PAPER

Operative Failure in the Era of Focused Parathyroidectomy

A Contemporary Series of 845 Patients

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Hypothesis: Focused parathyroidectomy guided by intraoperative parathyroid hormone monitoring (IPM) may lead to higher failure rates because of missed multiglandular disease.

Design: Retrospective review of prospectively collected data.

Setting: Tertiary referral center.

Patients: From September 8, 1993, through January 30, 2009, a total of 845 consecutive patients with sporadic primary hyperparathyroidism underwent focused parathyroidectomy guided by IPM at a single institution.

Main Outcome Measures: Parathyroid hormone dynamics and perioperative data were analyzed for factors affecting outcome. *Operative failure* was defined as hypercalcemia with elevated parathyroid hormone levels within 6 months after parathyroidectomy. Detailed intraoperative data from the failed operations were also reviewed.

Results: Of 723 patients followed up for at least 6 months, 702 (97.1%) had successful parathyroidectomy, and 21 (2.9%) had failed parathyroidectomy. The major cause of operative failure was the surgeon's inability to find the abnormal parathyroid gland (16 of 21 patients [76.2%]). In the remaining patients, IPM results were false-positive in 5 of 21 patients (23.8%) or 0.7% overall. Among the cohort, IPM correctly identified missed multiglandular disease in 33 of 38 patients (86.8%). Patients having operative failure were more likely to have a history of thyroidectomy or parathyroidectomy and were less likely to have correct findings on technetium Tc 99m sestamibi or ultrasonographic localizing studies compared with patients having operative success.

Conclusion: Inability of the surgeon to find the abnormal parathyroid gland—not missed multiglandular disease—is the main cause of operative failure in focused parathyroidectomy guided by IPM.

Arch Surg. 2010;145(7):628-633

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SINCE ITS INTRODUCTION MORE than 15 years ago, focused parathyroidectomy guided by intraoperative parathyroid hormone monitoring (IPM) has become an attractive alternative to bilateral neck exploration (BNE) for the surgical treatment of patients with sporadic primary hyperparathyroidism (SPHPT).[1-6] Preoperative parathyroid localization and IPM are essential components of focused parathyroidectomy that allow for the excision of all abnormal parathyroid glands without actual examination of the other normally secreting glands. Intraoperative parathyroid hormone monitoring helps guide the extent of parathyroidectomy based on real-time parathyroid hormone dynamics and gland hypersecretion, with many specialized centers using this adjunct in the surgical treatment of SPHPT.

The prevention of operative failure caused by missed multiglandular disease (MGD) was the original reason for developing a fast-acting laboratory test for measuring parathyroid hormone levels in the operating room. Intraoperative parathyroid hormone monitoring is a quantitative test for measuring parathyroid hormone levels during surgery that is used to confirm when all hypersecreting parathyroid tissue has been removed, predicting a return to postoperative eucalcemia. An insufficient parathyroid hormone level decrease warrants successive intraoperative parathyroid hormone (IOPTH) testing and further surgical exploration of the neck until all hyperfunctioning parathyroid glands are excised. With the predominance of single-gland disease in 85% to 96% of patients with SPHPT, focused parathyroidectomy guided by IPM allows for shortened operative time and minimal neck dissection, with success rates exceeding 95%, equivalent to those of conventional BNE.[1-5,7-9]

Since its inception, focused parathyroidectomy guided by IPM remains controversial, with some surgeons advocating routine BNE in all patients with identification of all parathyroid glands and excision of all enlarged glands. Critics of the focused approach to parathyroidectomy argue that IPM is inaccurate in determining complete excision among patients with MGD.[10-14]

Improved success rates with focused parathyroidectomy guided by IPM have been reported, but these outcomes have not been universal, with some investigations showing no substantial decrease in operative failure compared with conventional BNE.[10-15] Although focused parathyroidectomy guided by IPM has a high success rate similar to that achieved by BNE, this surgical approach is imperfect, and operative failure can occur. This study describes the causes of operative failure in the era of focused parathyroidectomy guided by IPM at a single medical center.

METHODS

A series of 845 consecutive patients with SPHPT underwent focused parathyroidectomy guided by IPM at the University of Miami Health System from September 8, 1993, through January 30, 2009. All patients with a secure biochemical diagnosis of SPHPT (ie, elevated serum calcium and parathyroid hormone levels) underwent technetium Tc 99m sestamibi (hereafter sestamibi) imaging and/or surgeon-performed ultrasonography to localize parathyroid glands before surgery. Indications for parathyroidectomy in asymptomatic patients followed the guidelines defined at the 1991 National Institutes of Health Consensus Development Conference.[16] Focused parathyroidectomy guided by IPM was the initial procedure in all patients. The intraoperative criterion used for predicting successful parathyroidectomy was a decrease of intact parathyroid hormone levels exceeding 50% from the highest preincision or preexcision hormone level in a peripheral blood sample obtained 10 minutes after removal of all abnormal parathyroid tissue. If this criterion was met, surgical exploration of the neck was completed and the incision closed. If the 10-minute sample did not meet the criterion, a delayed sample at 20 minutes was usually measured at the discretion of the surgeon. Further surgical exploration of the neck was continued until all hypersecreting glands were removed (confirmed by another >50% decrease in hormone level from the highest preexcision level).[17] Secretory activity of parathyroid glands was determined exclusively by parathyroid hormone levels measured during surgery and not by gland size or histopathologic findings. When sestamibi and/or ultrasonographic images were negative, intraoperative differential venous sampling was performed in an attempt to lateralize the hypersecreting gland to one side of the neck. If this maneuver proved indeterminate, one side was chosen to be explored first.

The accuracy of IPM in predicting postoperative calcium levels has been previously described.[3,9] Relevant to this study, IOPTH levels were considered a true-negative result when the postexcision parathyroid hormone level did not decrease more than 50%, and the patient remained hypercalcemic or further excision of additional abnormal glands was necessary until a significant hormone level decrease was accomplished. Intraoperative parathyroid hormone levels were considered a false-positive result when the postexcision parathyroid hormone levels decreased more than 50% but the patient remained hypercalcemic after surgery.

Table 1. Demographic, Biochemical, and Surgical History in 723 Patients With Primary Hyperparathyroidism

Variable	Operative Success (n=702)	Operative Failure (n=21)	*P* Value
Age, mean (SD), y	59 (13)	65 (19)	.76
Sex, No. (%)			
Male	167 (23.8)	5 (23.8)	>.99
Female	535 (76.2)	16 (76.2)	
Previous surgery, No. (%)			
Parathyroidectomy	49 (7.0)	4 (19.0)	.04
Thyroidectomy	24 (3.4)	3 (14.3)	.03
Preoperative level, mean (SD)			
Calcium, mg/dL	11.9 (1.2)	11.8 (1)	.71
Parathyroid hormone, pg/mL	194 (193)	169 (98)	.56
Creatinine, mg/dL	0.98 (0.38)	1.10 (0.39)	.34

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; parathyroid hormone to nanograms per liter, multiply by 1.0; and creatinine to micromoles per liter, multiply by 88.4.

Operative failure was defined as hypercalcemia with elevated parathyroid hormone levels within 6 months after parathyroidectomy. *Operative success* was defined as continuous eucalcemia for 6 months or longer after parathyroidectomy. *Multiglandular disease* was defined by the known involvement of more than 1 gland at the time of the initial operation as determined by persistently elevated IOPTH levels, despite removal of 1 hypersecreting gland or when removal of a single parathyroid gland resulted in operative failure. Serum calcium and parathyroid hormone levels were measured at 2 months, 6 months, and yearly to determine operative outcome. Patients with multiple endocrine neoplasia, parathyroid cancer, or secondary, tertiary, or familial hyperparathyroidism were excluded from the study.

Biochemical and perioperative data of the study patients were prospectively collected in an institutional review board–approved database and were analyzed for factors affecting outcome. Detailed intraoperative data from the failed operations were also collected and reviewed. Statistical analyses were performed using commercially available software (SPSS, version 17; SPSS Inc, Chicago, Illinois). $P \leq .05$ was considered statistically significant.

RESULTS

Of 845 consecutive patients with SPHPT who underwent focused parathyroidectomy guided by IPM, 723 were followed up for at least 6 months. Although the remaining 122 patients were followed up within 6 months of operation and were eucalcemic, they were followed up only within 6 months of operation and were, therefore, excluded from the study. Of the group followed up for at least 6 months, 702 patients (97.1%) had successful parathyroidectomy, and 21 patients (2.9%) had failed parathyroidectomy. Patients having operative failure were more likely to have a history of thyroidectomy or parathyroidectomy and were less likely to have correct localization on sestamibi or ultrasonographic imaging compared with patients who had operative success (**Table 1**). At the time of surgery, patients who were operative failures were more likely to have MGD and undergo BNE compared with patients who had operative successes (**Table 2**). In the entire cohort, 38 patients had MGD, among whom IPM correctly identified MGD in 33 patients (86.8%).

Table 2. Perioperative Findings and Outcomes in 723 Patients With Primary Hyperparathyroidism

Variable	Operative Success (n=702)	Operative Failure (n=21)	*P* Value
True-positive result, No./total No. (%)			
Technetium Tc 99m sestamibi	533/655 (81.4)	2/18 (11.1)	<.001
Ultrasonography	294/384 (76.6)	1/11 (9.1)	<.001
Gland location, No. (%)			
Mediastinum	19 (2.7)	1 (4.8)	.45
Thymus	19 (2.7)	1 (4.8)	.45
Gland largest linear size, mean (SD), cm	1.80 (0.99)	1.60 (0.73)	.60
Operative time, mean (SD), min	62 (46)	159 (73)	<.001
Bilateral neck exploration, No. (%)	93 (13.2)	16 (76.2)	<.001
Missed multiglandular disease, No. (%)	30 (4.3)	8 (38.1)	<.001
Follow-up period, mean (SD), mo	45 (40)	37 (33)	.35
Postoperative level, mean (SD)			
Calcium, mg/dL	9.5 (0.6)	10.6 (0.9)	<.001
Parathyroid hormone, pg/mL	51 (33)	126 (105)	<.001
Creatinine, mg/dL	1.03 (0.62)	1.14 (0.59)	.90

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; parathyroid hormone to nanograms per liter, multiply by 1.0; and creatinine to micromoles per liter, multiply by 88.4.

Table 3. Causes of Operative Failure and Predictions by Intraoperative Parathyroid Hormone Monitoring (IPM) in 21 Patients Undergoing Parathyroidectomy

Cause of Operative Failure	IPM Prediction	No. (%) of Patients
Inability to find the abnormal parathyroid gland	Correct (true-negative result)	**16** (76.2)
Gland found in subsequent localization studies or successful reoperation		7
Unknown gland location to date		6
Incomplete exploration because of patient comorbidity		3
Missed multiglandular disease	Incorrect (false-positive result)	**5** (23.8)

The major cause of operative failure was the surgeon's inability to find the abnormal parathyroid glands (16 of 21 patients [76.2%]) (**Table 3**). In more detail, the following intraoperative findings were noted in patients with operative failure. Among all 16 patients in whom the surgeon was unable to locate and excise the abnormal parathyroid glands, results of IPM were true-negative and correctly predicted operative failure. In 7 patients, the surgeon was able to locate and excise the abnormal parathyroid gland in subsequent localization studies or during successful reoperation: 4 of these patients were found to have ectopic parathyroid glands in submandibular, retropharyngeal, intrathyroidal, and mediastinal locations, whereas the other 3 patients had an abnormal parathyroid gland missed by the surgeon after initial parathyroidectomy that was later discovered in an orthotopic location at the time of the second operation. Among 6 patients in whom the surgeon was unable to excise the abnormal parathyroid gland, it still remains in an unknown location. In the final 3 patients, other significant health issues (including cardiac or pulmonary comorbidities) precluded extended 4-gland surgical exploration. Based on surgeon judgment, only one side of the neck was surgically explored in these operations.

Intraoperative parathyroid hormone monitoring results were false-positive in 5 of 21 patients with operative failure (23.8%), or 0.7% overall (Table 3). In these 5 patients, IPM missed MGD and incorrectly predicted operative success. Their intraoperative findings are summarized in **Table 4**. Focused surgical exploration of the first patient resulted in the excision of a ruptured parathyroid cyst with an extremely high preexcision hormone level during this operation. Although IOPTH levels decreased 62% at 10 minutes and 80% at 20 minutes, the final parathyroid hormone level was 220 pg/mL (to convert parathyroid hormone level to nanograms per liter, multiply by 1.0), but the surgeon ended the operation without further surgical exploration. The second patient, who had 2 left glands and one-half of a right gland removed in a previous operation, underwent a second operation that involved the removal of a right inferior parathyroid gland and partial right thyroidectomy. Her IOPTH level decreased 56% at 10 minutes caused by a technical error recognized after the operation. The technical error involved the processing of a wrong blood specimen from another patient with SPHPT. In the third patient, there was a 65% parathyroid hormone level decrease, but the final parathyroid hormone level was 134 pg/mL at 10 minutes. The fourth patient underwent parathyroidectomy in which a right superior parathyroid gland was removed. Although the patient's IOPTH levels decreased 55% at 10 minutes and 66% at 20 minutes, this patient had a final parathyroid hormone level of 215 pg/mL. In the fifth patient, a left parathyroid gland was excised with a 54% parathyroid hormone level decrease at 10 minutes, and the final parathyroid hormone level was 69 pg/mL.

Table 4. Operative Details of 5 Patients With Intraoperative Parathyroid Hormone Monitoring False-Positive Results

Patient No.	Parathyroid Hormone Level, mg/dL[a] Preincision	First Preexcision	First 5 min	First 10 min	At 20 min or Second Preexcision	Second 5 min	Second 10 min	Comments
1	172	1100	558	414 (62)	220 (80)	. . .	. . .	Ruptured parathyroid cyst, 20-min level remained high
2	96	126	. . .	. . .	822	88	56 (56% From first preexcision or 93% from second preexcision)	Decrease close to 50%, 822 mg/dL was laboratory technical error
3	388	353	366	332 (17)	. . .	177	134 (65)	Final level remained high
4	627	346	275	282 (55)	215 (66)	. . .	. . .	Level at 10 min > level at 5 min, final level remained high
5	100	149	90	69 (54)	. . .	. . .	. . .	Decrease close to 50%

Abbreviation: Ellipses, not applicable.
SI conversion factor: To convert parathyroid hormone to nanograms per liter, multiply by 1.0.
[a]First refers to the first gland or structure removed; second, the second gland or structure removed; and values in parentheses, the parathyroid hormone level drop from the highest preincision or preexcision level.

COMMENT

With the predominance of single-gland disease in 85% to 96% of cases, focused parathyroidectomy guided by IPM has become the initial procedure of choice for treatment of most patients with SPHPT over the past 15 years.[1-6] Advantages of focused parathyroidectomy include less dissection, improved cosmetic results with smaller incisions, decreased pain, shorter operative time, use of ambulatory surgery, rapid postoperative recovery, and reduced postoperative hypocalcemia.[1-5] Several studies[1-5] from large series of patients indicate that focused parathyroidectomy guided by IPM has an operative success rate exceeding 95%. Nevertheless, operative failure occurs in these patients, with failure rates ranging from 1% to 5%.[7,18-20]

Essential to the success of any parathyroidectomy is the recognition of MGD as autonomous hypersecretion of more than 1 parathyroid gland in patients with SPHPT. The impetus for developing a quick laboratory test for measuring hormone levels in the operating room was to determine if and when all hypersecreting parathyroid tissue had been removed. This quantitative test measuring parathyroid hormone levels is used to recognize the continued hypersecretion of any other remaining parathyroid glands after the surgeon has excised the presumed abnormal gland causing hyperparathyroidism. The monitoring of parathyroid hormone levels during parathyroidectomy has shown to be a helpful adjunct to the surgeon, with 98% accuracy in predicting postoperative eucalcemia at 6 months.[9,21] Despite several investigations reporting the usefulness of IPM, some surgeons believe that IPM is least useful when it is most needed and may miss MGD, leading to unacceptable rates of operative failure.[10-14]

In this study, focused parathyroidectomy guided by IPM performed in patients with SPHPT had an operative success rate of 97.1%. Patients who had operative failure were more likely to have a history of thyroidectomy or parathyroidectomy, negative or equivocal findings on localization studies, and MGD. On further examination of intraoperative findings, the main cause of these failed parathyroid operations was not missed MGD but rather the surgeon's inability to find the abnormal parathyroid gland. In 16 of 21 patients (76.2%) with operative failure, the operating surgeon was (1) able to locate and excise the abnormal gland in subsequent localization studies or successful reoperation, (2) unable to excise the abnormal gland that remained in an unknown location, or 3) unable to perform a complete surgical exploration of the neck (despite an insufficient decline in IPM results) because of patient health issues that precluded safe 4-gland surgical exploration. In these operations, IPM correctly indicated inadequate resection to the surgeon before leaving the operating room and predicted operative failure.

In 5 remaining patients who had operative failure (0.7% of the overall cohort), IPM missed MGD and incorrectly predicted operative success. In these patients, there was more than a 50% decrease in parathyroid hormone level at 10 minutes, which predicted operative success. On closer examination of intraoperative findings, most patients with operative failure had a marginal parathyroid hormone level decrease of more than 50%, with a final parathyroid hormone level that remained high. In such circumstances, surgeon judgment and experience are important, with procurement of another IOPTH measurement at 20 minutes; if an insufficient decline or inappropriate parathyroid hormone dynamics are again measured, surgical exploration of the neck should be continued.

To prevent these rare operative failures caused by false-positive IPM predictions, stricter criteria have been suggested, including return of the 10-minute parathyroid hormone level to within normal range or a decrease to a level below the preincision parathyroid hormone level.[19,20] In a subsequent study,[22] such stricter criteria were estimated to increase operative success only by 0.3% but significantly increase unnecessary BNE to 20%. Studies[13,19,20] advocating more stringent criteria indicate that additional enlarged glands may be found with further BNE, despite more than a 50% decrease in parathyroid hormone levels and suggest that this criterion significantly misses MGD and leads to significant operative failure rates among patients who undergo focused parathyroidectomy guided by IPM. However, the results of such studies should be interpreted cautiously because the function of these additional removed glands cannot be evaluated. Furthermore, mounting evidence suggests that most of these unexplored "enlarged" glands will not cause operative failures or recurrences with affirmation that IPM-guided focused parathyroidectomy has success rates exceeding 95%.[7,22-28]

In conclusion, most operative failures in the era of focused parathyroidectomy guided by IPM are caused by inability of the surgeon to find the abnormal parathyroid glands in the neck and not false-positive IPM results. In most cases of operative failure, IPM correctly indicates inadequate resection to the surgeon before leaving the operating room. When there is a marginal IOPTH level decrease of more than 50% and a final parathyroid hormone level that remains high, surgeon judgment and experience become paramount in the direction and ultimate success of these operations. In such circumstances, another IOPTH measurement at 20 minutes should be obtained, and if an insufficient decline or inappropriate parathyroid hormone dynamics are again measured, further surgical exploration of the neck is warranted. Nevertheless, IPM remains an invaluable adjunct to the surgeon and has helped transform the operative management of patients with SPHPT from BNE to a focused approach with less dissection and minimal operative failure.

Accepted for Publication: January 25, 2010.
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Author Contributions: *Study concept and design:* Lew. *Acquisition of data:* Lew and Rivera. *Analysis and interpretation of data:* Lew, Irvin, and Solorzano. *Drafting of the manuscript:* Lew and Rivera. *Critical revision of the manuscript for important intellectual content:* Lew, Irvin, and Solorzano. *Statistical analysis:* Lew and Solorzano. *Administrative, technical, and material support:* Lew and Irvin. *Study supervision:* Lew.
Financial Disclosure: None reported.
Previous Presentation: This paper was presented at the 117th Scientific Session of the Western Surgical Association; November 9, 2009; San Antonio, Texas; and is published after peer review and revision. The discussions that follow are based on the originally submitted manuscript and not the revised manuscript.
Additional Contribution: Raquel E. Layton, BS, assisted in the data collection and patient follow-up required for the preparation of the manuscript.

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DISCUSSION

Nancy Perrier, MD, Houston, Texas: The authors have been paramount in establishing IOPTH level into clinical care. In fact, it was their contribution more than 15 years ago that altered the standard surgical paradigm for parathyroid operations. Today, this group has provided us with data from a large series of 845 patients operated on during a 15-year period. Of the 723 patients followed up, 97% were cured, a success rate that is to be applauded as it is comparable to results of standard cervical exploration but with the benefits of a more directed dissection on an outpatient basis.

The lessons we have learned during the evolution of parathyroid surgical intervention over the past 1½ decades are 3-fold: (1) preoperative imaging suggests where to start the operation, (2) IPM suggests when to stop the operation, and (3) these modalities must enhance but not replace good surgical wisdom.

The purpose of this study was to describe the cause of operative failure in the era of focused parathyroidectomy guided by IOPTH at a single medical center. The findings reinforce the age-old importance of good surgical principles. The findings support that most failures resulted from the surgeon's failure to identify the offending gland, not MGD. The results reinforce the importance of surgeon judgment, experience, and a thorough understanding of the anatomy and embryology that are paramount in the ultimate success of parathyroid intervention. Information gained from other disciplines, such as radiology and laboratory medicine have proven that they add to the options of information but must not be mistaken as being equivalent to sound surgical skill.

I have the following questions for the authors:

1. Five percent (38 of 723) of patients in the series had MGD. In only 13% of these cases (5 of 38) IOPTH was not predictive. In these 5, what were the operative findings of the excised gland? Tell us more about the preoperative imaging characteristics, the pathology of the glands excised, and, most importantly, the intraoperative findings.

2. Three percent (21 of 723) of patients had failed operations. In 16, the event can be attributed to the inability to locate the adenoma, and these were all predicted by IOPTH measurements. Most of these were found at reoperation. Can you share more with us about why they were missed?

3. In clinical care, what do you do in cases in which at 20 minutes the IOPTH level drops? How is this information considered in clinical decision making? Do you close then? Are there cases in which the operating surgeon waited for the 20-minute decrease, found it higher than 50% of baseline, and thus ceased the surgical exploration? What is the long-term outcome in those cases? Can you explain the delayed decrease?

4. In the "Methods" section, your description included only patients with biochemical diagnosis of primary hyperparathyroidism and positive localization studies. Since only one-third of patients with MGD have positive localizing studies, what became of the other cohort of those with equivocal or negative imaging? Your conclusion states that operative failures were more likely in patients with negative or equivocal studies. As such, how did you decide where to start the operation, and have you changed your approach to consider using another imaging modality or bilateral cervical exploration in such cases?

5. What is the status of the 122 (14.4%) patients lost to follow-up? The text suggests that they were excluded owing to eucalcemia within 6 months of follow-up. Please elaborate, as 14% is not an insignificant number.

Dr Lew: To address your first question about the 5 operative failures where IPM incorrectly predicted cure in these patients, 1 patient had good localization preoperatively, but the parathyroid gland proved to be cystic, and during manipulation the cyst was ruptured. The final parathyroid hormone level was elevated, so one could deduce the contents of the cyst may have been the cause of the failure. Another patient who had 2 left-sided parathyroid glands and apparently one-half of a right gland removed underwent reoperation. Localization suggested an abnormal gland on the right side. This case was complicated by a technical error in processing of the sample—a very high spike at the second preexcision level. This may have caused a false reading, which indicated to the surgeon that they had successfully completed the operation. In another reoperative patient, papillary thyroid cancer was found, which complicated the case, and there may have been other variables that caused the failure in this patient. In the other 2 cases, there seemed to be straightforward preoperative localization. Glands were removed from these patients, but although there was a greater than 50% decrease in parathyroid hormone levels, the final parathyroid hormone levels were borderline elevated.

To address your second question, 21 patients were considered operative failures, 16 of whom were because of the surgeon's inability to find the abnormal parathyroid gland; IPM was accurate. We classified these failures into 3 categories. First, comprising 7 patients, glands were subsequently found at either reoperation or on subsequent localization studies. Second, including 6 patients, the abnormal parathyroid glands remained in unknown locations. Third, comprising 3 patients, other significant health issues precluded complete surgical exploration of the neck.

To address your third question, in those cases in which a 20-minute sample was obtained, if a greater than 50% PTH decrease was obtained, the operation was completed. Unfortunately, we do not have a good explanation for these delayed decreases.

To address your fourth question about operating with equivocal or negative imaging studies, it can be a very humbling experience. We thoroughly reevaluate these patients, including their history, any prior operative reports, reimaging, and use of 4-dimensional computed tomography. We sometimes use jugular venous sampling. We advise the patients that there may be a risk that the offending gland may not be discovered. What this study shows is that there are certain circumstances where adjuncts are not helpful.

Financial Disclosure: None reported.