ORIGINAL ARTICLE

An Optimal Algorithm for Intraoperative Parathyroid Hormone Monitoring

Melanie L. Richards, MD; Geoffrey B. Thompson, MD; David R. Farley, MD; Clive S. Grant, MD

Background: A minimally invasive approach to primary hyperparathyroidism is equivalent to bilateral exploration when intraoperative parathyroid hormone (IOPTH) monitoring is used. The optimal strategy for the monitoring has been debated.

Hypothesis: There exists an optimal strategy for IOPTH monitoring.

Design: Retrospective study.

Setting: Tertiary referral hospital.

Patients and Methods: A total of 1882 patients underwent parathyroidectomy for primary hyperparathyroidism with IOPTH monitoring. Successful exploration was defined as a 50% or more decline in IOPTH level from baseline and a normal or near-normal IOPTH level at 10 minutes postexcision. These results were compared with those of alternative strategies for IOPTH monitoring, including a 50% decline at 10 minutes, 50% decline at 5 minutes, and normal IOPTH levels at 10 minutes, using the preoperative parathyroid level as baseline.

Results: A curative operation was performed in 1830 patients (97.2%). The current strategy had a sensitivity of 96% and an accuracy of 95%. Multiglandular disease was present in 271 patients (14.5%); 134 of 1858 patients (7.2%) whose outcomes failed to reach curative criteria had confirmed multiglandular disease. Using only a 50% decline from baseline as the curative criterion would result in a failed operation in 22.4% of patients with multiglandular disease. A 50% decline at 10 minutes was 96% sensitive and 94% accurate. A 5-minute value was 79% sensitive and 80% accurate. With use of the 5-minute value, unnecessary bilateral exploration would have been performed in 272 of 1460 patients (18.6%) compared with 62 of 1750 patients (3.5%) when using a 10-minute value. A normal 10-minute value is 91% sensitive and 90% accurate.

Conclusions: A 10-minute postexcision IOPTH level that decreased 50% from baseline and is normal or near normal is highly successful. Relying on a 50% decrease alone increases the rate of operative failure in patients with multiglandular disease.

Arch Surg. 2011;146(3):280-285

INTRAOPERATIVE PARATHYROID hormone (IOPTH) assay has allowed a directed parathyroid exploration with cure rates (>97%) comparable with those of bilateral exploration in patients with primary hyperparathyroidism (HPT).[1-4] This success has led 90% of surgeons to practice-directed parathyroidectomy and 95% of high-volume surgeons to use IOPTH monitoring.[5] The debate between bilateral exploration and a focused approach has transitioned to development of an optimal strategy for IOPTH testing and interpretation. This strategy should involve a minimal number of blood draws and a reduction in operative time and be highly predictive of cure. To reduce complications, the strategy should minimize unnecessary bilateral exploration and decrease the likelihood of resecting parathyroid glands that are not hypersecreting. The success of this strategy will depend on its usefulness for detecting multiglandular disease (MGD).

The earliest method for monitoring IOPTH was described by Irvin et al in 1991,[6] and the recommendation for a 50% decline from preexcision IOPTH level was established in 1993.[7] This "Miami criterion" was refined to be a 50% decline from the highest preincision or preexcision IOPTH level obtained 10 minutes after excision of the hypersecreting parathyroid gland.[8] It has become one of the most widely used methods for defining a cure following a directed parathyroidectomy. However, the implementation into clinical practice raised questions about the accuracy of a 50% drop alone to define cure. Patients were found to have a 50% decline despite the presence of additional enlarged or hypercellular parathyroid glands.[9-11] Proponents of the 50% decline alone believed that the histologically abnormal parathyroid glands were strictly a

Author Affiliations: Department of Surgery, Mayo Clinic, Rochester, Minnesota.

morphologic finding and that the morphology does not necessarily predict function.

In our practice, we also had observed the presence of MGD despite a 50% drop in the IOPTH level. Excision of additional hypercellular glands coincided with biochemically significant drops in the IOPTH level to normal or near normal. This suggested that these morphologically enlarged glands were producing an excess of IOPTH and that it was necessary to develop more stringent criteria for IOPTH monitoring. Our practice algorithm was modified to include a normal or near-normal IOPTH level at the completion of the operation. The ideal timing for determination of the postexcision IOPTH levels was not known. The purpose of this study was to compare IOPTH monitoring techniques to define an optimal algorithm for cure.

METHODS

A prospective database of 2925 patients who underwent an operation for primary HPT from June 1998 to November 2008 at the Mayo Clinic, Rochester, Minnesota, was retrospectively reviewed to identify patients who had IOPTH monitoring during a primary operation. The patients' medical records were reviewed for demographics, parathyroid hormone (PTH) levels, serum calcium levels, imaging results, operative findings, pathologic findings, and outcomes.

The preferred Mayo protocol for IOPTH monitoring consisted of determination of IOPTH levels at baseline, 5 minutes postexcision, and 10 minutes postexcision of the suspicious parathyroid gland or glands. Blood samples were obtained from the jugular vein, radial artery, or a peripheral vein. The baseline jugular vein samples were obtained either before dissection or after mobilization of the abnormal gland. Peripheral vein samples were obtained preincision. The timing of each postexcision IOPTH test was confirmed to be at 5, 10, 15, or more than 20 minutes. Parathyroid hormone values recorded in picomoles per liter were converted to picograms per milliliter using a conversion factor of 9.03. Intraoperative PTH levels were measured using a standard immunoradiometric assay with either the Immulite (Diagnostics Product Corporation, Los Angeles, California) or the Roche Cobas e411 (Roche Diagnostics Corporation, Indianapolis, Indiana) analyzer.

Successful exploration was defined as a 50% or more decline from baseline to a normal or near-normal IOPTH level at 10 minutes. *Normal* IOPTH was considered a level within the reference range. Due to variability in IOPTH levels, *near normal* was defined by the surgeon. If a surgeon considered the operation curative with a near-normal IOPTH level, the data were assessed at that end point. A patient who met curative criteria at 5 minutes was assumed to meet those criteria at 10 minutes.

Patients with imaging results that were highly suspicious for bilateral parathyroid disease underwent bilateral exploration. Those with equivocal imaging results on the contralateral side underwent bilateral exploration when the IOPTH level did not meet curative criteria after a focused exploration. Patients who met the curative criteria after a focused exploration did not undergo bilateral exploration.

A *true-positive* test result was defined as the IOPTH level confirming cure and the patient was cured (no hypercalcemia at 6 months or longer follow-up confirmed with biochemical results or personal communication of biochemical results via survey or telephone conversation with the patient). A *true-negative* test result was defined as the IOPTH level confirming the presence of additional hypercellular parathyroid tissue and additional hypercellular tissue was confirmed either intraoperatively or on biochemical testing. A *false-positive* test result was defined as the IOPTH level confirming cure but the patient was not cured. A *false-negative* (FN) test result was defined as the IOPTH level suggesting the presence of additional hypercellular parathyroid tissue but no additional hypercellular tissue was confirmed either intraoperatively or on biochemical testing. Patients in whom the IOPTH levels did not meet curative criteria and the surgeon did not proceed with a bilateral exploration were classified according to the curative criteria. For example, the surgeon removes a solitary adenoma, the IOPTH level decreases by 40%, the surgeon does not proceed with a bilateral exploration, and the patient is cured. This patient's IOPTH level would be classified as a FN. Patients who were retrospectively determined to have an uncertain diagnosis of primary HPT or an uncertain cure were not classified. Patients who were determined to have falsely low baseline PTH levels secondary to possible devascularization or hemolysis were excluded from IOPTH analysis.

The IOPTH test results were used to compare alternative strategies for IOPTH monitoring by determining the sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy. The strategies were selected based on potential economic advantages from less testing or shorter duration of testing. They were also selected based on the current practice and controversies that exist with IOPTH monitoring. Specifically, the results using a 50% decline of the IOPTH level from baseline were compared with those found using a 10-minute normal or near-normal IOPTH level, with each of the following strategies for defining cure:

1. 50% decline from the baseline IOPTH level at 10 minutes postexcision,
2. 50% decline from the baseline IOPTH level at 5 minutes postexcision,
3. single 10-minute postexcision IOPTH level that is normal, and
4. use of the preoperative PTH level as the baseline value, with a 50% decline in IOPTH level at 10 minutes postexcision.

Statistical analysis was performed with SPSS version 14.0 (SPSS Inc, Chicago, Illinois). $P < .05$ was considered significant. The study was approved by the Mayo Clinic Institutional Review Board.

RESULTS

There were 1882 patients (age, 10-97 years; mean, 61 years) who underwent a primary parathyroidectomy for primary HPT using IOPTH. Many (74.7%) were women. Data on follow-up for 6 months or longer were available on 98.9% of the patients. The mean (SD) preoperative serum calcium level was 11.0 (0.7) mg/dL (reference range, 8.9-10.1 mg/dL) and the mean (SD) preoperative PTH level was 161 (302) pg/mL (reference range, 15-65 pg/mL). (To convert to millimoles per liter, multiply by 0.25.) There were an additional 4 patients who had an uncertain diagnosis and 567 who underwent a reoperation who were excluded.

IMAGING

Parathyroid subtraction scintigraphy was performed in 1731 patients (92.0%) and neck ultrasonography was obtained in 581 patients (30.9%). Fourteen patients (0.7%) underwent parathyroidectomy without any

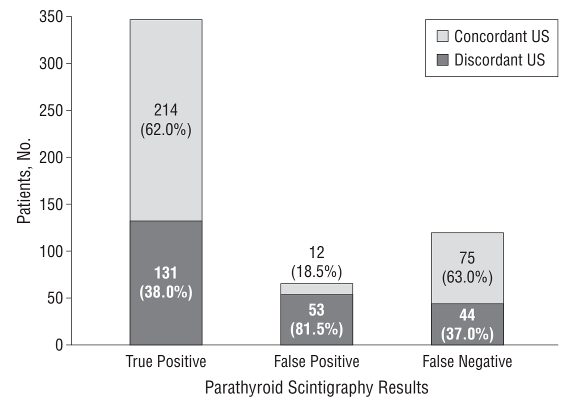

Figure. Comparison of ultrasound (US) and parathyroid scintigraphy results in 529 patients who underwent both imaging studies.

imaging. The parathyroid subtraction imaging had a sensitivity of 85% and an accuracy of 78%. Neck ultrasonography had a sensitivity of 58% and an accuracy of 55%. There were 529 patients who underwent both parathyroid subtraction scintigraphy and ultrasonography (**Figure**). Negative or discordant imaging results occurred in 57.3% of the patients (303 of 529) who underwent both studies. Imaging results that were concordant for localization on both studies were correct in 94.7% of the patients (214 of 226).

USE OF IOPTH

Intraoperative PTH level was used to define cure in 1882 patients. Baseline IOPTH levels were obtained in 1834 patients (97.4%). The mean (SD) baseline IOPTH level was 278 (422) pg/mL. Five- and 10-minute IOPTH levels were obtained in 1484 (78.8%) and 1809 (96.1%) patients, respectively; the mean (SD) levels were 64 (91) pg/mL and 39 (88) pg/mL, respectively. Fifteen-minute samples were obtained in 20 patients. Seven of these patients had FN 10-minute values and a 15-minute value that met curative criteria; the surgeon did not proceed with bilateral exploration. Sixteen patients had an IOPTH level at baseline that was deemed to be falsely low relative to the preoperative PTH level. These baseline PTH values were less than 50% of the preoperative PTH level and were normal, ranging from 14 to 51 pg/mL (mean [SD], 36 [10] pg/mL). In these cases, the surgeon used the preoperative PTH level as the baseline.

PATHOLOGY

In 1874 patients, a single adenoma was excised in 1602 patients (85.5%) and MGD was found in 271 (14.5%). Ten patients had negative explorations. The number of parathyroid glands excised in patients with MGD included 2 in 130 patients, 2½ in 8 patients, 3 in 104 patients, and 3½ in 4 patients. Multiple endocrine neoplasia 1 was confirmed in 26 of 271 patients (9.6%) with MGD; 2 patients (0.7%) were diagnosed with multiple endocrine neoplasia 2. The mean (SD) weight of the excised parathyroid glands was 751 (1073) mg for the first gland, 240 (311) mg for the second, and 109 (128) mg for the third. Overall, the mean (SD) weight of 3963 excised glands was 663 (1011) mg.

IOPTH MONITORING STRATEGIES

The Mayo criteria had a sensitivity of 96%, PPV of 99%, and an accuracy of 95% (**Table 1**). A 50% decline from baseline at 10 minutes had a sensitivity of 96%, PPV of 97%, and an accuracy of 94%.There were 134 of 1858 patients (7.2%) with MGD who failed to reach the Mayo criteria for cure. Using only a 10-minute postexcision 50% decline from baseline would have resulted in a failed operation in 30 of 134 patients (22.4%) with MGD ($P < .05$). There were 121 of 1654 patients (7.3%) who met the Mayo criteria for cure who had a 50% decline to a near-normal PTH level at 10 minutes (mean [SD], 77 [33] pg/mL), and 86.7% of these patients had more than a 70% decline.

Theoretically, 66 of 1858 patients (3.6%) would have undergone unnecessary bilateral explorations because of a FN IOPTH using the Mayo criteria (**Table 2**). Failing to decline to 50% from baseline at 10 minutes, used as the only criteria, would have led to an equivalent number of unnecessary bilateral explorations in 62 of 1750 patients (3.5%). In practice, 20 of 66 patients (30.3%) in the Mayo FN group did not undergo bilateral exploration because the surgeon determined that they were cured, despite not reaching a 50% decline in IOPTH level. The baseline IOPTH level in this group was less than 70 pg/mL in 14 patients (70.0%). One patient had a 10-minute IOPTH level that was erroneously elevated (33% above baseline); a second test showed a curative decline. The remaining 19 patients had a mean (SD) 10-minute decline of 35% (5%) from baseline. Based on the biochemical findings, test results on these patients were included in the calculations as FN.

Use of baseline and 5-minute values would have a sensitivity of 79%, a PPV of 98%, and an accuracy of 80%. Unnecessary bilateral exploration would have been performed in 272 of 1460 patients (18.6%). A single 10-minute IOPTH level that is normal has a sensitivity of 91%, a PPV of 98%, and an accuracy of 90%; this would result in 151 of 1800 patients (8.4%) undergoing unnecessary bilateral exploration.

Using the preoperative PTH level as a baseline results in a lower mean PTH value compared with the IOPTH level as baseline (161 vs 278 pg/mL; $P < .001$). This method has a sensitivity of 82%, a PPV of 98%, and an accuracy of 82%. Use of the preoperative PTH level as the baseline would result in 422 of 1773 patients (23.8%) having less than a 50% decline in the 10-minute postexcision IOPTH level. This compares with 182 of 1769 patients (10.3%) with less than a 50% decline from the baseline PTH when it is obtained intraoperatively, resulting in an increased likelihood of unnecessary bilateral exploration.

OUTCOMES

A curative operation was performed in 1830 patients (97.2%). Patients with a solitary adenoma had a successful operation 99.6% of the time compared with 84.9% of

Table 1. Comparison of Mayo Protocol With Other Proposed Strategies for Using IOPTH Testing to Define Cure in Primary Hyperparathyroidism

	%				
Strategy	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Mayo protocol (N=1858)	96	86	99	68	95
50% Decline from IOPTH baseline at 5 min (n=1460)	79	87	98	31	80
50% Decline from IOPTH baseline at 10 min (n=1750)	96	68	97	63	94
50% Decline from preoperative PTH at 10 min (n=1751)	82	86	98	31	82
Normal IOPTH at 10 min (n=1800)	91	82	98	46	90

Abbreviations: IOPTH, intraoperative parathyroid hormone; PTH, parathyroid hormone.

Table 2. Results of IOPTH Monitoring Using Different Strategies for Defining Cure

	No. (%)			
Strategy	True Positive	True Negative	False Positive	False Negative
Mayo protocol (N=1858)	1631 (87.8)	139 (7.5)	22 (1.2)	66 (3.6)
50% Decline from IOPTH baseline at 5 min (n=1460)	1047 (71.7)	123 (8.4)	18 (1.2)	272 (18.6)
50% Decline from IOPTH baseline at 10 min (n=1750)	1533 (87.6)	105 (6.0)	50 (2.9)	62 (3.5)
50% Decline from preoperative PTH at 10 min (n=1751)	1308 (74.7)	130 (7.4)	22 (1.3)	291 (16.6)
Normal IOPTH at 10 min (n=1800)	1492 (82.9)	129 (7.2)	28 (1.6)	151 (8.4)

Abbreviations: See Table 1.

the time in patients with MGD (**Table 3**). There were 5 operative failures; it was not known whether the patients had a solitary adenoma or MGD. Of the 41 patients with MGD who did not have a curative operation, 22 (53.7%) had true-negative results and 18 (43.9%) had false-positive results; complete IOPTH test results were not available on 1 patient (2.4%). In 30 operative failures secondary to MGD, the patients had a single parathyroid gland removed at the primary operation. Five patients had 2 glands removed and 6 patients had 3 glands removed. There was no relationship between operative success and age, sex, serum calcium level, or preoperative PTH level ($P > .05$). Three patients experienced recurrent laryngeal nerve injuries. The length of hospitalization was less than 24 hours in 91.0% of the patients (n=1713). Three patients developed recurrent primary HPT, defined as hypercalcemia and hyperparathyroidism occurring more than 6 months postoperatively.

COMMENT

To improve outcomes in primary HPT, investigators have been challenged to define the optimal method for monitoring IOPTH. This study has defined a practice for IOPTH monitoring that had limited imaging, reduced the number of IOPTH tests, minimized bilateral explorations, and cured 97.2% of the patients.

The Mayo protocol had the highest sensitivity (96%), PPV (99%), and accuracy (95%) compared with the other strategies evaluated here. While use of only a 50% drop at 10 minutes was competitive in performance, there was 1 difference: the IOPTH monitoring failure rate in patients with MGD would increase by 22%. The clinical effect of this finding is dependent on the incidence of MGD. Our 14.5% incidence of MGD is comparable to rates reported by most other groups.[1,11-13] The Miami group[2] reported a 4% incidence of MGD.

The Miami group uses the highest preincision or preexcision IOPTH level as the baseline to potentially reduce unnecessary bilateral exploration secondary to PTH level spikes related to manipulation. It can be argued that the highest baseline IOPTH level is not a true reflection of the patient's PTH level. A 50% decline from this falsely elevated PTH level can be postulated to result in increased failure; however, the success is 97%.[2] This success may be attributed to the low rate of MGD in that study. Irvin et al[8] also noted that the Miami criterion had a decreased performance in MGD, with sensitivity, specificity, and accuracy of 90%, 94%, and 92%, respectively. Intraoperative PTH monitoring with the Mayo protocol has a sensitivity, PPV value, and accuracy of 95%, 100%, and 97%, respectively, in MGD.[14]

The variation in rates of MGD may be related to regional distributions of familial disease, vitamin D deficiency, patient selection, or referral patterns. There has also been criticism that centers with higher rates of MGD assess only parathyroid morphologic characteristics and not function. This controversy stems from the inability of surgeons to reach a consensus on the definition of MGD—whether it should be based on function, histopathologic features, or size. Our 14.5% incidence of MGD was based on function, with 7.2% of the patients showing multigland uptake on parathyroid scintigraphy and 7.2% confirmed to have MGD on IOPTH measurement alone. Thirty patients who did not have a curative operation had a single hypercellular gland removed at the primary operation and were classified as having MGD. It could be postulated that there was an over-call on his-

Table 3. Patient Characteristics Associated With a Curative Operation

Characteristic	Cure (n=1830)	Persistent HPT (n=53)	*P* Value
Age, mean (SD), y	61.0 (14.0)	59.6 (13.0)	.37
Sex, No. (%)[a]			.26
Female	1371 (74.9)	36 (67.9)	
Male	456 (24.9)	17 (32.1)	
Serum calcium, mean (SD), mg/dL	11.0 (0.7)	11.1 (0.1)	.24
Serum PTH, mean (SD), pg/mL	160 (296)	225 (451)	.12
Solitary adenoma, No. (%)[b]	1595 (99.6)	7 (0.4)	
MGD, No. (%)[c]	230 (84.9)	41 (15.1)	<.001

Abbreviations: HPT, primary hyperparathyroidism; MGD, multiglandular disease; PTH, parathyroid hormone.

SI conversion factor: To convert calcium to millimoles per liter, multiply by 0.25.

[a]The sex was unavailable in 3 patients.

[b]Single adenoma excised in 1602 patients.

[c]MGD identified in 271 patients.

topathologic test results or that patients had normally functioning, but morphologically abnormal, glands removed. If the disease in these patients was reclassified as affecting 1 gland, the cure rate for MGD would be 90.9% (219 of 241 patients) and the incidence of MGD would be 12.8%.

The 50% decrease from the baseline IOPTH level to normal or near normal at 5 minutes was highly accurate (98%) but had the lowest sensitivity (78%). Its usefulness will be determined by the process of measuring IOPTH (Can we get a result sooner?) and the cost of a 10-minute test. The sensitivity is not high enough for this strategy to be the sole method for defining cure because nearly 30% of the patients would require a repeat PTH test, or a bilateral exploration with no negative findings would be performed in approximately 20% of the patients.

A normal IOPTH level at 10 minutes and the use of the preoperative PTH level as the baseline with a 50% decline were not optimal methods. Their use should be limited to patients in whom a baseline IOPTH level has not been determined; this usually is a result of hemolysis or the inability to obtain access prior to gland devascularization. In these cases, the surgeon would have the best outcomes using a normal PTH level at 10 minutes as opposed to a 50% decline from the preoperative PTH level.

There have been several studies[15-18] comparing strategies for IOPTH testing. These studies often included patients at low risk for MGD, making it difficult to assess IOPTH detection of MGD. Barczynski et al[18] studied 260 patients with presumed solitary adenomas based on concordant imaging. The Miami criterion had the highest accuracy (97%) compared with the Halle (PTH level low normal at 15 minutes), Rome (>50% decline to normal at 20 minutes and/or <7.5 ng/L lower than the 10-minute value), and Vienna (≥50% decline at 10 minutes) criteria. Only 3.5% of the patients had MGD. The Rome criterion, which was most similar to ours, was best for identifying MGD. However, it would increase unnecessary bilateral exploration (FN rates) by 11%, and a 0.5% improvement in success was deemed not worth the cost and potential morbidity.

We found FN rates of only 4% for both the Mayo strategy and the 50% decline at 10 minutes alone. O'Neal et al[19] used a decline of more than 50% from baseline PTH level to a normal range and had FN results in 8% of the patients. By obtaining a second blood sample for determination of the IOPTH level if the disease matched the imaging, fewer than1% of the patients had an unnecessary bilateral exploration. This underscores the role of clinical judgment in the interpretation of IOPTH. In addition, patients who have increased manipulation of the excised gland are at risk for FN values and may benefit from a 15- or 20-minute determination of the IOPTH level. One limitation of our strategy is that there was clinical judgment in defining the 7.3% of patients with an acceptable near-normal value, which contributed to the lower FN rate. The finding that 86.7% of these patients had declines in the 10-minute IOPTH level of more than 70% could assist in quantifying the surgeon judgment.

It has been debated as to whether IOPTH monitoring is even necessary. A review by Mihai et al[20] led to a recommendation that patients with concordant imaging results could undergo parathyroidectomy without IOPTH determination and have 95% success. However, this recommendation was founded on 2 studies[13,14] with follow-up of 3 to 6 months. In addition, only 42.7% of our patients undergoing both ultrasonography and sestamibi scintigraphy had concordant results for localizing abnormal parathyroid glands. Other investigators[21] have shown that IOPTH monitoring improves success from 95% to 99% in patients who have imaging studies that localize abnormal parathyroid glands.

We applied IOPTH monitoring to a broad cohort of patients with primary HPT. The inclusion of patients with suspected MGD and those without definitive imaging results allowed us to test the performance of IOPTH monitoring, as its primary purpose is to identify MGD. We found that IOPTH monitoring is complementary to imaging and a critical adjunct for the detection of MGD. A baseline IOPTH level that has decreased 50% to normal or near normal at 10 minutes is highly predictive of cure and reduces the risks associated with unnecessary bilateral exploration. The success of this strategy allows us to expand the use of IOPTH monitoring to patients with equivocal imaging and to those at high risk of MGD.

Accepted for Publication: January 27, 2010.

Correspondence: Melanie L. Richards, MD, Department of Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (richards.melanie@mayo.edu).

Author Contributions: *Study concept and design:* Richards and Thompson. *Acquisition of data:* Richards and Grant. *Analysis and interpretation of data:* Richards, Farley, and Grant. *Drafting of the manuscript:* Richards. *Critical revision of the manuscript for important intellectual content:* Richards, Thompson, Farley, and Grant. *Statistical analysis:* Richards. *Administrative, technical, and material support:* Grant.

Previous Presentation: This study was presented at the Western Surgical Association 2009 Annual Meeting; November 9, 2009; San Antonio, Texas.

Financial Disclosure: None reported.

REFERENCES

1. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. *Ann Surg*. 2002;235(5):665-672..
2. Carneiro DM, Solorzano CC, Irvin GL III. Recurrent disease after limited parathyroidectomy for sporadic primary hyperparathyroidism. *J Am Coll Surg*. 2004; 199(6):849-855.
3. Genc H, Morita E, Perrier ND, et al. Differing histologic findings after bilateral and focused parathyroidectomy. *J Am Coll Surg*. 2003;196(4):535-540.
4. Grant CS, Thompson G, Farley D, van Heerden J. Primary hyperparathyroidism surgical management since the introduction of minimally invasive parathyroidectomy: Mayo Clinic experience. *Arch Surg*. 2005;140(5):472-479.
5. Greene AB, Butler RS, McIntyre S, et al. National trends in parathyroid surgery from 1998 to 2008: a decade of change. *J Am Coll Surg*. 2009;209(3):332-343.
6. Irvin GL III, Dembrow VD, Prudhomme DL. Operative monitoring of parathyroid gland hyperfunction. *Am J Surg*. 1991;162(4):299-302.
7. Irvin GL III, Dembrow VD, Prudhomme DL. Clinical usefulness of an intraoperative "quick parathyroid hormone" assay. *Surgery*. 1993;114(6):1019-1023.
8. Irvin GL III, Solorzano CC, Carneiro DM. Quick intraoperative parathyroid hormone assay: surgical adjunct to allow limited parathyroidectomy, improve success rate, and predict outcome. *World J Surg*. 2004;28(12):1287-1292.
9. Gauger PG, Agarwal G, England BG, et al. Intraoperative parathyroid hormone monitoring fails to detect double parathyroid adenomas: a 2-institution experience. *Surgery*. 2001;130(6):1005-1010.
10. Haciyanli M, Lal G, Morita E, Duh QY, Kebebew E, Clark OH. Accuracy of preoperative localization studies and intraoperative parathyroid hormone assay in patients with primary hyperparathyroidism and double adenoma. *J Am Coll Surg*. 2003;197(5):739-746.
11. Siperstein A, Berber E, Barbosa GF, et al. Predicting the success of limited exploration for primary hyperparathyroidism using ultrasound, sestamibi, and intraoperative parathyroid hormone: analysis of 1158 cases. *Ann Surg*. 2008; 248(3):420-428.
12. Tezelman S, Shen W, Shaver JK, et al. Double parathyroid adenomas: clinical and biochemical characteristics before and after parathyroidectomy. *Ann Surg*. 1993;218(3):300-309.
13. Chen H, Mack E, Starling JR. A comprehensive evaluation of perioperative adjuncts during minimally invasive parathyroidectomy: which is most reliable? *Ann Surg*. 2005;242(3):375-383.
14. Richards ML, Grant CS. Current applications of the intraoperative parathyroid hormone assay in parathyroid surgery. *Am Surg*. 2007;73(4):311-317.
15. Chiu B, Sturgeon C, Angelos P. Which intraoperative parathyroid hormone assay criterion best predicts operative success?: a study of 352 consecutive patients. *Arch Surg*. 2006;141(5):483-488.
16. Carneiro DM, Solorzano CC, Nader MC, Ramirez M, Irvin GL III. Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: which criterion is the most accurate? *Surgery*. 2003;134(6):973-981.
17. Lupoli GA, Fonderico F, Panico A, et al. Stricter criteria increase the validity of a quick intraoperative parathyroid hormone assay in primary hyperparathyroidism. *Med Sci Monit*. 2009;15(3):CR111-CR116.
18. Barczynski M, Konturek A, Hubalewska-Dydejczyk A, Cichon S, Nowak W. Evaluation of Halle, Miami, Rome, and Vienna intraoperative iPTH assay criteria in guiding minimally invasive parathyroidectomy. *Langenbecks Arch Surg*. 2009;394 (5):843-849.
19. O'Neal PB, Poylin V, Mowschenson P, et al. When initial postexcision PTH level does not fall appropriately during parathyroidectomy: what to do next? *World J Surg*. 2009;33(8):1665-1673.
20. Mihai R, Simon D, Hellman P. Imaging for primary hyperparathyroidism—an evidence-based analysis. *Langenbecks Arch Surg*. 2009;394(5):765-784.
21. Riss P, Scheuba C, Asari R, Bieglmayer C, Niederle B. Is minimally invasive parathyroidectomy without QPTH monitoring justified? *Langenbecks Arch Surg*. 2009; 394(5):875-880.