ORIGINAL ARTICLE

Prospective Evaluation of Total Parathyroidectomy and Autotransplantation for the Treatment of Secondary Hyperparathyroidism

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Objective: To evaluate the clinical effectiveness of total parathyroidectomy with autotransplantation for the treatment of hyperparathyroidism and the recurrence rate of hyperparathyroidism after this procedure.

Design: A prospective study of total parathyroidectomy and autotransplantation in 19 consecutive patients with severe secondary (renal) hyperparathyroidism.

Setting: University hospital department of surgery.

Patients: Nineteen patients operated on for the treatment of secondary hyperparathyroidism between March 1993 and March 1996. Eighteen had been receiving long-term hemodialysis, and 1 had a functioning renal graft.

Intervention: Total parathyroidectomy and autotransplantation of excised parathyroid tissue into the brachioradialis muscle of the arm opposite that in which the arteriovenous fistula had been placed for dialysis.

Main Outcome Measures: Clinical and biochemical improvement, morbidity, mortality, and recurrence rates of hyperparathyroidism after the procedure.

Results: The conditions of 13 (72%) of 18 patients followed up improved, and the clinical and laboratory variables indicating secondary hyperparathyroidism returned to normal. One patient died 50 days after surgery. In 2 patients (10%), mild hypoparathyroidism developed, and in 1 patient (5%), persistent hyperparathyroidism developed and required reoperation. In 2 patients (10%), recurrent hyperparathyroidism developed, and 1 (5%) required reoperation.

Conclusions: Total parathyroidectomy with autotransplantation effectively relieves the symptoms of hyperparathyroidism, and the recurrence rate of hyperparathyroidism is low. Because all procedures used resulted in good control of clinical and biochemical variables, the method used for the surgical treatment of secondary hyperparathyroidism depends on the surgeon's preference.

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A PROLONGED chronic deficiency of calcitriol secondary to long-standing renal failure is the major cause of increased secretion of parathyroid hormone (PTH) and hypertrophy and hyperplasia of the parathyroid glands. In advanced cases, the treatment of vitamin D deficiency is ineffective for correcting hypersecretion of the parathyroid glands, and surgical removal is warranted.

See Invited Critique at end of article

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In 1994, according to the European Dialysis and Transplantation Registry Report, 1.3% of patients with end-stage renal disease who were receiving hemodialysis required parathyroidectomy because of severe secondary hyperparathyroidism that caused bone pain, extraosseous soft tissue calcification, and severe pruritus.[1] Three types of surgical techniques have been proposed for this disease. The first technique was subtotal parathyroidectomy, performed in 1960.[2] Subsequently, total parathyroidectomy was suggested, but a severe form of disabling osteomalacia was reported secondary to this surgical procedure, which then fell out of favor. However, during the following years, it became clear that such a complication was related to a preexisting accumulation of aluminum in the bone and not the surgical procedure, which has been reintroduced. In 1968, Alveryd[3] reported the first experience of total parathyroidectomy with autotransplantation of fresh parathyroid tissue. Since that time, subtotal parathyroidectomy and total parathyroidectomy with autotransplantation have been considered comparable procedures. In 1991, Rothmund et al[4] reported the results of a randomized trial comparing the 2 procedures in 40 patients with secondary hyperparathyroidism. They concluded that total parathyroidectomy with autotransplantation is preferable to subtotal parathy-

PATIENTS AND METHODS

Between March 1993 and March 1996, 19 consecutive patients were operated on at the University of Rome Department of Surgery, Rome, Italy, for the treatment of secondary hyperparathyroidism. Eighteen had been receiving long-term hemodialysis for a mean of 7.7 years, and 1 had a functioning renal graft. The 9 men and 10 women ranged in age from 30 to 72 years (mean, 50.2 years). Chronic renal failure was caused by glomerulonephritis in 8 patients, polycystic kidney disease in 4, nephrolithiasis in 3, vesicoureteral reflux in 2, diabetic nephropathy in 1, and urate nephropathy in 1.

Preoperative examinations included serial estimations of serum calcium, phosphorus, and alkaline phosphatase concentrations. Serial intact PTH concentrations also were obtained. In all patients, a bone biopsy was performed before surgery to obtain tissue for histological analysis. All patients underwent dialysis the day before operation.

The indications for surgery in the 19 patients are shown in the following tabulation.

Indication	No. (%) of Patients
Bone pain	19 (100)
Hyperparathyroidism	19 (100)
Medical therapy	19 (100)
Pruritus	18 (95)
Muscle weakness	14 (74)
Spontaneous hypercalcemia	8 (42)

All procedures were performed by the chief surgeon (M. C.), and the exploration of the neck was done according to the technique suggested by Rothmund and Wagner.[5] The procedure involved the excision of all identified parathyroid glands and of the thyrothymic ligament. Intraoperatively, all resected specimens were examined microscopically to confirm the diagnosis. Cervical thymectomy was required for 6 patients (32%). For each patient, 20 pieces of tissue ranging from 1 to 2 mm^3 were implanted into the brachioradialis muscle of the arm opposite that in which the arteriovenous fistula had been placed for dialysis, as described by Wells et al.[6] Surplus fragments were sent to the laboratory for cryopreservation, which was performed according to the method of Wagner et al.[7]

We found 4 parathyroid glands in 17 patients and 5 in 1 patient. We found 3 parathyroid glands in the other patient.

Patients were treated and followed up by the referring dialysis centers after discharge. During the first 48 hours, supplemental calcium was given intravenously according to actual serum calcium concentrations. Subsequently, during the first 6 months, calcium and calcitriol supplements were administered orally according to the trends in the serum calcium concentration. The objective effects of surgical treatment on clinical symptoms and the function of the parathyroid glands were evaluated prospectively in all patients by measurement of the serum calcium, phosphorus, alkaline phosphatase, and PTH concentrations. The subjective response to surgical treatment was measured by using a questionnaire completed by the patient and the referring nephrologist during each follow-up examination. The duration of follow-up ranged from 13.6 to 50.6 months (mean ± SE, 27.9 ± 2.9 months). All examinations were performed at 1, 6, and 12 months after surgery and then every year.

All laboratory and clinical data were analyzed by using repeated measures analysis of variance. The level of significance was set at .05.

roidectomy for patients with renal osteodystrophy. Actually, total parathyroidectomy with autotransplantation is a widely accepted surgical treatment for secondary hyperparathyroidism, and a wide range of recurrence rates have been reported.

The aim of the present study was to evaluate the clinical effectiveness of total parathyroidectomy with autotransplantation and the recurrence rate of hyperparathyroidism after this procedure.

RESULTS

Eighteen patients were followed up; 1 (5%) of the 19 patients died 50 days after surgery of a cerebrovascular accident. No perioperative complications occurred. Improvement, defined by a return to normal in the clinical and laboratory variables that indicate secondary hyperparathyroidism, occurred in 13 (72%) of the patients.

The biochemical and clinical data before and after operation are shown in the **Table**. Serum concentrations of intact PTH were normalized on the first postoperative day in all but 1 patient who had persistent hyperparathyroidism. The serum calcium concentration decreased progressively during the first postoperative week, and the clinical symptoms improved. **Figure 1** through **Figure 7** show the time trend for each variable.

There were 2 cases (11%) of postoperative hypoparathyroidism among the 18 patients who survived, which was defined by a serum concentration of intact PTH less than 1.1 pmol/L 12 months after surgery. Both patients are without symptoms, and a low-dose oral calcium and cholecalciferol regimen has resulted in only slight hypocalcemia. Therefore, they are not candidates for reoperation. Of note, 1 of these patients is the only patient in the present series with a functioning renal graft. Of the 19 patients, 1 experienced persistent hyperparathyroidism (5% persistence rate), defined as a reduction of the serum PTH concentration to less than 30% of the preoperative value 1 month after surgery. At the first operation, only 3 parathyroid glands were detected and removed. Postoperatively, the presence of a missed ectopic gland was confirmed by sestamibi scan, and at subsequent reexploration we found the fourth gland in the mediastinum. In 2 of 18 patients, recurrent hyperparathyroidism developed, which was defined as a serum PTH concentration of more than 21.1 pmol/L 1 year after surgery (11% recurrence rate). In one of these patients, further exploration of the neck was successful, with removal of a fifth hyperplastic parathyroid gland from the thymus. The second patient with recurrent disease has not undergone reoperation, but he is undergoing diagnostic evaluation to identify the site of recurrence. The diagnostic procedures (ultrasonography, scintigraphy, and arm-dependent serum PTH concentrations) excluded an autograft-dependent hyperparathyroidism.

Preoperative and Postoperative Data*

	Baseline	Postoperative Interval, mo						F	P
		1	6	12	24	36	48		
No. of cases	19	19	18	18	17	9	1	. . .	. . .
Laboratory test results									
Calcium, mmol/L	2.60 ± 0.07	2.09 ± 0.08	2.21 ± 0.06	2.35 ± 0.08	2.35 ± 0.05	2.34 ± 0.05	25	0.54	.77
PTH, pmol/L	131.7 ± 12.5	16.8 ± 7.8	16.2 ± 8.2	9.9 ± 2.2	11.8 ± 2.6	9.2 ± 2.1	2.3	26.89	<.001
Phosphorus, mmol/L	1.78 ± 0.12	1.09 ± 0.08	1.49 ± 0.08	1.76 ± 0.09	1.66 ± 0.10	1.74 ± 0.17	1.68	0.27	.93
ALP, U/L	919.5 ± 221.8	762.5 ± 171.8	370.9 ± 67.6	178.5 ± 22.6	237.7 ± 22.6	194.9 ± 29.5	204	1.76	.25
Clinical symptoms									
Bone pain	8.26 ± 0.30	3.05 ± 0.63	2.00 ± 0.64	1.61 ± 0.57	1.05 ± 0.39	0.22 ± 0.14	0.00	4.46	.046
Pruritus	4.57 ± 0.79	1.68 ± 0.67	1.61 ± 0.70	1.38 ± 0.61	1.05 ± 0.39	0.77 ± 0.40	0.00	1.00	.50
Muscle weakness	7.42 ± 0.52	3.21 ± 0.70	1.55 ± 0.62	0.66 ± 0.25	0.50 ± 0.24	0.00 ± 0.00	0.00	8.35	.01

*Data are given as mean ± SE. *F* and P values obtained by repeated measures analysis of variance. PTH indicates parathyroid hormone; ALP, alkaline phosphatase; and ellipses, not applicable. To convert calcium to milligrams per deciliter, divide by 0.25. To convert PTH to picograms per milliliter, divide by 0.1053. To convert phosphorus to milligrams per deciliter, divide by 0.3229.

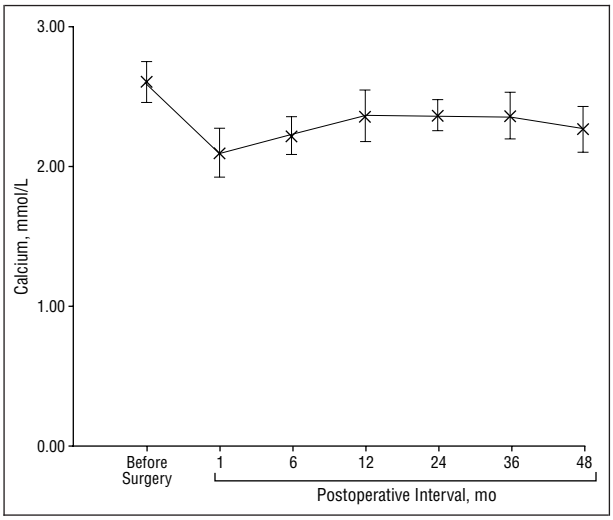

Figure 1. *Time trend of mean preoperative and postoperative serum calcium concentrations. Error bars represent 95% confidence intervals. To convert the calcium concentration from millimoles per liter to milligrams per deciliter, divide by 0.25.*

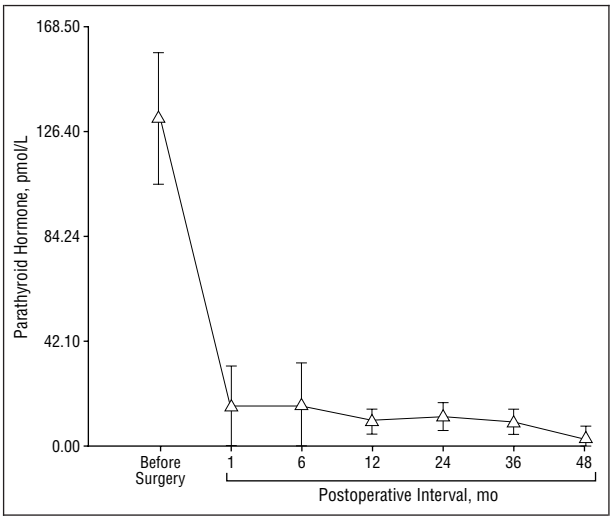

Figure 2. *Time trend of mean preoperative and postoperative serum parathyroid hormone concentrations. Error bars represent 95% confidence intervals. To convert the parathyroid hormone concentration from picomoles per liter to picograms per milliliter, divide by 0.1053.*

COMMENT

Secondary hyperparathyroidism is a classic feature of chronic renal failure. It is controlled in many patients by the use of calcium and vitamin cholecalciferol supplements, but this prophylactic therapy is not always effective. In such cases, we usually perform a total parathyroidectomy with autotransplantation. In all patients, a bone biopsy was performed to determine whether aluminum had accumulated in the bone. When this has occurred, it is important that a parathyroidectomy not be performed because symptoms will not improve, the patient's condition may deteriorate, and increased aluminum deposition may occur on the bone surfaces.[8] In the present series, good subjective improvement of symptoms was noted, similar to that reported in the literature.[4,9-11]

The most appropriate operation for secondary hyperparathyroidism remains a matter of debate. In theory, total parathyroidectomy with autotransplantation is better than subtotal parathyroidectomy, because recurrence in forearm autografts is more easily controlled by excision under local anesthesia. Cervical reoperations for recurrence in the neck are more invasive, require greater surgical expertise, and are associated with a substantial risk of hypoparathyroidism and damage to the recurrent laryngeal nerve. Some authors agree that total parathyroidectomy with autotransplantation complicates the issue when there is a recurrence, because in theory the offending parathyroid tissue may be in the neck, in the mediastinum, or at the site of the graft. On the other hand, when a subtotal parathyroidectomy has been performed, there are only 2 possible sites for the source of PTH. Casanova and coworkers[12] described a new and intriguing technique to solve the aforementioned problem. A complete ischemic blockade of the arm in which the graft was placed quickly reflects acute changes in the PTH concentration in cases of graft-dependent hyperparathyroidism. This finding is based on the short half-life of PTH, and the technique also permits the intraoperative monitoring of the effectiveness of the parathyroidectomy, even for secondary hyperparathyroidism.[13] Concentrations are determined by using a modified immunochemiluminometric assay. In the present series, intraoperative PTH concentrations were determined for the last 3 patients, and results are under evalu-

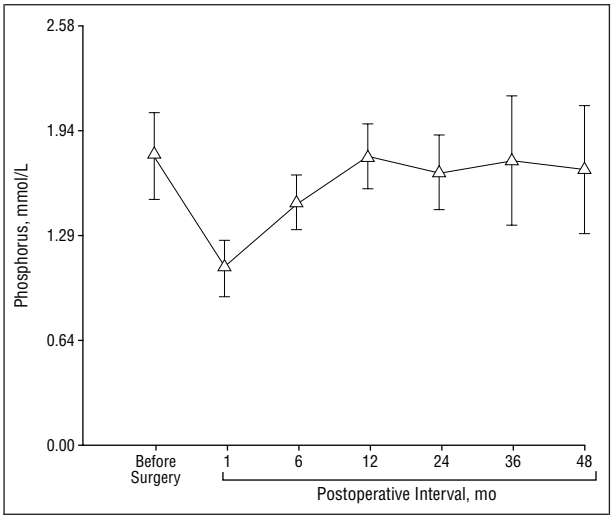

Figure 3. *Time trend of mean preoperative and postoperative serum phosphorus concentrations. Error bars represent 95% confidence intervals. To convert the phosphorus concentration from millimoles per liter to milligrams per deciliter, divide by 0.3229.*

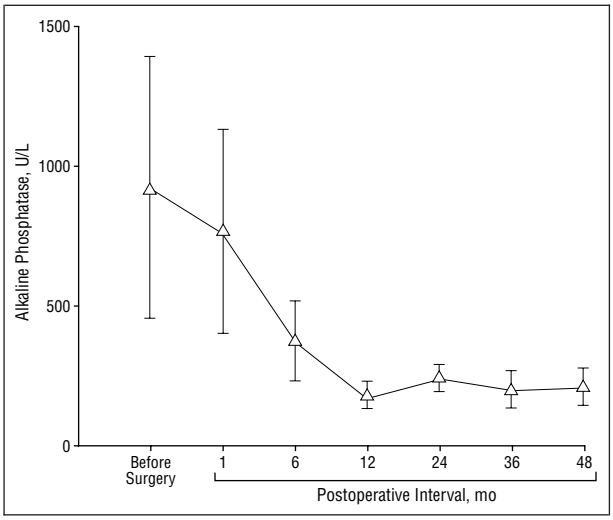

Figure 4. *Time trend of mean preoperative and postoperative serum alkaline phosphatase concentrations. Error bars represent 95% confidence intervals.*

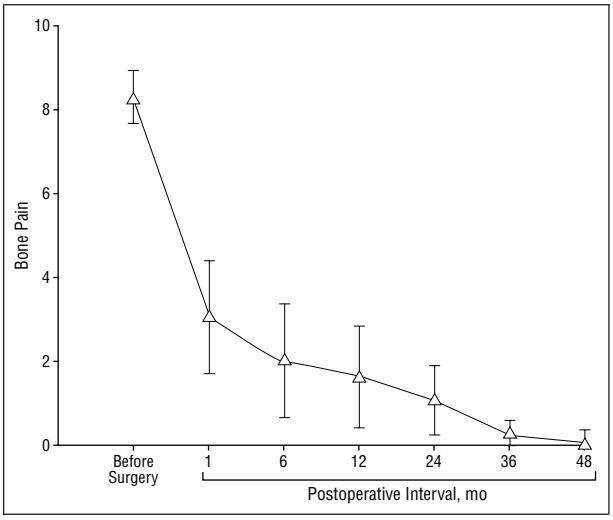

Figure 5. *Time trend of mean subjective intensity of bone pain. Error bars represent 95% confidence intervals. In visual analog scale, 0 indicates no pain; 10, worst pain ever experienced.*

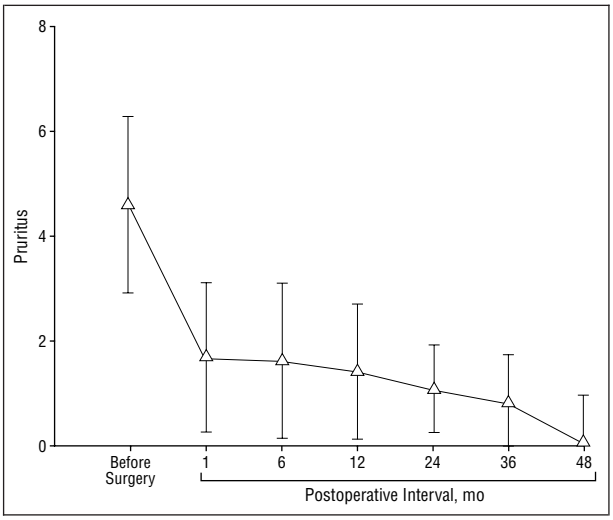

Figure 6. *Time trend of mean subjective intensity of pruritus. Error bars represent 95% confidence intervals. In visual analog scale, 0 indicates no pruritus; 10, worst pruritus ever experienced.*

ation. All 3 patients had substantial decreases in PTH concentrations 10 minutes after total parathyroidectomy (mean, 80% decrease). Long-term follow up and more experience gained by the authors and other groups[13] correlated with standard serum PTH concentration determinations, and results could make the method described helpful during parathyroidectomy for the treatment of secondary hyperparathyroidism.

Furthermore, according to some authors,[9,10] excision of grafted parathyroid tissue in case of graft hyperfunction is not a simple procedure, as the glandular tissue can infiltrate muscle planes, particularly in cases of nodular hyperplasia. Actually, this infiltration also can happen in the neck at the level of the parathyroid remnant. In fact, the capsule is opened, and, therefore, cells can spill and seed in the operative field, although the specimens are macroscopically removed.[14] Therefore, the risk of infiltration should not be used as an argument for one or another procedure, since it can be avoided by an adequate intraoperative histological examination. Intraoperative histological examination of the parathyroid glands is quick and easy to perform, and when performed by a skilled pathologist, it enables selection of the correct gland to be transplanted in the forearm. Hematoxylin-eosin, periodic acid–Schiff, and oil red O are the routine stains used for histological examination of frozen sections of the parathyroid glands. Pathologists determine whether the tissue submitted for intraoperative evaluation is parathyroid tissue, whether the parathyroid tissue is hyperplastic, whether the hyperplasia is nodular or diffuse, and whether the tissue selected is suitable for transplantation. The answers to these questions enable the surgeon to implant the appropriate tissue to avoid recurrent hyperparathyroidism from the graft and iatrogenic hypoparathyroidism. Recent findings enable the evaluation on frozen sections of the proliferative rate of the chief cells of each parathyroid gland. This can be performed by counting the Ki-67–positive cells with a simple 1-step immu-

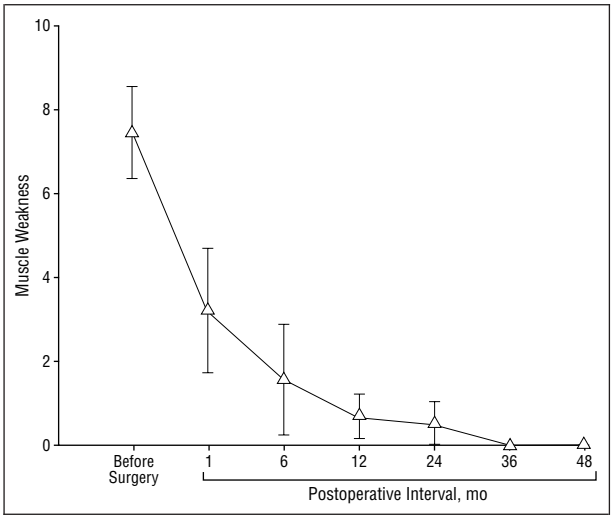

Figure 7. *Time trend of mean subjective intensity of muscle weakness. Error bars represent 95% confidence intervals. In visual analog scale, 0 indicates no muscle weakness; 10, worst muscle weakness ever experienced.*

noperoxidase stain. Studies are directed toward the shortening of time required for the immunostaining.

In our experience, total parathyroidectomy with autotransplantation effectively relieved the symptoms of hyperparathyroidism, and a low rate of recurrence of hyperparathyroidism was associated with this procedure. The method used for the surgical treatment of secondary hyperparathyroidism depends on the surgeon's preference, because the data reported in the literature indicate that all procedures described result in good control of clinical and biochemical variables. Further study is needed of the role of intraoperative monitoring of PTH concentrations and of the evaluation of the proliferative rate of the chief cells of the parathyroid glands on frozen sections.

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Invited Critique

Advanced secondary (renal) hyperparathyroidism (HPT) induced by long-standing chronic renal insufficiency can be a serious complication for patients receiving long-term hemodialysis. As Zaraca and colleagues have pointed out, parathyroidectomy is indicated for patients with advanced secondary HPT that is refractory to medical management; many patients feel dramatically better within days of the operation. The questions that remain, therefore, are when to operate and which operation to perform. Zaraca et al address the second question.

Since 1960, the surgical treatment of secondary HPT has evolved from total parathyroidectomy, to subtotal parathyroidectomy, to total parathyroidectomy with autotransplantation of a portion of 1 gland. The reason that all surgeons are not performing the same operation is that it is unclear which of the latter 2 of these operations has superior long-term results. Although most surgeons have abandoned total parathyroidectomy, numerous reports describe relatively equal short- and long-term clinical success rates for subtotal parathyroidectomy and total parathyroidectomy with autotransplantation (the latter is supported nicely in the article by Zaraca et al).

All patients with secondary HPT will have multigland disease, almost exclusively 4-gland hyperplasia. Because of this, all operations for the treatment of secondary HPT must include bilateral exploration and identification, biopsy, and removal of all 4 (or 3½) glands. There should be little if any use for localizing studies before neck exploration for the treatment of secondary HPT, and in fact, sestamibi scanning should not be used unless it is for reoperation to find a single recurrent gland. This is in stark contrast to patients with primary HPT, which is due to a single adenoma in 87% of patients.[1] Sestamibi scanning is extremely accurate for identifying single adenomas (specificity almost 100%),[1] so minimally invasive parathyroidectomies are now possible. As the newer techniques are embraced, surgeons must realize that secondary HPT has a completely different cause and is not suitable for minimally invasive unilateral operations.

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