Hypothesis: For a specific subset of patients with sporadic primary multiple-gland parathyroid disease, subtotal parathyroidectomy results in long-term normocalcemia in the majority of patients, with a minimal complication rate.


Setting: A multidisciplinary endocrine service based at a tertiary referral center.

Patients: Patients undergoing subtotal parathyroidectomy for primary hyperparathyroidism due to sporadic multiple-gland disease identified from a single surgeon’s operative records (A.E.G.).

Main Outcome Measures: Data analyzed included demographic factors, operative and pathologic findings, and postoperative and long-term clinical and laboratory results, including calcium and intact parathyroid hormone levels.

Results: Of 379 patients undergoing parathyroidectomy for hyperparathyroidism between 1984 and 1999, 49 (13%) had sporadic multiple-gland disease. Median preoperative calcium and intact parathyroid hormone (iPTH) levels were 2.7 mmol/L (10.8 mg/dL) and 11.79 pmol/L, respectively. Postoperative calcium and iPTH levels were available in 39 patients, and median values were 2.28 mmol/L (9.1 mg/dL) and 2.84 pmol/L, respectively. Long-term follow-up was available for 36 patients (73%), and duration ranged from 6 to 180 months (median, 44 months). Median calcium and iPTH levels at follow-up were 2.3 mmol/L (9.2 mg/dL) and 3.26 pmol/L, respectively, with 3 (8%) of 36 patients having evidence of persistent or recurrent hyperparathyroidism. No patient had biochemical evidence of hypoparathyroidism at long-term follow-up. Five patients (14%) had persistent elevated iPTH levels (range, 8.11-10.95 pmol/L) and normal calcium levels.

Conclusions: Subtotal parathyroidectomy for sporadic primary multiple-gland disease resulted in a long-term normocalcemia rate of 92%, with minimal complications. Selective subtotal parathyroidectomy can yield excellent long-term results in patients with multiple-gland disease.

Long-term Management and Outcome of Parathyroidectomy for Sporadic Primary Multiple-Gland Disease

D. Michael Rose, MD; Thomas F. Wood, MD; Andre J. Van Herle, MD; Pejman Cohan, MD; Frederick R. Singer, MD; Armando E. Giuliano, MD
PATIENTS AND METHODS

A single surgeon’s (A.E.G.) operative records were examined to identify patients undergoing operation for HPT. A formalized protocol was approved by the institutional review board of the John Wayne Cancer Institute and the Saint John’s Health Center, Santa Monica, Calif, and patients participated in the study after providing informed consent. The protocol included completion of a questionnaire requesting information on number of operations for HPT, complications following operation, and current care by an endocrinologist. Patients were requested to have blood drawn for an evaluation of current calcium and intact parathyroid hormone (iPTH) levels.

Data obtained included demographic factors, presenting symptoms, preoperative clinical data, operative and pathologic factors, immediate postoperative clinical and laboratory findings, and long-term clinical and laboratory findings. Patients with secondary or tertiary HPT, evidence of MEN syndrome, or familial HPT were excluded from analysis. Operative and pathologic reports were reviewed, and patients who had both intraoperative evidence of multiple-gland enlargement and who had undergone complete excision of at least 2 histopathologically hypercellular glands were included in the study.

All patients in this study underwent formal bilateral neck exploration without preoperative localization. At operation, all 4 glands were identified and inspected for enlargement. Failure to identify 4 glands prompted exploration of the carotid sheath and retroesophageal space, transcervical thymectomy, and ipsilateral thyroid lobectomy if the fourth gland remained unidentified. In cases of 4-gland enlargement, a subtotal parathyroidectomy was performed, leaving approximately 100 mg of parathyroid tissue in an anatomically accessible position should reexploration be required. This remnant was marked with a metallic clip and permanent suture to aid identification during subsequent reexploration. Parathyroid autotransplantation was performed only if the remaining glands were possibly compromised. In patients with asymmetric hyperplasia or multiple adenomas, biopsies were performed on grossly normal glands, which were left in place, and all grossly enlarged glands were excised.

intervention remains uncertain. To determine the results of a standardized operative approach in a homogeneous subset of patients with sporadic multiple-gland disease, we evaluated immediate postoperative and long-term clinical and biochemical outcomes of a single surgeon’s experience throughout the last 15 years.

RESULTS

PATIENT DEMOGRAPHICS

Between 1984 and 1999, 379 patients underwent parathyroidectomy for HPT. Three hundred seventeen patients (84%) had a single adenoma, 49 (13%) had sporadic multiple-gland disease, 9 (2%) had secondary or tertiary HPT, and 4 (1%) had MEN syndromes. The 49 patients with multiple-gland disease had a median age of 64 years (range, 26-77 years) and a male-female ratio of 15:34. Their symptoms at initial visit are presented in Table 1. Of note, 55% of the patients were symptomatic, usually with multiple symptoms. Median preoperative calcium and iPTH levels were 2.7 mmol/L (10.8 mg/dL) (range, 2.28-3.35 mmol/L [9.1-13.4 mg/dL]) and 11.8 pmol/L (range, 5.37-141.31 pmol/L), respectively.

OPERATIVE PROCEDURES AND FINDINGS

The majority of the 49 patients with sporadic multiple-gland disease underwent a single operation (Table 2). Of the 10 patients (20%) who underwent multiple surgical procedures, 8 had recurrent HPT after undergoing a previous parathyroidectomy elsewhere (resection of a single abnormal gland in 7 patients, and 2 abnormal glands in 1 patient). These patients visited the service 2 to 180 months (median, 72 months) following their initial surgical procedure. Two other patients failed to achieve normocalcemia on immediate postoperative analysis and underwent a second exploration within 72 hours. One patient underwent conversion to a subtotal 3 1/2-gland parathyroidectomy, and the second patient was found to have a fifth hypercellular gland and underwent excision of 4 1/2 parathyroids.

Four glands were identified in 43 (88%) of the 49 cases. For purposes of analysis, a properly identified gland was any gland removed by an outside surgeon during prior exploration, or any gland identified by our group during subsequent operation. The total number of resected glands is presented in Table 2; the majority of patients...
underwent a 3½-gland resection for 4-gland hyperplasia. Patients undergoing resection of fewer than 3½ glands had grossly normal parathyroid glands identified intraoperatively; biopsies were performed on these normal-appearing glands for frozen-section examination. All resected glands had histopathologic evidence of increased cellularity and decreased fat content consistent with hyperplasia. The median weight of the removed glands was 200 mg (range, 21-10400 mg). Two patients underwent autotransplantation of parathyroid tissue because of concern about the viability of the remaining gland.

**POSTOPERATIVE AND LONG-TERM RESULTS**

Postoperative calcium and ipTH levels were available in 39 patients, and median values were 2.28 mmol/L (9.1 mg/dL) (range, 1.95-2.75 mmol/L [7.8-11.0 mg/dL]) and 2.84 pmol/L (range, 0.21-15.58 pmol/L), respectively. Only 1 patient had elevated calcium and ipTH levels in the immediate postoperative period; however, an additional 5 patients had elevated ipTH levels and normal calcium levels, suggestive of secondary HPT. Long-term data were available for 36 patients (73%), who were followed up for a range of 6 to 180 months (median, 44 months). The 13 patients unavailable for follow-up had either died or moved with no forwarding information. A single patient suffered a temporary recurrent laryngeal nerve injury following parathyroidectomy. Of note, this patient concomitantly underwent a total thyroidectomy for incidental malignant material found at operation; however, she subsequently had normal vocal cord mobility, which was documented endoscopically, and she is currently asymptomatic with a normal voice. Median calcium and ipTH levels at follow-up were 2.3 mmol/L (9.2 mg/dL) (range, 2.1-2.9 mmol/L [8.4-11.6 mg/dL]) and 3.26 pmol/L (range, 0.63-54.86 pmol/L), respectively. No patient had biochemical evidence of permanent hypoparathyroidism. Three (8%) of the 36 patients had evidence of recurrent or persistent HPT, and an additional 5 patients (14%) had elevated ipTH levels (range, 8.10-10.95 pmol/L), with normal calcium levels.

Of the 3 patients who failed to achieve normocalcemia, 1 underwent a subtotal 3½-gland parathyroidectomy in 2 operative procedures with transplantation and was noted to have marginal recurrent HPT 24 months postoperatively (calcium=2.63 mmol/L [10.5 mg/dL]; ipTH=8.53 pmol/L). A second patient underwent 3 operations throughout 7 years, with the removal of 3 glands, including a 10.4-g mediastinal parathyroid; the patient has persistent HPT. The last patient underwent removal of 2 enlarged glands; however, the right inferior parathyroid was not identified at operation. She has refused further operative intervention.

**COMMENT**

Parathyroidectomy is the only curative option, and the treatment of choice in patients with primary HPT. The benefit of parathyroidectomy as treatment of this condition has been well documented in multiple studies. In an attempt to provide adequate controls, Chan et al compared symptomatic and clinical outcomes in patients undergoing parathyroidectomy, with patients undergoing thyroidectomy used as controls. At a mean follow-up of 20 months, the 121 parathyroid patients had fewer symptoms and lower rates of hematuria, bone fracture, joint swelling, weight loss, duodenal and gastric ulcerations, and hypertension. Burney et al also demonstrated significant improvement in functional status and patient perception of health status following parathyroidectomy for primary HPT. A recent nonrandomized prospective study of patients with primary HPT evaluated outcomes following parathyroidectomy vs close follow-up. Recommendations for resection in this study were based on guidelines from the National Institutes of Health Consensus Conference. Of the 61 patients undergoing parathyroidectomy in this study, 49 were asymptomatic and 12 were symptomatic with nephrolithiasis preoperatively. At 10 years’ follow-up, biochemical parameters were normal, bone mineral density was significantly increased, and all 61 patients remained free of symptoms.

The debate regarding the appropriate operative intervention for sporadic primary multiple-gland disease has continued unabated for decades. The operative approaches include a routine 3½-gland resection (leaving approximately 50-100 mg of the most “normal-appearing” gland), excising only those glands that are grossly enlarged at operative exploration, and a total 4-gland parathyroidectomy with subsequent autotransplantation. All 3 techniques have yielded excellent results in multiple series. Unfortunately, many of these reports are based on heterogeneous groups that include patients with solitary adenomas and familial disease. This heterogeneity substantially complicates analysis of postoperative outcomes in patients with sporadic multiple-gland disease. The paucity of information on this specific subset of patients led to the current study. In addition, there are very few long-term data on ipTH levels in patients undergoing parathyroidectomy for sporadic multiple-gland disease.

Results of studies reporting long-term outcomes for subtotal parathyroidectomy and including patients with all causes of multiple-gland disease are summarized in the first portion of Table 3. Of note, these study groups...
include heterogeneous populations of patients with diagnoses including familial HPT, MEN syndromes, and secondary HPT. All of these authors followed a policy of selective subtotal parathyroidectomy, in which only grossly enlarged glands were excised, leaving grossly normal parathyroids in place. The percentage of patients who were rendered normocalcemic postoperatively ranged from 73% to 90%, with a trend toward improvement in the more recent series. Proye et al reported the largest experience in this heterogeneous group to date, with excellent long-term outcomes. They concluded that “conservative surgery is an acceptable treatment for primary HPT due to multiglandular disease discovered at first cervicotomy.”

Other studies have examined outcomes following subtotal parathyroidectomy in more specific subgroups of patients with multiple-gland disease, including those with sporadic primary hyperplasia, and sporadic primary multiple adenomas and hyperplasia. Therefore, the clinical management remains identical for any degree of multiple-gland disease found at operation, all of these patients can be successfully treated with selective subtotal parathyroidectomy. Whether the remaining glands are normal or hyperplastic on a microscopic level seems to have no clinical ramifications.

Twenty percent of the patients in the current series underwent multiple operative procedures, primarily owing to recurrent hypercalcemia after previous parathyroidectomy elsewhere. This is not unexpected in this patient population because multiple-gland disease has been previously recognized as a risk for reoperative parathyroidectomy. Shen et al found that 37% of failed parathyroidectomies reflected incomplete resection of multiple abnormal glands. In another review of reoperative cases, Weber et al concluded that the most common causes of persistent or recurrent HPT were either inadequate neck exploration or inadequate resection of hyperplastic tissue. Similar to our own series, Doherty et al noted that 7 of 8 patients who had undergone previous operation elsewhere had abnormal glands that were not resected at the initial operation. Clearly, patients with primary HPT secondary to multiple-gland disease are at risk for inadequate resection, and should undergo complete exploration by an experienced endocrine surgeon.

Of note, 14% of the patients for whom long-term follow-up was available had evidence of elevated iPTH levels and normal serum calcium levels. This phenomenon has been noted by other authors, including Mandal and Udelsman, who reported secondary HPT in 12% of their patients following parathyroidectomy. These findings were noted in the immediate postoperative period and had largely resolved within 6 months, in contrast to the findings in our series. This secondary hyperparathyroid profile may be the result of remaining microscopic parathyroid hyperplasia or an alteration in the set point required to maintain a normal calcium level. Regardless, in no normocalcemic patient have we found this to be of clinical concern, and we do not recommend further intervention.

In conclusion, selective subtotal parathyroidectomy for patients with sporadic primary multiple-gland disease can result in excellent long-term normocalcemia.
mia with minimal complications. Based on analysis of a homogenous group of patients with primary sporadic multiple-gland disease found during cervical exploration, we recommend conservative resection of all grossly abnormal glands with biopsy of normal-appearing glands at operative exploration, or a 3½-gland resection in the case of 4-gland disease. In addition, a complete neck exploration and identification of all glands by an experienced surgeon is of paramount importance for optimal treatment of this group of patients.


Reprints: Armando E. Giuliano, MD, John Wayne Cancer Institute, 2200 Santa Monica Blvd, Santa Monica, CA 90404 (e-mail: giuliano@jwci.org).

REFERENCES

on failures and on our reoperation rate, I think there may have been some misunderstanding. We had 10 patients who had reoperation. Eight of those were referred to us after prior exploration. In our hands we had only 2 patients who were re-explored. One patient had 4 abnormal glands identified at operation. We did a 3½-gland resection only to find that the calcium did not fall. We went back and found a fifth gland. So our own reoperation rate is not as high as it would appear. You can often predict failures among patients with sporadic multigland disease. Those tend to occur in patients who have had prior operation, and patients in whom you do not personally identify all 4 glands.

Dr O'Connell, it is not clear to me what the persistent elevated PTH with normal calcium years after the operation signifies. Secondary hyperparathyroidism is reported following parathyroidectomy for primary hyperparathyroidism. It usually resolves in 6 to 12 months. These patients had longer follow-up and still had some persistently elevated hormone levels and normal calcium. Whether that represents some low-grade persistent hyperparathyroidism, some change in the set point for parathyroid hormone, or some secondary hyperparathyroidism is unknown.

Dr Mack, none of these patients had radiation. I am not sure about lithium. These are relatively straightforward patients, who were explored for hyperparathyroidism.

Intraoperative PTH may be of value in these patients. We have not started using this technique, and this may be a group of patients who would benefit from it.

Dr van Heerden, I think I commented on the fact that only 2 of these patients in our hands required a second operation. Dr Organ, these patients were asymptomatic when their calcium and parathyroid levels were corrected. Most were asymptomatic preoperatively.

We eliminated patients with family history. I think some could have MEN syndrome, although we doubt that many could. We have had excellent long-term results, Dr Thompson. Thank you for your kind comments. Our 1 transient nerve injury was in a patient who had an incidental carcinoma of the thyroid who had a total thyroidectomy at the same time. Fortunately, that complication resolved and we are very pleased to have no hypoparathyroidism. We noted no difference in outcome, Dr Prinz, for patients who had selective operation and those who had a 3½-gland operation. However, we do not routinely do 3½-gland resections. We undertook this study because while rotating on my service, Dr Rose pointed out to me that my approach appeared to be a very subjective approach to the management of this often difficult problem and because one of our endocrinologists said point blank that hyperplasia is not a surgical disease because of poor published results. So we sought to find out our long-term results, especially with respect to parathyroid hormone levels, which has not been well studied previously. While there may be subjectivity in the determination of what is a normal-sized gland, I prefer, Dr Rose, the term “experience” rather than subjectivity. We believe our results show that the overwhelming majority of patients with sporadic multiglandular disease treated with selective parathyroidectomy have favorable long-term outcomes with normalization of both calcium and parathyroid hormone.