Optimization of Minimally Invasive Radio-Guided Parathyroidectomy: The Importance of Neck Ultrasonography and Intraoperative Parathyroid Hormone Assay

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Original Article

OPTIMIZATION OF MINIMALLY INVASIVE RADIO-GUIDED PARATHYROIDECTOMY: THE IMPORTANCE OF NECK ULTRASONOGRAPHY AND INTRAOPERATIVE PARATHYROID HORMONE ASSAY

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ABSTRACT

Objective: To determine whether close collaboration between a neck ultrasound–certified endocrinologist and a skilled endocrine surgeon can optimize minimally invasive radio-guided parathyroidectomy (MIRP) surgical outcomes.

Methods: Outcome data were collected on patients with primary hyperparathyroidism whom we intended to treat with MIRP at the induction of anesthesia between October 1, 2005, and December 31, 2007. Patients underwent preoperative gamma camera sestamibi scanning (GCSS), intraoperative gamma probe sestamibi scanning (IOSS), and preoperative neck ultrasonography. Intraoperative parathyroid hormone (PTH) monitoring was performed. Postoperative surgical success was defined as a serum calcium concentration between 8.0 and 10.4 mg/dL within 4 weeks of surgery.

Results: During the study period, MIRP was planned for 46 patients. Of the 46 patients, 39 had preoperative neck ultrasonography; 7 underwent evaluation by an endocrinologist or internist who was not ultrasound certified and they therefore did not undergo preoperative ultrasonography. IOSS correctly identified 1 adenomatous gland in 38 of 46 patients (83%), while GCSS correctly localized 1 adenomatous gland in 30 of 46 patients (65%). In 11 GCSS–negative patients, IOSS identified the abnormal gland in 7 (64%), while ultrasonography identified the abnormal gland in 8 (73%). The surgical approach was converted to traditional parathyroidectomy in 3 patients. Every patient exhibited at least a 51% drop in intraoperative PTH levels with resection of the final adenoma; average decrement for the entire group was 79 ± 8% from the highest baseline level. Forty-five patients (98%) demonstrated sustained normalization of serum calcium within several days of surgery.

Conclusion: A collaborative endocrinology and surgical endocrine oncology practice arrangement, emphasizing careful preoperative physician-supervised neck ultrasonography and the use of intraoperative PTH measurement, optimizes MIRP outcomes. **(Endocr Pract. 2008;14: 856-862)**

Abbreviations:
GCSS = gamma camera sestamibi scanning; **IOSS** = intraoperative gamma probe sestamibi scanning; **MIP** = minimally invasive parathyroidectomy; **MIRP** = minimally invasive radio-guided parathyroidectomy; **PTH** = parathyroid hormone

INTRODUCTION

The development of minimally invasive radio-guided parathyroidectomy (MIRP) has clearly benefited the patient with primary hyperparathyroidism caused by a single adenomatous parathyroid gland. Extensive neck explorations through 4- to 8-cm incisions have been replaced by procedures performed through tiny neck incisions (less than 2.5 cm long) requiring less than 60 minutes of operating time. Patients no longer spend 24 to 48 hours in the hospital; in fact, most are discharged to home after an hour or 2 in the recovery area (1,2). MIRP is based on the premise that the agent used for radio-guidance, technetium Tc 99m sestamibi, is generally effective (sensitive and specific) in the detection of hyperfunctional parathyroid glands (3-5). While investigators argue about the relative efficacy of preoperative gamma camera sestamibi scanning (GCSS) vs intraoperative gamma probe sestamibi scanning (IOSS), most agree that sestamibi localization in the patient with multigland disease is occasionally inadequate or even misleading (5,6). Unfortunately, 5% to 15% of patients with

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primary hyperparathyroidism harbor multiple hyperfunctional glands that often defy conventional localization efforts (7).

In this article, we report our MIRP outcomes over the past 26 months and review the literature regarding minimally invasive surgical approaches to sestamibi-negative and multigland hyperparathyroidism. We illustrate our approach to preoperative and intraoperative parathyroid localization by describing the case of a patient with multigland primary hyperparathyroidism. It is our intention to demonstrate that close collaboration between a neck ultrasound–certified endocrinologist and a skilled, minimally invasive endocrine surgeon can optimize MIRP surgical outcomes, especially in the patient with sestamibi-negative hyperparathyroidism and/or multiple parathyroid adenomas.

METHODS

We began performing MIRP at our institution (Imperial Point Medical Center, Fort Lauderdale, Florida) in October 2005. In this article, we report outcomes data on every patient whom we intended to treat with MIRP at the induction of anesthesia between October 1, 2005, and December 31, 2007. All demographic and biochemical data are reported as arithmetic mean ± standard deviation.

Demographic information including age and sex were collected along with baseline biochemistry values for parathyroid hormone (PTH), serum calcium, and serum creatinine. All patients underwent preoperative GCSS and IOSS. Patients had preoperative neck ultrasonography performed by the author RMH or underwent evaluation by another endocrinologist or internist who was not ultrasound certified and, therefore, did not undergo office ultrasonography preoperatively. Every patient underwent intraoperative PTH testing as described in the following text.

MIRP was initially offered at our institution as a 23-hour stay procedure. Outpatient surgery became our standard of care after postoperative bleeding and/or hypocalcemia were not noted in any of our initial patients. All procedures were performed through a 2- to 2.5-cm mid-neck incision. Enlargement of the incision to greater than 2.5 cm was considered conversion to an open-neck exploration. Twenty-five mCi of technetium Tc 99m sestamibi (Cardiolyte) was given intravenously approximately 2 hours before the start of the surgical procedure, and radionuclide localization was accomplished using the Gamma Probe (Gamma Surgery, Boca Raton, Florida). Intraoperative PTH monitoring was performed during all of the operative procedures. Intraoperative PTH levels were evaluated as surgery commenced, immediately before ligating the blood supply to the parathyroid adenoma, and subsequently 5 and 10 minutes after gland excision using an 8-minute chemiluminescent PTH assay (Future Diagnostics, Inc, Wijchen, Netherlands). Successful resection of hyperactive parathyroid tissue is defined by a greater than 50% PTH concentration reduction from the highest preoperative level to the lowest postoperative value (3). Patients were discharged to home on 1000 mg of elemental calcium given as calcium carbonate twice daily.

Postoperative surgical success was defined as a serum calcium concentration between 8.0 and 10.4 mg/dL within 4 weeks of the surgical procedure.

In an effort to elucidate our standard operating procedure, we present our entire evaluation and treatment of 1 illustrative patient with multigland primary hyperparathyroidism.

RESULTS

Illustrative Case

The illustrative patient was a 52-year-old white woman with hypercalcemia (serum calcium, 11.5 mg/dL), elevated serum intact PTH (89 pg/mL), and recurrent calcium oxalate nephrolithiasis. Her renal function was normal with a serum creatinine concentration of 0.9 mg/dL. After a complete endocrine consultation with RMH, office-based high-resolution ultrasonography revealed bilateral, disk shaped, hypoechoic masses posterior to the lower right and left thyroid lobes compatible with bilateral parathyroid adenomas (Fig. 1). A preoperative, gamma camera technetium Tc 99m sestamibi scan demonstrated high uptake in a right lower parathyroid position (Fig. 2). On May 8, 2007, the patient was taken to the operating theater for right lower gland MIRP. The IOSS revealed right lower neck uptake compatible with a parathyroid adenoma (968 counts/min in the surgical specimen with the Norman 20% rule exceeded). After resection of this 400-mg gland, the patient's intraoperative PTH concentration decreased from 170 to 136 pg/mL—a 20% drop. Based on the patient's preoperative ultrasonography, the surgeon elected to investigate the left neck without enlarging the MIRP incision. A dissection in the area posterior to the left lower thyroid lobe revealed a sestamibi-negative subcapsular mass. After resection of the 300-mg mass, the patient's intraoperative PTH decreased 75% to 42 pg/mL. At this point, the surgery was deemed complete, and the patient's 2.5-cm incision was closed with subcuticular suture and skin glue (Fig. 3). Subsequent serum PTH and calcium levels returned to the reference range.

Demographics and Baseline Biochemistries

Between October 1, 2006, and December 31, 2007, we planned MIRP surgery on 46 patients with primary hyperparathyroidism in the surgery suites of Imperial Point Medical Center in Fort Lauderdale, Florida.

Our patient population averaged 60.4 ± 12.6 years of age and was 48% female. All patients had primary hyperparathyroidism as documented by hypercalcemia (serum calcium concentrations averaged 11.6 ± 0.7 mg/dL) and

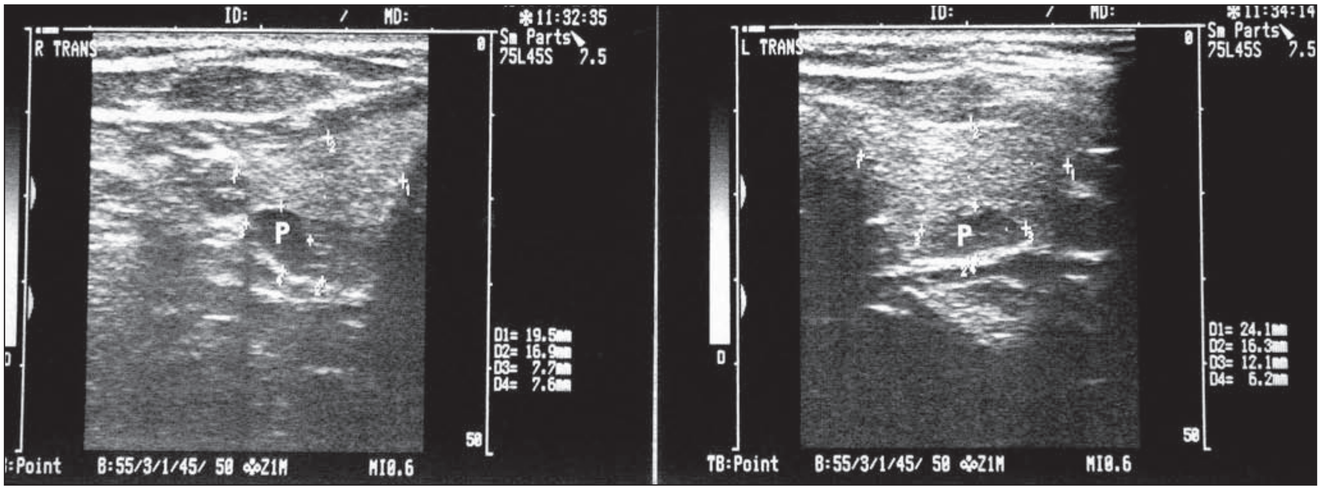

Fig. 1. Office-based high-resolution ultrasonography image of the illustrative patient revealing bilateral, disc-shaped, hypoechoic masses posterior to the lower right and left thyroid lobes compatible with bilateral parathyroid adenomas.

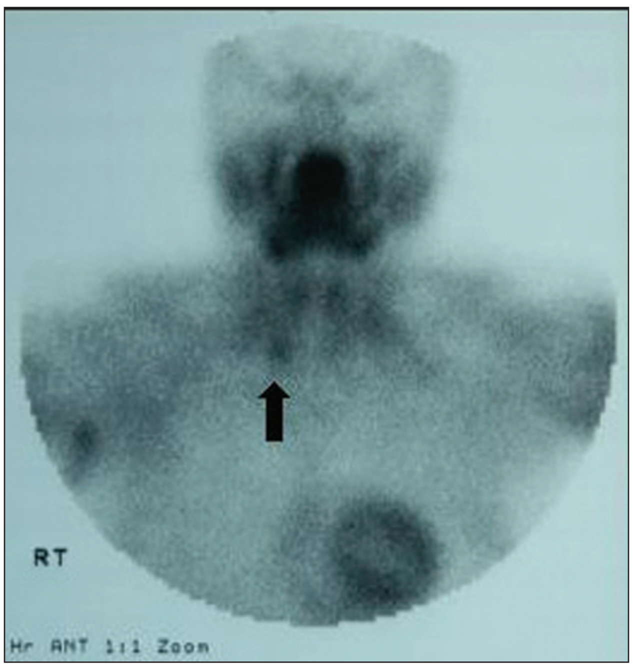

Fig. 2. Preoperative gamma camera technetium Tc 99m sestamibi scan of the illustrative patient, demonstrating high uptake in a right lower parathyroid position (*arrow*).

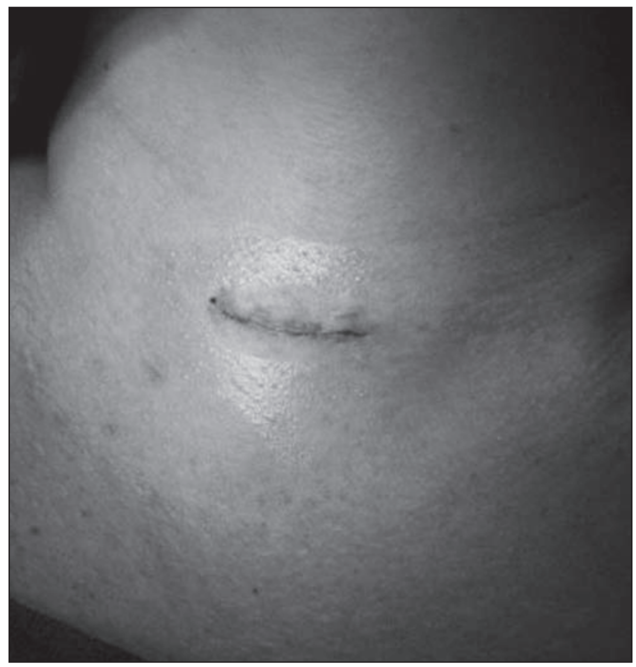

Fig. 3. Photograph of the illustrative patient's 2.5-cm incision closed with subcuticular suture and skin glue.

elevated intact PTH concentrations (155 ± 101 pg/mL). Calcium nephrolithiasis was historically present in 20% of the patients. No patients were receiving dialysis treatment or exhibited serum creatinine concentrations exceeding 2.5 mg/dL. Only 2 patients had serum creatinine concentrations exceeding 2.0 mg/dL.

Localization Data

All patients underwent outpatient GCSS, IOSS, and intraoperative PTH testing. Thirty-nine of the 46 patients also had preoperative outpatient ultrasonography of the neck for gland localization performed by the author RMH. Seven patients underwent evaluation by another endocrinologist or internist who was not ultrasound certified and, therefore, these 7 did not undergo office ultrasonography preoperatively (all were sestamibi positive and cured by resection of the single gland identified by both GCSS and IOSS). When both sestamibi technologies demonstrated a hyperactive gland, their localizations were almost always concordant (28 of 31 patients). In the 3 instances of discordant sestamibi localization, IOSS was always correct. Overall, IOSS correctly identified 1 adenomatous gland in 38 of 46 patients (83%), while GCSS correctly localized 1 adenomatous gland in only 30 of 46 patients (65%). Additionally, in 5 of the 46 patients (11%), GCSS was falsely positive, demonstrating uptake in an area where no abnormal gland was found. In no instance did GCSS correctly localize an adenomatous parathyroid gland that was not also localized by either preoperative ultrasonography or IOSS.

Our 46-patient operative group contained 3 patients with multigland hyperparathyroidism documented surgically. In these 3 patients, neither GCSS nor IOSS identified more than 1 adenomatous gland.

Unfortunately, in 11 of our 46 patients (24%), GCSS did not identify any hyperactive glands. In the 11 GCSS–negative patients, IOSS subsequently recognized the abnormal gland in 7 (64%), while ultrasonography was marginally better, recognizing the abnormal gland in 8 (73%). Ultrasonography had the additional benefit of recognizing the abnormal parathyroid when both GCSS and IOSS were negative in 1 patient and revealing an abnormal gland in another patient who was GCSS negative and had an inaccurate localization with IOSS. Finally, IOSS was negative in 5 patients, 3 of whom were correctly localized by outpatient preoperative ultrasonography. In summary, preoperative ultrasonography served as an important adjunct to IOSS in localizing parathyroid adenomas before MIRP.

Surgical Approaches

Three of the 46 patients had their surgical approach converted to traditional parathyroidectomy through a 4- to 5-cm neck incision. Two of these patients had coexistent Hashimoto thyroiditis with fibrotic inflammatory thyroid beds and exuberant lymphadenopathy (recognized preoperatively with ultrasonography) that complicated dissection and made parathyroid recognition more difficult. The third patient who underwent conversion to traditional parathyroidectomy had conflicting findings from localization procedures. After a small parathyroid adenoma was resected from an IOSS–positive left thymic location, the intraoperative PTH fell only 28%. A second sestamibi-negative, ultrasonography-negative adenoma was eventually discovered in a right upper pole location after the MIRP incision was extended and a full neck exploration was performed. The patient's intraoperative PTH concentration subsequently decreased 71%. The remaining 43 patients underwent standard MIRP.

Intraoperative PTH Results

All 46 patients had at least 3 intraoperative PTH levels assessed, and every patient exhibited at least a 51% drop with resection of the final adenoma. The average decrement for the entire group was 79 ± 8% from the highest baseline level. In our single patient who was not cured by MIRP, the PTH concentration decreased 84% after resection of a left upper pole parathyroid adenoma, but in retrospect, the pattern of the decrease suggested that the last value might have been spurious (preresection: 124 pg/mL, 133 pg/mL and postresection: 127 pg/mL, 120 pg/mL, 21 pg/mL).

Calcemic Outcomes

Of the 46 patients, 45 (98%) demonstrated sustained normalization of the serum calcium (serum calcium between 8.0 and 10.4 mg/dL) within several days of surgery. No episodes of postoperative hypocalcemia were documented. The single patient who did not achieve calcemic cure showed an initial decrease in serum calcium from 12.5 to 10.2 mg/dL, but subsequently the serum calcium level rebounded into the 11 mg/dL range and the patient was treated with cinacalcet, 30 mg/d.

Multiglandular Disease

Of the 46 patients, 3 (7%) were found to have 2 or more functional adenomas. One patient's serum calcium concentration did not normalize after what appeared to be a curative surgery (described in "Calcemic Outcomes"). The second underwent conversion from MIRP to conventional parathyroidectomy (she had coexistent Hashimoto thyroiditis) and her serum calcium concentration normalized after a 2-gland resection (described in Surgical Approaches). The third patient underwent bilateral lower pole gland resection through a MIRP incision and achieved normocalcemia (described in "Illustrative Case").

Because of concern that our MIRP experience (1 MIRP surgeon: DNB) might underestimate the incidence of multigland hyperparathyroidism because of selection bias, we reviewed all of our hospital's pathology reports of patients who had undergone parathyroidectomy (6 different neck surgeons) since August 2005 when we first introduced the intraoperative PTH assay. When patients receiving dialysis and patients with chronic renal insufficiency (serum creatinine concentrations in excess of 2.5 mg/dL) were excluded from the analysis (9 cases), the calculated incidence of multigland disease was 14% (15 of 107 cases).

DISCUSSION

Interpretation of the MIRP surgical literature is fraught with difficulty. Every major surgical center has slightly different ideas regarding which imaging modalities and physiologic tests of parathyroid function are necessary to construct a minimally invasive roadmap for parathyroidectomy. Most parathyroid specialty centers report high success rates with MIRP or minimally invasive parathyroidectomy (MIP, which is MIRP without the use of intraoperative sestamibi), but usually do not mention the results of surgery performed on patients who have negative preoperative or intraoperative localization attempts (probably because these patients undergo full neck explorations rather than MIRP or MIP). This selection bias may lead referring physicians and patients to a falsely inflated expectation for

MIRP/MIP success. In addition, the paucity of discussion on the important issue of the sestamibi-negative patient or the patient with multigland parathyroid disease does not serve to improve care for this significant subset of patients with hyperparathyroidism. In our view, the optimization of MIRP to deal with multigland disease demands the use of a multimodality approach to localization and physiologic intraoperative assessment of PTH concentrations. In the ensuing discussion, we review the medical literature on MIRP–treated multigland/sestamibi-negative hyperparathyroidism and concomitantly discuss findings based on our experience with 46 patients.

Our review of sestamibi-negative/multigland approaches in the MIRP/MIP literature is presented in Table 1. We located 4 papers in which minimally invasive surgery was the primary focus and found that the percentage of outpatient gamma camera sestamibi–negative patients ranged from 12% to 21% (8-11). Consistent with our findings, McGreal et al and Murphy and Norman find that a properly applied intraoperative sestamibi probe evaluation is a significant improvement over outpatient gamma camera sestamibi studies, with McGreal et al localizing 78% of outpatient sestamibi-negative patients using probe technology (10,11). In contrast, the Livingston group found no added localization power with the gamma probe, and they have a strong preference for surgeon-performed intraoperative ultrasonography as a localization modality (8). They describe finding parathyroid adenomas with ultrasonography in 81% of their preoperative sestamibi-negative patients. Lal and Chen take a multimodality approach using jugular vein PTH sampling and subtraction thallium scanning to supplement preoperative ultrasonography and sestamibi (9). Importantly, Lal and Chen were able to cure 47 of 90 sestamibi-negative patients (52%) using multimodality imaging for localization and intraoperative PTH to document complete removal of all adenomatous parathyroid tissue in the operating theater (9).

Multigland disease rates range from 2% to 8% in those groups that report only patients undergoing minimally invasive procedures and from 2% to 15% in groups that report data on all patients evaluated (8-11). The Livingston group, once again, favor intraoperative ultrasonography performed by the operating surgeon as their most reliable technology for demonstrating multigland involvement (8). None of the groups used endocrinologist-directed preoperative ultrasonography, and only Lal and Chen advocate intraoperative PTH measurements (9) for documentation of cure. Thus, there is no consensus among surgeons as to what constitutes the most efficient set of localization procedures for sestamibi-negative hyperparathyroidism and multigland disease. Moreover, in the published literature, there is no precedent for a collaborative endocrinology/surgical oncology parathyroid practice with automatic endocrinologist-directed ultrasonography localization.

Based on our 26-month collaborative community practice experience using multiple anatomic localization modalities and physiologic intraoperative PTH assessment, we suggest that surgical success in MIRP depends on patient selection, the reliability of preoperative and intraoperative localization techniques, the skill of the surgeon, and the use of the intraoperative PTH assay. All 4 of these variables factored into our restoration of normocalcemia in 42 of 43 patients treated with MIRP (98% success rate) at Imperial Point Medical Center from October 2005 to December 2007. We believe that both sestamibi and ultrasonography localization technologies add different perspectives to the process of surgical planning and that intraoperative PTH monitoring decreases the likelihood of persistent hyperparathyroidism postoperatively.

In our collaborative model, we first recommend endocrine consultation and a careful preoperative parathyroid ultrasonography evaluation supervised by a treating physician (either an endocrinologist or another parathyroid disease expert) with extensive neck ultrasonography experience. This procedural sequence ensures appropriate patient selection, precise anatomic parathyroid gland localization, and assessment of coexistent thyroid pathology. In our hands, ultrasonography localized 8 of 11 patients (73%) with negative preoperative sestamibi scans (GCSS) who subsequently underwent MIRP (Table 1). Our data are concordant with the recent report of Livingston et al who found that intraoperative ultrasonography successfully localized single adenomas in 17 of 21 sestamibi-negative patients (81%) with primary hyperparathyroidism (8).

Our data suggest that GCSS is less sensitive than IOSS with the Gamma Probe in the detection of parathyroid tumors. In no case did GCSS localize an adenomatous gland that was not also demonstrated by either preoperative ultrasonography or IOSS. In response to this finding, we are currently considering the elimination of GCSS as part of our preoperative localization process.

The localization process continues in the operating theater with the use of IOSS and the operative skill of the surgical endocrine oncologist. While GCSS and IOSS results are usually concordant, in 8 of our 46 cases (17%), discrepant results led to changes in operative decision-making. In contrast to the experience of Livingston et al (8), we found that in 7 of 11 patients with negative findings from GCSS, IOSS findings were positive and informative. In our 3 cases where GCSS and IOSS were both positive but discrepant, IOSS was always correct.

Although ultrasonography and sestamibi imaging procedures add value to the overall localization process, we have occasionally observed that all currently available localization techniques still manage to overlook some hyperactive glands, particularly in patients with multiple adenomas. Technetium Tc 99m sestamibi typically accumulates and persists in the plentiful mitochondria of adenoma-

Table 1
Data Summary of Patients With Negative Preoperative Gamma Camera Sestamibi Scan Findings in 5 Studies of Minimally Invasive Radio-Guided Parathyroidectomy

Study	Patients, No.	Success Rate, %	Multigland Disease in Patients Undergoing MIRP, %	Multigland Disease in All Patients Undergoing Parathyroidectomy, %	Sestamibi Scan Negative, %	Sestamibi Scan Negative, IOSS Positive, %	Sestamibi Scan Negative, U/S Positive, %	Multigland Disease Detected by Intraoperative PTH Assay, %
Current study	46	98	7	14	24	64	72	67
Livingston et al (8)	100	99	2	2	21	0	81	NA
Lal and Chen (9)	516	99	NA	15	20	NA	NA	NA
McGreal et al (10)	75	97	8	8	12	78	NA	NA
Murphy and Norman (11)	345	100	NA	NA	13	NA	NA	NA

Abbreviations: IOSS, intraoperative gamma probe sestamibi scanning; MIRP, minimally invasive radio-guided parathyroidectomy; NA, not available; PTH, parathyroid hormone; U/S, ultrasonography.

tous parathyroids over a 2-hour scanning interval, but not all adenomas demonstrate either mitochondrial hyperplasia or technetium Tc 99m sestamibi avidity (12,13). Thus, sestamibi does not universally localize all adenomas and frequently does not delineate the second or third adenoma in the patient with multigland disease (7).

In contrast, high-resolution ultrasonography is a highly operator-dependent technology (thus our recommendation that this procedure be performed or supervised by an experienced ultrasound-certified endocrinologist/physician) that may recognize multiple adenomas, but cannot localize adenomas situated deep in the tracheoesophageal groove or below the clavicles. We have no grounds for comparing the efficacy of endocrinologist/internist vs surgeon-directed neck ultrasonography. We do suggest that the ultrasonographer should be intimately aware of the details of the patient's history and physical examination, carry formal certification in neck ultrasonography, and have copious experience in locating parathyroid pathology with ultrasonography.

Finally, given the 14% prevalence of multigland disease in our referral population and the inherent localization limitations of ultrasonography and sestamibi in this context, we advocate the use of the intraoperative PTH assay to optimize MIRP outcomes. Dr. George Irvin at the University of Miami developed and championed the use of a fast chemiluminescent PTH assay during parathyroidectomy in the early 1990s (3). His assay technology allows neck surgeons to document PTH physiology while the patient is under anesthesia. If the chemiluminescent PTH concentration drops by more than 50% from the pre-parathyroidectomy baseline after parathyroid adenoma resection, the patient is said to be "cured" by physiologic testing, and the neck incision is closed (14). Some critics have suggested that multigland disease is too infrequent to merit the use of intraoperative PTH assays, and others have questioned assay accuracy, effectiveness, and cost (15). In our patient population, intraoperative PTH assessment has allowed us to avoid suboptimal surgical outcomes on several occasions where anatomic procedures (GCSS, ultrasonography, and IOSS) gave incomplete information (see "Illustrative Case" and "Surgical Outcomes"). In our illustrative case, we demonstrate surgical cure in a hyperparathyroid patient with double adenomas in the right and left lower pole positions using a minimally invasive approach. This patient's multigland disease was recognized by the use of preoperative ultrasonography and the intraoperative PTH assay, with sestamibi technology completely missing the left lower pole adenoma both preoperatively and intraoperatively.

Despite all our attempts to localize glands anatomically and physiologically, 1 of our 46 patients did not achieve postoperative normocalcemia. Indeed, no combination of currently available anatomic imaging modalities and physiologic testing can detect all hyperactive glands in every patient with primary hyperparathyroidism. Fortunately, in our initial 46 MIRP procedures, 2 patients who would not otherwise have achieved normocalcemia were prevented from having a failed MIRP by intraoperative PTH assay results that encouraged further neck exploration.

Undoubtedly, this multimodality approach adds cost when compared with traditional MIRP localization protocols. In-office ultrasonography carries a charge of $90 to $180, depending on the insurer. An intraoperative chemiluminescent PTH kit costs approximately $1000, but costs can be minimized by using economies of scale and scheduling several MIRP surgeries back-to-back (1 kit can be split between 2 patients). Based on our experience, these extra costs could be mitigated by the elimination of the preoperative GCSS (typical charge to insurers is in the $1600 range), without a loss of localization sensitivity. We suggest that the avoidance of the expense of repeat parathyroidectomy or lifelong cinacalcet use ($350 to $700 per month) far outstrips the cost of ultrasonography technology and intraoperative PTH measurement in those 5% to 15% of hyperparathyroid patients with multigland disease who stand to benefit from our comprehensive localization and intraoperative cure documentation efforts.

CONCLUSION

Based on the presented data, we suggest that our collaborative endocrinology and surgical endocrine oncology practice arrangement, emphasizing careful preoperative physician-supervised neck ultrasonography and the use of a rapid intraoperative PTH assay, optimizes MIRP outcomes.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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