Biochemical cure rate in patients with negative sestamibi scan results was lower, even when considering only patients who underwent an initial operation for primary hyperparathyroidism¹ and when considering that the rate of persistent hyperparathyroidism is higher.¹⁵

Other authors could not find any proof for a higher incidence of multiglandular disease in patients with primary hyperparathyroidism and negative scintigraphy, finding a high incidence of single parathyroid gland disease; the majority of these patients (60%) had a single adenoma.^{1,14} This contradicts the common perception that a negative sestamibi scan indicates a diagnosis of parathyroid hyperplasia.¹⁴ Moreover, patients with a single positive MIBI focal point in the neck and a negative ultrasound have an unusually high incidence of posteriorly located upper glands.⁶

In our experience, the incidence of multigland disease was 3.5% in group A, 12% in group B, and 9.09% in group C, thus showing a higher incidence in patients with discordant studies, even if not statistically significant, which may have been the case for the small number of patients. This result is similar to others reported in the literature,^{1,14} but the incidence of multigland disease in the present study is significantly lower than that of most of the studies that show a dramatic increase in the incidence of multigland disease in these patients.^{5,13,15}

In a study by Dy et al,⁴ the success rate of surgery with a negative MIBI and a negative ultrasound was 89%, which is similar to the 90% cure rate for patients with no ultrasound performed and a negative MIBI. In a study by Bergenfelz et al,¹⁰ when both studies were negative prior to the operative intervention, the failure rate of surgery approached 18%.⁴ Patients with negative localization on imaging have lower cure rates than those with localizations (90% versus 98%).⁴

In our study, the success rate was 99.12% in group A, 98% in group B, and 91% in group C, which is very high and similar to other reports in the literature,⁴ confirming the high probability of successful treatment in high-volume centers; the patients in group C had a lower success rate, but the rate was still very high. The patients in group B had a lower negative

predictive value (85.7%), while patients in group C had a lower accuracy rate (90.9%) and a lower positive predictive value (90.9%), confirming the greatest difficulties faced in diagnosis and treatment, especially in patients who are MIBI-negative.

The use of intraoperative PTH in patients with negative or discordant localization procedures was recommended by most authors^{2,16} as well as in a recent position statement of the European Society of Endocrine Surgeons.¹⁰ In a study by Bergenfelz et al,¹⁰ the use of intraoperative PTH decreased the risk for persistent primary hyperparathyroidism from 26% to 8%, and the risk for medically treated hypocalcemia was reduced from 16% to 8% at the 6-week follow-up point. Even so, the risk for persistent primary hyperparathyroidism and medically treated hypocalcemia is high.¹⁰

In the opinion of Thier et al,¹ limited parathyroid exploration with the aid of intraoperative PTH measurement can be performed in primary hyperparathyroidism patients with negative sestamibi scintigraphy, resulting in a high cure rate (94.3%). However, in the opinion of most authors, these patients may be referred to high-volume medical centers.^{5,17}

In our experience, 2.6% of patients in group A and 10% of patients in group B would not have been cured without intraoperative PTH, which is similar to other reports in the literature,¹⁰ which confirms the importance of the use of intraoperative PTH in patients with discordant preoperative studies. Based on these results, we believe (and in agreement with other authors^{2,10,16}) that the use of intraoperative PTH remains useful, but is not essential, in patients with concordant studies, while it is fundamental for patients with discordant studies and in MIBI-negative patients.

In conclusion, the use of intraoperative PTH achieves to obtain excellent results in the treatment of primary hyperparathyroidism in high-volume centers, even in the most difficult cases: MIBI-negative and discordant preoperative imaging studies. When preoperative localization study results are negative, the patient has a high risk of multiglandular disease, and a conventional cervicotomy with identification of the 4 glands is strongly recommended. Intraoperative



PTH monitoring remains essential for performing successful parathyroidectomy in patients with discordant imaging.

Author Contributions

Wrote the first draft of the manuscript: PGC, GL, FM. Contributed to the writing of the manuscript: GP, AT, SP. Agree with manuscript results and conclusions: PGC, AT, SP, AN. Jointly developed the structure and arguments for the paper: PGC, GL, FM, GP. Made critical revisions and approved final version: PGC, GL, FM, AN. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

REFERENCES

1. Thier M, Nordenström E, Bergenfelz A, Westerdahl J. Surgery for patients with primary hyperparathyroidism and negative sestamibi scintigraphy—a feasibility study. *Langenbecks Arch Surg.* 2009;394(5):881–884.
2. Barczynski M, Konturek A, Cichon S, Hubalewska-Dydejczyk A, Golkowski F, Huszno B. Intraoperative parathyroid hormone assay improves outcomes of minimally invasive parathyroidectomy mainly in patients with a presumed solitary parathyroid adenoma and missing concordance of preoperative imaging. *Clin Endocrinol (Oxf).* 2007;66(6):878–885.
3. Phillips IJ, Kurzawinski TR, Honour JW. Potential pitfalls in intraoperative parathyroid hormone measurements during parathyroid surgery. *Ann Clin Biochem.* 2005;42(pt 6):453–458.
4. Dy BM, Richards ML, Vazquez BJ, Thompson GB, Farley DR, Grant CS. Primary hyperparathyroidism and negative Tc99 sestamibi imaging: to operate or not? *Ann Surg Oncol.* 2012;19(7):2272–2278.
5. Elaraj DM, Sippel RS, Lindsay S, et al. Are additional localization studies and referral indicated for patients with primary hyperparathyroidism who have negative sestamibi scan results? *Arch Surg.* 2010;145(6):578–581.
6. Harari A, Mitmaker E, Grogan RH, et al. Primary hyperparathyroidism patients with positive preoperative sestamibi scan and negative ultrasound are more likely to have posteriorly located upper gland adenomas (PLUGs). *Ann Surg Oncol.* 2011;18(6):1717–1722.
7. Berber E, Parikh RT, Ballem N, Garner CN, Milas M, Siperstein AE. Factors contributing to negative parathyroid localization: an analysis of 1000 patients. *Surgery.* 2008;144(1):74–79.
8. Boi F, Lombardo C, Cocco MC, et al. Thyroid diseases cause mismatch between MIBI scan and neck ultrasound in the diagnosis of hyperfunctioning parathyroids: usefulness of FNA-PTH assay. *Eur J Endocrinol.* 2013;168(1):49–58.
9. Mihai R, Gleeson F, Buley ID, Roskell DE, Sadler GP. Negative imaging studies for primary hyperparathyroidism are unavoidable: correlation of sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. *World J Surg.* 2006;30(5):697–704.
10. Bergenfelz AO, Wallin G, Jansson S, et al. Results of surgery for sporadic primary hyperparathyroidism in patients with preoperatively negative sestamibi scintigraphy and ultrasound. *Langenbecks Arch Surg.* 2011;396(1):83–90.
11. Calò PG, Pisano G, Tatti A, et al. Intraoperative parathyroid hormone assay during focused parathyroidectomy for primary hyperparathyroidism: is it really mandatory? *Minerva Chir.* 2012;67(4):337–342.
12. Calò PG, Tatti A, Medas F, et al. New techniques in parathyroid surgery [in Italian]. *G Chir.* 2010;31(6–7):322–324.
13. Sebag F, Hubbard JG, Maweja S, Misso C, Tardivet L, Henry JF. Negative preoperative localization studies are highly predictive of multiglandular disease in sporadic primary hyperparathyroidism. *Surgery.* 2003;134(6):1038–1041; discussion 1041–1042.
14. Lal A, Chen H. The negative sestamibi scan: is a minimally invasive parathyroidectomy still possible? *Ann Surg Oncol.* 2007;14(8):2363–2366.
15. Harari A, Allendorf J, Shifrin A, DiGorgi M, Inabnet WB. Negative preoperative localization leads to greater resource use in the era of minimally invasive parathyroidectomy. *Am J Surg.* 2009;197(6):769–773.
16. Lew JI, Solorzano CC, Montano RE, Carneiro-Pla DM, Irvin GL. Role of intraoperative parathormone monitoring during parathyroidectomy in patients with discordant localization studies. *Surgery.* 2008;144(2):299–306.
17. Chan RK, Ruan DT, Gawande AA, Moore FD. Surgery for hyperparathyroidism in image-negative patients. *Arch Surg.* 2008;143(4):335–337.