Original Article

RADIOGUIDED PARATHYROIDECTOMY IS SUCCESSFUL IN 98.7% OF SELECTED PATIENTS

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ABSTRACT

Objective: To examine an individualized approach to patients with primary hyperparathyroidism (PHPT) in an effort to identify factors that would differentiate patients who can be treated with radioguided parathyroidectomy (RP) from those that require more extensive parathyroid exploration (PE) using intraoperative parathyroid hormone (IOPTH) measurement and to compare rates of recurrent and persistent hypercalcemia.

Methods: A total of 100 patients were retrospectively studied. Patients with positive single photon emission computed tomography (SPECT) scans underwent surgeon-performed sonography (SPS) followed by RP. Patients with negative or equivocal SPECT scans underwent PE utilizing SPS as a guide and IOPTH. The success rate, recurrence and persistence rates, and rate of bilateral exploration were compared.

Results: Seventy-five percent of patients with PHPT had a positive SPECT scan and underwent RP, whereas 25% of patients had a negative SPECT scan and underwent PE with IOPTH utilizing SPS as a guide. Persistent hypercalcemia was noted in 1 patient (1.3%) and recurrent hypercalcemia in 2 patients (2.6%) in the RP group, whereas no persistent hypercalcemia was noted in the group undergoing PE utilizing SPS and IOPTH. Overall, 89% of patients were cured with unilateral surgery.

Conclusion: Patients with positive SPECT scans may undergo RP with an expected cure rate of 98.7%. Patients with negative SPECT scans should undergo SPS followed by PE using IOPTH and can expect a cure rate near 100%. Properly selected patients may undergo RP, with low rates of persistent (1.3%) and recurrent (2.6%) hypercalcemia. **(Endocr Pract. 2014;20:305-309)**

Abbreviations:
FGE = four-gland exploration; **IOPTH** = intraoperative parathyroid hormone; **MIRP** = minimally invasive radioguided parathyroidectomy; **PHPT** = primary hyperparathyroidism; **PE** = parathyroid exploration; **PTH** = parathormone; **RP** = radioguided parathyroidectomy; **SPECT** = single photon emission computed tomography; **SPS** = surgeon-performed sonography

INTRODUCTION

The surgical management of patients with primary hyperparathyroidism (PHPT) remains controversial. Management in the past included four-gland exploration (FGE), whereas more recent advances using sestamibi scanning advocate minimally invasive radioguided parathyroidectomy (MIRP) (1-10). A recent studies has advocated abandonment of MIRP, noting a high rate of persistent and recurrent hypercalcemia, and a return to FGE without intraoperative parathyroid hormone measurement (IOPTH) instead and using only radioactivity as a guide in all patients (11). In this study, we strove to discern whether an individualized surgical approach to patients with PHPT using surgeon-performed sonography (SPS) (12), single photon emission computerized tomography (SPECT) imaging, and IOPTH would allow us to apply a logical approach to these patients, thereby curing the disease while avoiding unnecessary bilateral explorations. We were especially interested in the resultant rates of recurrent and persistent hypercalcemia.

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METHODS

We retrospectively analyzed data for 100 patients operated on by the author between January 1, 2009 and December 31, 2012. During that period, our entire practice of 7 surgeons performed 383 operations for parathyroid disease, and of that number, the author was the primary surgeon for 110 patients (5 patients with familial hyperparathyroidism and 5 patients with secondary hyperparathyroidism were excluded from this study). This group of 100 patients operated on by a single senior surgeon was chosen to highlight a logical and consistent approach to patients presenting with PHPT.

Patients with PHPT were seen and examined by the author. All patients had preoperative SPS, SPECT, and measurements of serum calcium and parathormone (PTH) levels. A detailed preoperative face-to-face examination was also performed.

Patients with definitely positive preoperative SPECT scans and SPS underwent radioguided parathyroidectomy (RP), defined as parathyroid surgery performed through a 4- to 5-cm incision, directed at the location identified on preoperative SPECT and SPS and performed under general endotracheal anesthesia as an outpatient. Patients undergoing RP had preoperative SPECT that clearly showed a single intensive focus consistent with a parathyroid adenoma. This location was confirmed by SPS. At the time of actual dissection, the gamma probe was not used for localizing purposes unless difficulty was encountered in finding the adenoma; this was necessary in 10% of patients. The gamma probe was used to measure radioactivity utilizing the 20% rule, as previously described (10). The 20% rule can be briefly described as follows: once the surgeon has identified and removed the suspected parathyroid adenoma, the gamma probed is used to measure the radioactivity of the area from which the adenoma was removed. This measurement becomes the denominator. Next, the surgeon uses the gamma probe to measure the radioactivity of the suspected adenoma ex vivo; this value becomes the numerator of the equation. The 20% rule states that a parathyroid adenoma will exhibit radioactivity equivalent to at least 20% of the measured radioactivity of the area from which it was removed. Conversely, fatty tissue and lymph nodes will not be radioactive. Frozen-section examination and IOPTH measurement were not performed in these patients. Patients were discharged on oral elemental calcium carbonate (1,000 mg) and vitamin D (500 international units [IU]) by mouth three times daily. Patients were rendered vitamin D-sufficient preoperatively. We feel that the term "radioguided parathyroidectomy" better reflects the reality of the procedure and now use this term in place of "minimally invasive radioguided parathyroidectomy."

Patients with equivocal or negative SPECT scans underwent parathyroid exploration (PE) using IOPTH. SPS was used as a guide to the initial phase of the operation in these patients. Persistent hyperparathyroidism is defined as elevated serum calcium in the immediate postoperative period in a patient who has undergone parathyroid surgery. Recurrent hyperparathyroidism is defined as a return to hypercalcemia after a period of normocalcemia in a patient who has previously undergone parathyroid surgery. The success rate, morbidity, and rates of persistent and recurrent hypercalcemia were assessed.

Selection and Description of Participants

Between January 1, 2009 and December 31, 2012, our group of 7 surgeons operated on 383 patients with all forms of parathyroid disease. The author was the senior surgeon for 110 of these patients. A total of 5 patients with familial hyperparathyroidism and 5 patients with secondary hyperparathyroidism due to renal disease were excluded, and the remaining 100 patients constituted the population for this retrospective study.

A total of 69% of all patients were symptomatic; 22% of these had a history of nephrolithiasis, 74% reported significant musculoskeletal pain, and 4% exhibited depression attributed to PHPT by the referring physician. Of the total patient population, 31% were deemed asymptomatic; all met the "Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism," as stated by the Third International Workshop (13). Of these patients, 51% presented with a serum calcium level 1 mg/dL greater than normal, 42% presented with a T-score of <2.5, and 7% were included because their age was less than 50 years. The patients in this study were referred by board-certified endocrinologists in 76% of instances and by board-certified internists in 16% of cases. A total of 8% of cases were self-referrals. A total of 17% of patients were followed for 1 year and 83% were observed for 2 to 4 years. The referring endocrinologists and internists were contacted to provide follow-up data and any information regarding recurrent or persistent disease. Individual patients were also contacted in an effort to identify recurrent disease.

Technical Information

Preoperative evaluation included serum calcium (normal, 8.5 to 10.0 mg/dL), serum PTH (normal, <65 pg/mL), serum protein electrophoresis, urinary calcium determination, SPECT imaging, and SPS. Our procedure and results for RP (10) and SPS (12) have been reported previously. Rapid measurement of intraoperative PTH has also been previously described (14).

Operative therapy was accomplished under general endotracheal intubation without long-acting muscle relaxation. Two surgeons were present for each operation, including the author in all cases and a partner or resident as an assistant. A neoprobe (model 2300, Neoprobe Corp) was used to measure focal radioactivity. IOPTH measurement was utilized in patients with negative SPECT scans.

Statistics

Patients' charts were individually reviewed by the author, and the results were tabulated manually. Operative times were obtained from the hospital record using Compass software. Results were compared statistically using the Student's *t* test.

RESULTS

A total of 100 patients with PHPT were studied. Seventy-five patients (75%) had a positive preoperative SPECT scan and SPS and underwent RP. Twenty-five (25%) patients had an equivocal or negative SPECT scan and underwent SPS followed by PE utilizing IOPTH. The follow-up period ranged from 1 year to 4 years.

There were no significant differences in preoperative calcium level (average, 11.06 mg/dL vs. 10.92 mg/dL; *P* = not significant) or preoperative PTH level (average, 116 pg/mL vs. 117 pg/mL; *P* = not significant) when comparing RP versus PE with SPS and IOPTH.

A total of 16 patients (16%) had associated thyroid disease requiring operative treatment at the time of parathyroid surgery. Of these, 4 patients were found to have thyroid cancer, 3 cases of which were incidental and involved tumors <1 cm, whereas 1 case involved a tumor >1 cm that required thyroidectomy and central compartment dissection at a later operation. Patients requiring thyroid surgery were excluded from operative time comparisons. The operative time for PE with IOPTH was significantly longer than that for RP (107 minutes vs. 38 minutes; *P*<.0001).

With the exception of 1 patient in the RP group (discussed below), all patients had normal postoperative serum calcium levels. There was no significant difference in postoperative serum calcium level when comparing the RP and PE with IOPTH groups. At least one parathyroid demonstrating hyperplasia was removed in all patients. Nine patients (36%) in the PE with IOPTH group were found to have multiple enlarged parathyroid glands, which represented 9% of the total patient group.

There were 3 patients with intrathyroidal parathyroid adenomas that were completely contained within the thyroid parenchyma and not visible from the surface. These were noted on preoperative SPS and confirmed by pathologic examination after removal. One patient with multiple gland disease had a mediastinal adenoma accessible only through sternotomy.

All patients without associated thyroid disease were cared for as outpatients and discharged the same day as surgery. There were no instances of hemorrhage or infection. No patient demonstrated hypocalcemia severe enough to warrant intravenous calcium or hospital admission (all patients received oral calcium supplement for 1 week postoperatively). One patient who had previous thyroid surgery had temporary hoarseness related to recurrent laryngeal nerve stretching.

Within the group of patients that underwent RP, 1 patient who had a single adenomatous parathyroid removed at the initial operation had persistent hypercalcemia with both elevated calcium and PTH in the immediate postoperative period. In retrospect, this patient had associated thyroid nodules as well as an equivocal preoperative sestamibi scan. Using our current understanding and algorithm, this patient should have undergone PE utilizing IOPTH.

Two patients who underwent RP had normal calcium and PTH levels postoperatively and then presented an average of 3 years later with elevated calcium and elevated PTH and underwent second operations for a second adenoma. In both cases, the second adenoma was visible on SPECT scan and was removed during a second RP. This represented 2 cases of recurrent disease (Table 1).

Of 25 patients with negative sestamibi scans who underwent PE with IOPTH, SPS was positive in 15. Using preoperative SPS resulted in unilateral exploration, with correction of IOPTH in 14 of 25 patients. In patients undergoing PE, SPS, and IOPTH, 9 patients (36%) demonstrated multi-gland disease (again excluding those with familial history positive for parathyroid disease) (Table 2).

Table 1
Rates of Persistent and Recurrent Hypercalcemia

	Number of patients	Persistent hypercalcemia (%)	Recurrent hypercalcemia (%)
Total number of patients with PHPT	100		
Patients with positive SPECT and SPS and treated with RP	75	1.3	2.6
Patients with negative SPECT and treated with SPS, PE, and IOPTH	25	0	0

Abbreviations: IOPTH = intraoperative parathyroid hormone assay; PE = parathyhroid exploration; PHPT = primary hyperparathyroidism; RP = radioguided parathyroidectomy; SPECT = single photon emission computed tomography; SPS = surgeon-performed sonography.

Table 2
Rate of Bilateral Parathyroid Exploration

	Number of patients	Number of patients requiring bilateral exploration
Patients with PHPT	100	
Patients with positive SPECT and SPS and treated with RP	75	0
Patients with negative SPECT and treated with SPS, PE, and IOPTH	25	11

Abbreviations: IOPTH = intraoperative parathyroid hormone assay; PE = parathyhroid exploration; PHPT = primary hyperparathyroidism; RP = radioguided parathyroidectomy; SPECT = single photon emission computed tomography; SPS = surgeon-performed sonography.

DISCUSSION

In the past, surgeons felt obligated to perform FGE in all patients with PHPT. Approximately 90% of patients will have a single adenoma responsible for the disease (1,2,4,7,10). If the surgeon commits to performing FGE in a patient with only a single adenoma, finding all 4 glands can indeed be problematic, in that the unaffected glands are in most cases very small owing to suppression by the output of the abnormal gland. In addition, the anatomic location of normal parathyroid glands encompasses the length of the neck from the carotid bifurcation to the base of the thymus; intrathyroidal parathyroid glands do exist in 3 to 5% of patients (10,12) and would require a partial thyroidectomy to expose or remove. For this reason, it was with relief that surgeons welcomed the arrival of sestamibi scanning, which will localize an adenoma in 70 to 80% of patients with PHPT. This led to the development of MIRP. However, 20 to 30% of patients will have a negative scan and therefore not be candidates for a classic MIRP (10).

Surgeons learned to use sonography (12) in patients with both positive and negative sestamibi scans in an effort to better delineate the location of enlarged parathyroid glands. However, one recent study recommended that all patients with PHPT be subjected to FGE without the use of IOPTH and utilizing only radioactivity as a guide. It is hypothesized in this study that FGE will prevent persistent parathyroid disease and lead to a lower rate of recurrent parathyroid disease as compared to unilateral exploration (11).

In the current study, using a combination of preoperative examination, family history, SPECT scan, SPS, and IOPTH (when indicated), we were able to correct the problem in 99% of patients overall. Seventy-five percent of patients were candidates for RP and exhibited a 98.7% cure rate. Twenty-five percent of patients had negative SPECT scans and underwent SPS with IOPTH. In these patients, 56% were cured with unilateral exploration, and the operation terminated once the PTH returned to normal. Four-gland bilateral exploration was only necessary in 11% of patients overall.

There were 2 patients that developed recurrent disease years after the initial operation. One of these patients had normal postoperative calcium and developed mildly elevated calcium 1-year postoperatively and underwent another RP, with removal of an adenoma from the opposite side 2 years later. The second patient presented after having had RP. This patient had normal postoperative serum calcium and serum PTH, which remained well within the normal limit for 3 years postoperatively. She then presented with recurrent disease and underwent a second radioguided parathyroid operation, with the removal of a second parathyroid adenoma from the opposite side 4 years later. PTH once again returned to normal. It is not likely that FGE in these 2 patients would have identified glands that did not become active until 2 to 3 years postoperatively. In addition, there must be some patients, such as these, who develop disease in other glands years after the initial episode of treatment. FGE cannot be expected to identify and correct these patients at the initial operation.

The approximately 75% of patients that have a definitely positive SPECT scan and SPS can confidently be treated with RP and expect a 97.4% chance of long-term cure (although there is a 1.3% chance of persistent hypercalcemia and a 2.6% chance of recurrent hypercalcemia). These patients must be selected carefully. A detailed history to absolutely exclude a familial history of parathyroid disease is needed. SPECT scans are reviewed and any study that does not reveal “a single intensive focus” denoting parathyroid disease is deemed equivocal and is not a candidate for RP. Patients with a negative SPECT scan should undergo SPS, which is used as a guide during exploration in concert with IOPTH measurement. Unilateral exploration will be possible in 56% of these patients. IOPTH

measurement is valuable in these patients because a reduction in the PTH level equivalent to 50% of the preoperative value and a subsequent return to normal level indicates to the surgeon that the condition is corrected and that the operation may be terminated, avoiding an unnecessary search for remaining glands. The key to this approach is careful selection of patients. As we have become more experienced, we have learned that any patient with a positive family history, associated thyroid disease, or equivocal or negative SPECT scan should not undergo RP (10,12). In these more complicated patients, we set aside more operative time and plan PE based on any suspicious area on SPECT or SPS and utilize IOPTH.

It is certainly true that the use of IOPTH measurement lengthens operative time owing to the time necessary to transport specimens to the laboratory and process them. Its main use is in informing the surgeon that removal of the specimen has corrected the problem and that no further exploration is needed. This lack of unnecessary dissection is responsible for the observed absence of nerve injury and hypocalcemia requiring any treatment other than short-term oral calcium in this group of patients. IOPTH also provides a well-established quantitative measure that the measurement of radioactivity of suspected normal parathyroid tissue does not provide. The author is unaware of any study that documents the accuracy of utilizing radioactivity to identify normal or inactive parathyroid tissue. Normal thyroid or thyroid nodules masquerading as parathyroid tissue likewise will be radioactive.

CONCLUSION

Using the above-mentioned algorithm, the surgeon should be able to cure 99% of all patients presenting with PHPT and do so utilizing only unilateral exploration in 89% of these patients. Seventy-five percent of patients are candidates for RP, which entails less tissue dissection and less operative time. To accomplish this result, the surgeon must dedicate the time to see each patient individually, study SPECT scans intently, and perform sonography. This preoperative evaluation will determine the course of the operation and whether or not IOPTH and its attendant time requirements are needed.

DISCLOSURE

The author has no multiplicity of interest to disclose.

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