# Intraoperative Parathyroid Hormone Monitoring

## Optimal Utilization

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**KEYWORDS**

- Primary hyperparathyroidism • PTH • Intraoperative PTH monitoring
- Minimally invasive parathyroidectomy

**KEY POINTS**

- Advances in preoperative localizing studies and surgical adjuncts, such as the introduction of intraoperative parathyroid hormone (IOPTH) monitoring, have shifted the traditional bilateral operative approach for primary hyperparathyroidism to a focused surgery or minimally invasive parathyroidectomy.
- Focused parathyroidectomy guided by IOPTH monitoring makes this procedure safer, less invasive, and highly successful.
- The utilization of IOPTH interpretation criteria can predict operative success, minimize unnecessary bilateral exploration, decrease the likelihood of resecting parathyroid glands that are not hypersecreting, and prevent recurrence.

### INTRODUCTION

With an annual incidence of 21.6 per 100,000 persons in the United States,[1] primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia due to hypersecretion of parathyroid hormone (PTH) from one or more parathyroid glands. The incidence of PHPT is similar in men and women before the age of 45 but peaks in the seventh decade with most cases occurring in women (74%).[2] With the increasing utilization of calcium screening in the developed world, the clinical profile of PHPT, typically characterized by hypercalcemic symptoms, nephrolithiasis, bone disease, and neuromuscular symptoms, has shifted from symptomatic hyperparathyroidism to one with subtle or no specific symptoms.[3] After ruling out other causes of hypercalcemia, the diagnosis of PHPT is made via biochemical confirmation of an inappropriately

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normal or elevated serum PTH concentration in the setting of normal renal function. Most patients with PHPT present with a single adenoma (70%–95%), whereas close to 4% have double adenomas, 15% have parathyroid hyperplasia, and very few cases are due to parathyroid carcinoma.[4]

Surgery is the mainstay of treatment for PHPT, resulting in long-term cure and reversal of symptoms. Although medical therapy for secondary hyperparathyroidism is well established, its role in PHPT is limited to refractory disease and nonsurgical candidates.[5] Bilateral exploration (BE) is the traditional surgical approach, allowing the surgeon to visualize all parathyroid glands and remove one or more grossly enlarged glands. Although this approach has a high cure rate,[6] most patients with PHPT have one causative lesion, and a unilateral approach is feasible in most cases. The introduction of highly accurate parathyroid imaging techniques, such as sestamibi scintigraphy and high-resolution ultrasonography of the neck, and the implementation of surgical adjuncts such as intraoperative PTH (IOPTH) monitoring have heralded the idea of minimally invasive parathyroidectomy (MIP), with focused neck exploration and excision of only hypersecreting glands.[7–11] Focused parathyroidectomy has a lower incidence of postoperative hypocalcemia and decreased risk of recurrent nerve damage. By limiting the dissection, a favorable operative field is preserved in the event of reexploration. Focused surgery guided by IOPTH monitoring allows the surgeon to confirm the removal of all hypersecreting parathyroid glands, and to predict operative success and long-term cure from PHPT.

## INTRAOPERATIVE PARATHYROID HORMONE: HISTORICAL PERSPECTIVE

Focused parathyroidectomy relies on accurate preoperative localization of all abnormal parathyroid glands; however, many preoperative parathyroid imaging technologies are subject to missing double adenomas, parathyroid hyperplasia, and ectopically located glands. In these cases, focused parathyroidectomy guided by imaging studies alone would fail in a significant subset of patients. To overcome this deficit, in 1988 Nussbaum and colleagues[12] introduced postresection measurement of PTH as an adjunct to show cure. In 1991, Irvin and colleagues[13] introduced a rapid IOPTH assay to assess adequacy of resection. For the first time, a series of 21 patients had their parathyroid surgery guided by IOPTH using an immunoradiometric method. The short half-life of PTH (2–4 minutes)[14] makes it ideal for intraoperative use. In 1996, this rapid assay method was further developed to an immunochemiluminescence method, and the "quick" IOPTH assay became commercially available for intraoperative use.[15] The assay allowed surgeons to verify resection of hyperfunctioning parathyroid glands with a 15-minute turnaround and, after noting an appropriate decline in serum PTH, the surgeon could forgo visual inspection of the remaining glands. In contrast, a persistently elevated serum PTH prompted further exploration. The use of IOPTH monitoring to confirm cure as a practical adjunct of focused parathyroidectomy has since been validated.[15–17]

## OPERATIVE SUCCESS WITH INTRAOPERATIVE PARATHYROID HORMONE MONITORING

The utilization of IOPTH monitoring to determine the extent of surgery in the setting of PHPT is highly accurate, resulting in excellent outcomes when preoperative localization studies are implemented.[18–24] Patients with concordant preoperative localization studies represent the easiest to treat group of patients, as image-guided focused surgery results in cure rates exceeding 95% even in operations without IOPTH. When patients undergo focused surgery guided by IOPTH monitoring, this leads to similar or in some cases higher operative success rates ranging from 97% to 99% compared with

the operative success of BE, which exceeds 94%.[23–25] In a large series of patients with PHPT, focused resection led to a 99% cure rate compared to 97% with BE.[26] Numerous studies have reported decreased operative time, shorter incisional length, and shorter hospital stay with focused surgery or MIP.[9,26,27] Equivalence in long-term outcome has also been observed between focused surgery guided by IOPTH monitoring and BE.[28–31]

Higher estimated rates of unrecognized multiglandular disease (MGD) have been reported with focused surgery guided by IOPTH monitoring compared with BE.[32] In a series of 15,000 patients with a mean follow-up of 6 years, Norman and colleagues[33] examined the ongoing differences between unilateral and bilateral surgical techniques for 10-year recurrence, multigland removal, operative times, and length of hospital stay. Recurrence was 11 times more likely for unilateral explorations, causing gradual increases in BEs in their practice. Ten-year cure rates were unchanged for bilateral operations, and unilateral operations showed continued slow recurrence rates of 5%. Removal of more than one gland occurred 16 times more frequently with a bilateral operation, increasing cure rates to their current 99.4%. Of 1060 reoperations performed for recurrence, IOPTH levels fell greater than 50% in 22% of patients, yet a second adenoma was subsequently found. The investigators conclude that regardless of surgical adjuncts, unilateral parathyroidectomy carries a 1-year failure rate of 3% to 5% and a 10-year recurrence rate of 4% to 6%. They postulate that the only way to achieve 10-year cure rates greater than 94.5% is to examine all 4 parathyroid glands. Allowing rapid analysis of all 4 glands through the same 1-inch incision has caused this group to abandon unilateral parathyroidectomy. However, another 10-year follow-up study highlighted the successful utility of IOPTH monitoring during focused surgery to predict complete resection and recognize other hypersecreting glands, thus sparing normally secreting glands.[34] Additionally, randomized trials, in which patients with positive sestamibi scans had MIP versus BE with and without IOPTH guidance, have described a lower incidence of MGD with focused surgery when compared with patients who underwent BE and excision based on gland size.[35,36] This suggests that not all enlarged glands observed in BE are hypersecreting and contributing to hypercalcemia.[37]

## APPLICATION OF INTRAOPERATIVE PARATHYROID HORMONE MONITORING

Greater than 90% of high-volume parathyroid surgeons use IOPTH to guide extent of parathyroidectomy.[38] IOPTH monitoring aids the surgeon by (1) confirming that all hypersecreting parathyroid glands have been excised without the need for visual confirmation of normally functioning glands, (2) indicating additional hyperfunctioning glands by an insufficient IOPTH drop, thus requiring further neck exploration to achieve operative success, (3) differentiating parathyroid tissue from nonparathyroid tissue, and (4) identifying the side of the neck containing the hypersecreting parathyroid gland(s) with the use of differential jugular venous sampling.[39] Importantly, IOPTH monitoring value-adds to surgical decision-making in patients with discordant preoperative imaging.[40]

## INTRAOPERATIVE PARATHYROID HORMONE SAMPLING PROTOCOL

The timing of blood sample collection is critical for the success of focused surgery, which essentially takes advantage of PTH clearance rates to guide the extent of dissection. Therefore, it is essential that the surgeon has an understanding of PTH dynamics. Throughout the procedure, whole blood is collected at specific times: in the operating room before induction of anesthesia or skin incision (baseline), and at variable intervals

after parathyroid gland excision. The authors also obtain an IOPTH sample immediately after gland excision (at-excision IOPTH). It is known that approximately 20% of patients will experience a spike in IOPTH levels during surgery. In the absence of an at-excision IOPTH, a spike in the hormone level may be missed, thus prompting unnecessary BE. While waiting for PTH results to be reported, the surgeon normally proceeds with closure of the incision site, while avoiding manipulation of the remaining parathyroid glands, to minimize the chance that a false elevation in the PTH level occurs.[41] Importantly, it is the successful interpretation of changes in PTH levels that is essential for using this technique in a way to optimize cure. To reduce complications, the IOPTH criterion used to predict cure should minimize unnecessary BE and decrease the likelihood of resecting parathyroid glands that are not hypersecreting.

## INTRAOPERATIVE PARATHYROID HORMONE CRITERIA FOR PREDICTING OPERATIVE SUCCESS

The goal of parathyroidectomy guided by IOPTH monitoring is to achieve operative success, defined as eucalcemia for at least 6 months postoperatively. Alternatively, operative failure or persistent hyperparathyroidism is defined as hypercalcemia and elevated serum PTH levels within 6 months after surgery. When preoperative localization studies are concordant for single gland involvement, IOPTH monitoring may not significantly contribute to surgical success. In patients in whom the preoperative localization studies are discordant, the incidence of MGD is higher and thus the surgeon must carefully choose the protocol and IOPTH interpretation criteria that will result in complete cure.[40]

In 1993, Irvin and colleagues[42] first established that a 50% decline from a preexcision IOPTH level best predicted postoperative normocalcemia. The “Miami criterion” was later refined to be a drop of 50% or more from the highest PTH level, from either the preincision or preexcision level, occurring 10 minutes after the suspected gland is excised.[43] If the 10-minute PTH sample decreases sufficiently, then the procedure can be terminated; however, if the criterion is not met at this point, then the neck is reexplored and the protocol for blood sampling is once again repeated for each additional excised gland until all abnormal tissue is removed as indicated by an appropriate drop in serum PTH. The Miami criterion predicts postoperative normal or low calcium levels with an accuracy of 97% to 98%.[44–48]

A retrospective review of 260 patients with sporadic PHPT and concordant preoperative imaging evaluated the predictive values of the Miami, Halle, Rome, and Vienna IOPTH interpretation criteria.[49] Barczynski and colleagues[49] reported 97% accuracy in intraoperative prediction of cure using the Miami criterion followed by the Vienna criterion (92%). The Rome criterion followed by the Halle criterion performed better at detecting MGD. However, given their low negative predictive value, their application in patients qualified for MIP and concordant imaging studies would result in a significantly higher number of unnecessary conversions to BE, with only a marginal improvement in the success rate of the primary procedure. In another retrospective study, the Vienna and Halle criteria were better predictors of MGD than the Miami criterion.[50] Riss and colleagues attributed the success of the Vienna criterion to its defined baseline, a factor that can lead to inaccurate interpretation of the PTH curve. Similar findings have been supported elsewhere.[51]

The choice of IOPTH criteria to predict operative success remains controversial. There is a lack of standardization regarding baseline PTH samples, percent decline used as a cutoff, sampling times, and sampling frequency. There is a need for objective IOPTH criteria that accurately predict operative success, obviating the need for

further surgical exploration. It is worth noting that as IOPTH criteria become stricter, BE is performed more frequently and a greater number of enlarged but normally functioning glands are excised without improving operative success.[50–52] The most commonly used criteria for predicting the outcome of focused parathyroid surgery are summarized in **Table 1**.

## PREDICTING RECURRENCE WITH INTRAOPERATIVE PARATHYROID HORMONE

Based on a retrospective analysis of 194 patients who underwent focused surgery for PHPT guided by IOPTH,[56] the author currently uses a modified version of the Miami criterion: (1) a drop in PTH greater than 50% from baseline and a return to normal range (<65 pg/mL) of the final PTH sample and (2) an absolute final PTH level less than 40 pg/mL. Heller and Blumberg[56] have shown that patients with a final IOPTH less than 40 pg/mL had no disease recurrence at a median follow-up of 5 months. Wharry and colleagues,[57] who analyzed 1108 cases of sporadic PHPT using IOPTH monitoring, found that a final IOPTH that was within the normal range and dropped by greater than 50% from baseline was a strong predictor of operative success. Moreover, patients with a final IOPTH between 41 and 65 pg/mL had greater long-term recurrence. This observation was also recently confirmed by Rajaei and colleagues[58] in a retrospective review of 1371 patients with PHPT, grouped based on final IOPTH of less than 40, 40 to 59, and greater than 60 pg/mL with 2 years of follow-up. Patients with a final IOPTH less than 40 pg/mL experienced less hypercalcemia at 6-month follow-up and the lowest recurrence rate beyond 6 months postoperatively. Disease-free status was also greatest in patients with a final IOPTH less than 40 pg/mL beyond 2 years postoperatively. Thus, patients with a final IOPTH remaining above 40 pg/mL may be at an increased risk of having persistent PHPT and should be followed closely and indefinitely following surgery.

**Table 1**
**Commonly used intraoperative parathyroid hormone monitoring criteria for predicting outcomes of parathyroid surgery**

| Criterion | Definition | Sensitivity, % | Specificity, % | Accuracy, % |
|---|---|---|---|---|
| Miami[53] | Decay ≥50% from highest baseline value within 10 min after resection | 98 | 94 | 97 |
| Halle[50] | Decay into the low normal range (≤35 pg/L) within 15 min after resection | 70 | 87 | 72 |
| Rome[54] | Decay ≥50% from highest baseline value, and/or 20 min postexcision value within reference range, and/or ≤7.5 ng/L lower than 10 min postexcision value | 83 | 90 | 84 |
| Vienna[50] | Decay ≥50% from the preincision value within 10 min after resection | 92 | 89 | 92 |
| Charleston[55] | Decay >50% from highest baseline value 10 min after resection and return to normal range or decay >65%, or decay >50% and return to normal range within 20 min after resection | 97 | 98 | 97 |

In a retrospective review of 2185 patients who underwent surgery for PHPT guided by IOPTH monitoring, Wachtel and colleagues[59] performed multivariate and univariate analyses to determine factors associated with intraoperative failure. The intraoperative failure group had patients with more multigland disease and smaller glands. On multivariate analysis, PTH level was statistically, but not clinically, associated with intraoperative failure. Median IOPTH decrease was lower in patients with persistent disease. The investigators concluded that intraoperative failure is associated with higher rates of multigland disease and smaller parathyroid glands. Additionally, patients with persistent disease had significantly lower decreases in IOPTH, but half of patients who experienced failure by IOPTH criteria were eucalcemic 6 months postoperatively.

Schneider and colleagues[60] reported long-term results of 1368 parathyroid operations for PHPT guided by IOPTH monitoring, including 1006 MIP and 380 BE. There were no differences in recurrence between the MIP and BE groups, and the operative approach did not predict recurrent disease in a multivariate analysis. However, the percentage decrease in IOPTH was protective against recurrence for the entire cohort of patients. A higher postoperative IOPTH also independently predicted disease recurrence. This provides evidence that the percentage decrease in IOPTH is one of the many pieces of data a surgeon can use to decide whether to terminate the operation or undertake a BE, whereas the postoperative PTH level can guide patient follow-up.

## COST-EFFECTIVENESS OF INTRAOPERATIVE PARATHYROID HORMONE MONITORING

The added value of IOPTH monitoring has been debated in the context of adequate preoperative localization.[61] It remains a contested issue because its ability to prevent failed parathyroid surgery due to unrecognized MGD must be balanced against assay-related costs. To address this issue, Morris and colleagues[62] performed a literature review identifying 17 studies involving 4280 patients, permitting estimation of base case costs and probabilities by using a decision tree and cost analysis model. The base case assumption was that in well-localized PHPT, IOPTH monitoring would increase the success rate of MIP from 96.3% to 98.8%. The cost of IOPTH varied with operating room time used. The investigators found that IOPTH reduced overall treatment costs only when total assay-related costs fell below $110 per case. Inaccurate localization and high reoperation cost both independently increased the value of IOPTH monitoring. However, the IOPTH strategy was cost saving when the rate of unrecognized MGD exceeded 6% or if the cost of reoperation exceeded $12,000 (compared with the initial MIP cost of $3733). Setting the positive predictive value of IOPTH at 100% and reducing the false-negative rate to 0% did not significantly alter their findings. The investigators concluded that factors influencing the added value of IOPTH are institution-specific. In their model, IOPTH increased the cure rate marginally while incurring approximately 4% additional cost.[62]

The extent of IOPTH sampling in the setting of preoperative single gland involvement has also been questioned.[63] Gupta and colleagues[63] found that in 79% of their patients, with a preoperative diagnosis of a solitary adenoma, the procedure may have been successfully terminated following a 5-minute IOPTH drop by more than 50% from baseline. In this group, histopathology confirmed the preoperative diagnosis, and no recurrences and no failed resections were reported. Using the 23 patients who had 5-minute IOPTH levels drop greater than 50% but not into the normal range, the investigators estimated a total savings of $18,100 if the procedures had been terminated after the initial 5-minute sample. The estimated costs included the cost of running a PTH sample at their institution and additional intraoperative time.

Using the previously mentioned at-excision IOPTH, the investigators conducted a retrospective analysis of their institutional patient database to determine the utility of an at-excision IOPTH at predicting completion of surgery after parathyroid gland excision for PHPT. Importantly, all patients had preoperative localization studies confirming single gland involvement and were candidates for focused surgery. When the at-excision IOPTH declined by greater than 50% but not into the normal range, the surgeon obtained a success rate of 97%. Implementing the stricter criterion of a decline in the at-excision IOPTH level greater than 50% and into the normal range (<65 pg/mL) achieved a success rate of 98% and a failure rate of 2%. There were no recurrences at 6 months of follow-up. Had the procedure been terminated when the at-excision IOPTH declined by more than 50% from baseline, the surgeon would have achieved acceptable success rates. Thereby, when preoperative localization studies are concordant for single gland disease, adequate cure rates can be achieved using an at-excision IOPTH value alone, thus resulting in an overall time, risk, and potential cost benefit.

## SUMMARY

More than 80% of patients with sporadic PHPT have a single hyperactive parathyroid gland. Advances in preoperative localizing studies and surgical adjuncts, such as IOPTH, have shifted the traditional bilateral operative approach to a focused surgery or MIP. Focused surgery guided by IOPTH monitoring allows confirmation of cure and absence of MGD without intraoperative visualization of all parathyroid glands. The utilization of IOPTH during focused surgery makes this procedure safer, less invasive, and highly successful. It is imperative that the surgeon has an understanding of hormone dynamics and carefully chooses the appropriate IOPTH protocol and interpretation criteria that will best predict operative success and prevent recurrence. Focused parathyroidectomy guided by IOPTH monitoring may improve the success rate and low morbidity associated with BE, and may result in higher long-term cure rates when used as the procedure of choice for sporadic PHPT.

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