Surgical Treatment of Hyperparathyroidism in Patients With Multiple Endocrine Neoplasia Type 1

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Hypothesis: Three-gland parathyroidectomy with transcervical thymectomy and cryopreservation is the preferred initial surgical approach for hyperparathyroidism (HPT) in patients with multiple endocrine neoplasia type 1.

Design: Retrospective cohort study.

Setting: Tertiary referral center.

Patients: Thirty-seven patients with multiple endocrine neoplasia type 1 who underwent 1 or more surgical procedures for HPT from January 1, 1973, to April 30, 2004.

Results: At initial parathyroid surgery, 16 (43%) of 37 patients had fewer than 3 parathyroid glands resected (group 1); 16 (43%), had at least 3 but fewer than 4 glands (group 2); and 5 (14%), 4 or more glands (group 3). Follow-up of at least 6 months after initial surgery was complete for 31 (84%) of 37 patients. Recurrent HPT developed in 20 (65%) of 31 at a median of 4 years. Reoperation for recurrent HPT was performed in 16 (52%) of 31, including 12 patients (75%) in group 1 and 4 (25%) in group 2. No patient in group 3 required reoperative cervical surgery. Permanent hypoparathyroidism occurred in 1 patient (3%), despite autograft of parathyroid tissue to the forearm.

Conclusions: Recurrent HPT in patients with multiple endocrine neoplasia type 1 is frequent if fewer than 3 glands are removed at initial parathyroidectomy. Optimal surgical intervention must balance the risk of recurrent hypercalcemia with the morbidity of permanent hypoparathyroidism. Three-gland parathyroidectomy, transcervical thymectomy, and parathyroid cryopreservation constitute our preferred initial surgical procedure.

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tial subtotal parathyroidectomy and parathyroid cryopreservation, reserving forearm autografting for the second cervical operation, at which time completion total parathyroidectomy is usually necessary.

The present study was undertaken to investigate the outcome of surgical treatment of HPT in our MEN1 population to confirm or refute current management recommendations. We analyzed all MEN1 patients who underwent 1 or more surgical procedures for HPT at our institution during a 30-year period.

**METHODS**

The current report includes 37 affected individuals from 23 unrelated MEN1 kindreds retrieved from the MEN1 database in the Department of Surgical Oncology at The University of Texas M. D. Anderson Cancer Center, Houston. In accordance with the institutional review board, this database was developed by retrospective review of medical records from January 1, 1973, to April 30, 2004. The clinical diagnosis of MEN1 was based on accepted criteria as previously published. All patients underwent at least 1 operation for HPT at our institution.

The presence or absence of HPT, pancreatic endocrine tumors, pituitary neoplasms, carcinoid tumors, neoplasms of the adrenal glands, and other phenotypic characteristics of MEN1 were determined as the need for calcium and cholecalciferol supplements or the upper limits of the reference range (36 of 37 patients) or by clinical symptoms of HPT and a known personal or family history of MEN1 (1 of 37 patients). Most patients underwent assessment using intact serum PTH measurements; a PTH level of 10 to 65 pg/mL was considered normal. However, because of the 30-year time frame during which data were collected, some PTH levels were assessed using different techniques, including measurement of C-terminal and intact PTH levels with various reference ranges. The diagnosis of HPT was confirmed by histological documentation of parathyroid hyperplasia after parathyroidectomy in all patients.

Patients were divided into 1 of 3 groups based on the extent of parathyroid resection at the initial operation. Group 1 included those patients who underwent initial surgical resection of fewer than 3 parathyroid glands; group 2 included those patients who underwent initial resection of at least 3 but fewer than 4 parathyroid glands; group 3 included those patients who underwent initial resection of 4 or more parathyroid glands.

Parathyroidectomy was performed through a standard collar incision. The extent of neck exploration and gland resection and performance of transcervical thymectomy or thyroid lobectomy was determined by the attending surgeon and based on the patient’s surgical history and available results of adjunctive studies such as preoperative localization and intraoperative PTH (IOPTH) levels. Intraoperative pathological confirmation of parathyroid tissue within the surgical specimen was routinely performed. The use of parathyroid autografting was individualized and based on the extent of parathyroid gland resection, viability of residual in situ parathyroid tissue, and, in some operations, the final postexcision IOPTH level. Parathyroid autografts were performed by placing a small amount of histologically confirmed parathyroid tissue into 1 or more small pockets created in the brachioradialis muscle of the forearm (early in the experience of our department, 2 patients had autografts placed in the pectoralis major muscle). Cryopreservation of parathyroid tissue was performed at the discretion of the surgeon.

Patients were required to have a 6-month minimum period of postoperative follow-up to be considered for evaluation. Clinical outcomes of eucalcemia, persistent or recurrent HPT, and permanent hypoparathyroidism were reported at (1) initial follow-up, which was defined as the first set of laboratory data obtained at least 6 months after the first parathyroidectomy, and (2) the last clinical or verbal follow-up or the time of death. Eucalcemia was defined as a serum calcium level of less than 10.2 mg/dL (<2.6 mmol/L) with a serum PTH level within the reference range as specified by the assay used. Hyperparathyroidism was defined as a serum calcium level of at least 10.2 mg/dL (≥2.6 mmol/L) (18 [90%] of 20 patients), or a calcium level within the reference range in the setting of an elevated PTH level (2 [10%] of 20 patients). Hyperparathyroidism identified at initial follow-up was defined as persistent disease, and HPT occurring more than 6 months after parathyroidectomy was considered recurrent disease. Hypoparathyroidism was defined as the need for calcium and cholecalciferol supplements to maintain a serum calcium level of at least 8.0 mg/dL (≥2.0 mmol/L) in the setting of an intact PTH level of less than 10 pg/mL. Hypoparathyroidism was considered to be permanent if these conditions persisted for a minimum of 6 months postoperatively or were present at last follow-up or at the time of death. For patients who underwent placement of a parathyroid autograft, function was confirmed by (1) differential measurement of regional PTH levels (both right and left antecubital veins) in patients with forearm autografts; or (2) the finding of eucalcemia with a serum intact PTH level of greater than 10 pg/mL in patients with a history of total parathyroidectomy (>4 parathyroid glands removed).

Mutation analysis of the MEN1 gene was limited to the proband within each kindred. Once a mutation was identified in the proband, all blood relatives with documented MEN1 were assigned the same genotype. For mutation analysis, blood was collected from affected individuals with informed consent. The DNA was isolated from whole blood samples using a commercially available blood or tissue kit (Qiagen, Chatsworth, Calif.). Polymerase chain reaction assays and DNA sequence analysis were performed as previously described. In all cases, a detected mutation was confirmed by sequencing the opposite strand of a second sample and by restriction digestion when possible.

**RESULTS**

Thirty-seven patients with MEN1 (15 men and 22 women) underwent a total of 61 operations for HPT from January 1, 1973, to April 30, 2004. At least 1 operation per patient was performed by the Department of Surgical Oncology at The University of Texas M. D. Anderson Cancer Center. In total, 51 (84%) of the 61 operations were performed at our institution, including the first parathyroidectomy in 29 (78%) of 37 patients. The demographics and disease characteristics of all patients are reported in Table 1. Each of the 37 patients belonged to 1 of 23 MEN1 kindreds, and individual testing for the MEN1 gene was performed in at least 1 relative from 18 kindreds. Mutations in the MEN1 gene were identified in 14 of 18 kindreds, corresponding to a mutation detection rate of 78% and a known MEN1 genotype in 28 (78%) of 37 patients. There were no kindreds with the same MEN1 mutation. Additional MEN1-related neoplasms included pancreatic/duodenal neuroendocrine tumors in 20 patients (54%), pituitary tumors in 18 (49%), carcinoid tumors in 4 (11%), and pheochromocytoma in 1 (3%).
The median initial preoperative serum calcium level was 11.0 mg/dL (2.8 mmol/L) (range, 9.3-14.3 mg/dL [2.3-3.6 mmol/L]), and the median serum phosphorus level was 2.8 mg/dL (0.9 mmol/L) (range, 1.7-3.9 mg/dL [0.5-1.3 mmol/L]). Serum PTH levels were available before the first recorded operation in 19 of the 37 patients with elevated levels (above the upper limit of the reference range) in 17 (89%). Results of 24-hour urinary calcium excretion were available for 19 of the 37 patients before the initial parathyroid operation, with a median calcium excretion level of 321 mg/TV (range, 82-11350 mg/TV).

Eight patients underwent diagnostic studies to assess bone mass at the time of initial diagnosis of HPT and before the first parathyroid surgery. For 2 patients who were treated many years ago, plain radiographs were obtained to assess thinning of cortical bone. Results determined that they did not have significant loss of bone mass. Formal bone mineral density (BMD) testing was performed in 6 patients (2 men and 4 women). Osteoporosis or osteopenia was identified in all 6 patients at a median age of 30 years (range, 18-61 years). The median serum calcium level at the time of the BMD evaluation in these 6 patients was 10.6 mg/dL (2.7 mmol/L) (range, 9.7-11.4 mg/dL [2.4-2.9 mmol/L]), with a median intact PTH level of 66 pg/mL (range, 9.7-11.4 mg/dL [2.4-2.9 mmol/L]), with a median intact PTH level of 66 pg/mL (range, 9.7-11.4 mg/dL [2.4-2.9 mmol/L]).

The surgical management and clinical outcomes of all 37 patients are shown in Figure 1, Table 2, and Table 3. Thirty-one (84%) of the 37 patients had adequate follow-up to be considered for evaluation. At initial follow-up, 27 (87%) of 31 patients were eucalemic.

Sixteen (43%) of 37 patients had fewer than 3 glands resected at the initial surgery (group 1). A serum calcium level of 10.2 mg/dL or above (≥2.6 mmol/L) was confirmed before the initial operation in 11 (69%) of 16 patients. At initial operation, a median of 1 parathyroid gland was removed (range, 1-2.75), transcervical thyrectomy was performed in 4 patients (25%), the IOPTH assay was used in 5 operations (31%), and a parathyroid autograft was placed in the forearm in 1 patient (6%). Thirteen (81%) of 16 were able to undergo evaluation (hereafter referred to as evaluable patients) for outcome analysis after the first parathyroid operation. At initial follow-up, 11 (85%) of the 13 evaluable patients were eucalemic, and 2 (15%) were hyperparathyroid. Of the 11 patients with a preoperative serum calcium level of 10.2 mg/dL or above (≥2.6 mmol/L), 9 (82%) were eucalemic after initial parathyroidectomy.
Persistent or recurrent HPT developed in 12 (92%) of the 13 evaluable group 1 patients at a median of 4 years after the initial parathyroidectomy. Ten (83%) of 12 patients underwent a total of 16 additional parathyroid operations with the first reoperation, occurring at a median of 5.7 years after the initial parathyroidectomy. The median number of parathyroid glands removed from all cumulative surgical procedures in group 1 patients was 3 (range, 1-5). In total, transcervical thymectomy was performed in 10 (63%) of 16 patients, and parathyroid autografts were performed in 9 (56%) of 16 patients. Postoperative hypoparathyroidism requiring repeat autografting with cryopreserved parathyroid tissue occurred in 1 patient after reoperative parathyroidectomy. The IOPTH assay was used in 11 (34%) of the total 32 operations performed in this group. At last follow-up, none of the 13 evaluable group 1 patients were hypoparathyroid, and 6 (46%) were eucalcemic at a median follow-up of 10.5 months (range, 6 months to 15.2 years) from their last parathyroidectomy after a total of 15 operations (Figure 1). Recurrent HPT was present in 4 (31%) of 13 evaluable patients after a total of 7 operations, and 3 patients had incomplete follow-up.

Sixteen (43%) of 37 patients had at least 3 but fewer than 4 parathyroid glands resected at the initial surgery (group 2). Fourteen (88%) of the 16 were evaluable for outcome analysis after the first parathyroid operation. A serum calcium level of 10.2 mg/dL or above (≥2.6 mmol/L) was confirmed before initial operation in all 14 evaluable patients. At initial operation a median of 3 parathyroid glands (range, 3-3.75) were removed, transcervical thymectomy was performed in 5 patients (31%), the IOPTH assay was used in 6 (38%) of 16 operations, and parathyroid autografts were placed at the time of initial operation in 7 patients (44%). At initial follow-up, 13 (93%) of the 14 evaluable patients were eucalcemic, and 1 (7%) was hyperparathyroid. Persistent or recurrent HPT was diagnosed in 6 (43%) of 14 evaluable group 2 patients at a median time of 4.6 years after the initial parathyroidectomy. Four (67%) of the 6 patients underwent 4 additional parathyroid operations, with the first reoperation occurring at a median of 9.4 years after the initial parathyroidectomy. The median number of parathyroid glands removed from all cumulative surgical procedures in group 2 patients was 3.3 (range, 3-3.75). In total, transcervical thymectomy was performed in 7 (44%) of 16 patients, and parathyroid autografts were performed in 8 (50%) of 16 patients. The IOPTH assay was used in 8 (40%) of the 20 operations performed in this group. Postoperative hypoparathyroidism developed in 2 (14%) of the 14 evaluable patients. One of these patients underwent successful repeat autografting with cryopreserved parathyroid tissue. At last follow-up, 1 (7%) of the 14 evaluable group 2 patients remained hypoparathyroid, and 9 (64%) were eucalcemic at a median follow-up of 3.0 years (range, 10 months to 15 years) from their last parathyroidectomy after a total of 12 operations (Figure 1). Recurrent HPT was present in 3 (21%) of 14 patients after a total of 5 operations, and 1 patient had incomplete follow-up.

Five patients (14%) underwent resection of 4 or more parathyroid glands at the initial surgery (group 3). A serum calcium level of 10.2 mg/dL or above (≥2.6 mmol/L) was confirmed before initial operation in all 4 evaluable patients. At initial operation a median of 3 parathyroid glands (range, 3-3.75) were removed, transcervical thymectomy was performed in 5 patients (31%), the IOPTH assay was used in 6 (38%) of 16 operations, and parathyroid autografts were placed at the time of initial operation in 7 patients (44%). At initial follow-up, 13 (93%) of the 14 evaluable patients were eucalcemic, and 1 (7%) was hyperparathyroid. Persistent or recurrent HPT was diagnosed in 6 (43%) of 14 evaluable group 2 patients at a median time of 4.6 years after the initial parathyroidectomy. Four (67%) of the 6 patients underwent 4 additional parathyroid operations, with the first reoperation occurring at a median of 9.4 years after the initial parathyroidectomy. The median number of parathyroid glands removed from all cumulative surgical procedures in group 2 patients was 3.3 (range, 3-3.75). In total, transcervical thymectomy was performed in 7 (44%) of 16 patients, and parathyroid autografts were performed in 8 (50%) of 16 patients. The IOPTH assay was used in 8 (40%) of the 20 operations performed in this group. Postoperative hypoparathyroidism developed in 2 (14%) of the 14 evaluable patients. One of these patients underwent successful repeat autografting with cryopreserved parathyroid tissue. At last follow-up, 1 (7%) of the 14 evaluable group 2 patients remained hypoparathyroid, and 9 (64%) were eucalcemic at a median follow-up of 3.0 years (range, 10 months to 15 years) from their last parathyroidectomy after a total of 12 operations (Figure 1). Recurrent HPT was present in 3 (21%) of 14 patients after a total of 5 operations, and 1 patient had incomplete follow-up.

Sixteen (43%) of 37 patients had at least 3 but fewer than 4 parathyroid glands resected at the initial surgery (group 2). Fourteen (88%) of the 16 were evaluable for outcome analysis after the first parathyroid operation. A serum calcium level of 10.2 mg/dL or above (≥2.6 mmol/L) was confirmed before initial operation in all 14 evaluable patients. At initial operation a median of 3 parathyroid glands (range, 3-3.75) were removed, transcervical thymectomy was performed in 5 patients (31%), the IOPTH assay was used in 6 (38%) of 16 operations, and parathyroid autografts were placed at the time of initial operation in 7 patients (44%). At initial follow-up, 13 (93%) of the 14 evaluable patients were eucalcemic, and 1 (7%) was hyperparathyroid. Persistent or recurrent HPT was diagnosed in 6 (43%) of 14 evaluable group 2 patients at a median time of 4.6 years after the initial parathyroidectomy. Four (67%) of the 6 patients underwent 4 additional parathyroid operations, with the first reoperation occurring at a median of 9.4 years after the initial parathyroidectomy. The median number of parathyroid glands removed from all cumulative surgical procedures in group 2 patients was 3.3 (range, 3-3.75). In total, transcervical thymectomy was performed in 7 (44%) of 16 patients, and parathyroid autografts were performed in 8 (50%) of 16 patients. The IOPTH assay was used in 8 (40%) of the 20 operations performed in this group. Postoperative hypoparathyroidism developed in 2 (14%) of the 14 evaluable patients. One of these patients underwent successful repeat autografting with cryopreserved parathyroid tissue. At last follow-up, 1 (7%) of the 14 evaluable group 2 patients remained hypoparathyroid, and 9 (64%) were eucalcemic at a median follow-up of 3.0 years (range, 10 months to 15 years) from their last parathyroidectomy after a total of 12 operations (Figure 1). Recurrent HPT was present in 3 (21%) of 14 patients after a total of 5 operations, and 1 patient had incomplete follow-up.
Transcervical thymectomy was performed in 3 (60%) of the 5 patients, and parathyroid autografts were placed at the time of initial operation in all 5 patients. The IOPTH assay was not used in any patient in this group at the time of initial operation. Four (80%) of 5 were evaluable for outcome analysis after the first parathyroid operation. At initial follow-up, 3 (75%) of 4 evaluable patients were eucalcemic, and 1 (25%) was hypoparathyroid, despite the placement of a parathyroid autograft.

Recurrent HPT developed in 2 (50%) of the 4 evaluable patients at a median of 4.6 years after initial parathyroidectomy. Recurrent HPT in both patients was attributed to hyperfunctioning of a parathyroid autograft, and both underwent debulking of the hyperfunctioning grafts. One patient subsequently required 2 additional debulking procedures during a total treatment course of 11 years. At last follow-up, both patients who required debulking procedures for recurrent HPT remained eucalcemic. Successful autograft revision was performed in the patient who was hypoparathyroid, and at last follow-up, all 4 evaluable patients were eucalcemic at a median of 7.3 years (range, 4.6-12.1 years) after their last parathyroidectomy.

In total, 25 parathyroid autografts were performed in 22 (59%) of 37 patients. All 22 patients had at least 3 parathyroid glands removed from the neck. Eleven autografts were performed in 10 patients who underwent resection of less than 4 parathyroid glands (median number from all cumulative surgical procedures, 3.2 [range, 3-3.75]). The remaining 14 autografts were placed in 12 patients who underwent resection of 4 or more parathyroid glands (median number from all cumulative surgical procedures, 4.1 [range, 4-5]). At the time of last follow-up, 15 (60%) of 25 autografts were confirmed to be functional, 1 (4%) was nonfunctional, and assessment was incomplete for 6 autografts (24%).

Permanent hypoparathyroidism occurred in 4 patients (18%), despite parathyroid autografting. Two patients required emergency treatment and hospital readmission for aggressive calcium management in addition to frequent outpatient visits and serial assessment of serum calcium levels. Three (75%) of the 4 patients underwent autograft revision with cryopreserved parathyroid tissue. Although all 3 revised autografts were ultimately successful, 2 had significant delay in return of function (2.5 and 4 years, respectively). At last follow-up, the fourth patient remains hypoparathyroid, receives calcium and cholecalciferol replacement therapy, and is relatively asymptomatic, with serum calcium levels ranging from 7 to 8 mg/dL (1.8-2.0 mmol/L), despite an undetectable serum PTH level.

The IOPTH assay was used in 20 patients during 20 operations, including 11 initial parathyroid operations (55%) and 9 reoperations (45%); 8 cervical reoperative parathyroidectomies and 1 forearm autograft debulking procedure. Autografts were performed in 8 operations in which the IOPTH assay was used, including 2 initial parathyroid operations and 6 reoperations. Follow-up of at least 6 months was available for 14 (70%) of these 20 operations. In Figure 2, final postexcision IOPTH values are displayed based on clinical outcome (eucalcemic, hypoparathyroid, and hyperparathyroid) at the initial (Figure 2A) and last (Figure 2B) follow-ups. Levels of IOPTH dropped to less than or equal to 35 pg/mL (see “Comment” section), or at least 90% of baseline during 15 (75%) of 20 operations. Furthermore, levels of IOPTH dropped to less than 15 pg/mL (the lowest detectable level at our institution) in 6 of these 15 operations. Eucalcemia was present at initial follow-up after 13 (93%) of the 14 evaluable operations with a median preincision IOPTH level of 99 pg/mL, a median final postexcision IOPTH level of 23 pg/mL, and a median percentage decline in IOPTH level of 77%. Postoperative hypoparathyroidism occurred (despite autograft placement) after 1 operation, during which a preincision IOPTH level of 130 pg/mL dropped to a postexcision IOPTH level of less than 15 pg/mL. There were no cases of persistent HPT at initial follow-up.

At last follow-up (Figure 2B), eucalcemia persisted without further surgical or medical intervention after 11 (79%) of 14 evaluable operations (median follow-up, 11 months [range, 6 months to 5 years]). The single patient with postoperative hypoparathyroidism under-
went autograft revision with cryopreserved parathyroid tissue and was eucalcemic at last follow-up. Recurrent HPT subsequently developed in 2 (15%) of the 13 patients who were eucalcemic at initial follow-up at 3 and 3.8 years postoperatively. In these 2 patients, the preincision IOPTH levels were 114 and 70 pg/mL; the postexcision IOPTH levels were 26 (77% decline) and 30 pg/mL (57% decline), respectively. At present, one patient is receiving medical therapy because of the lack of positive localization of the source of recurrent HPT. The other patient has mild hypercalcemia and is undergoing conservative management with serial monitoring of serum levels of calcium and PTH and BMD testing.

The presence of supernumerary glands was confirmed in 1 patient. After 3 parathyroid operations and removal of 5 parathyroid glands, including an ectopic gland within the thymus, HPT persists in this patient, indicating the presence of additional, hyperfunctioning parathyroid tissue in an autograft or other unknown site. Ectopic parathyroid glands were found in 8 (22%) of 37 patients. Six of the 8 ectopic glands were located in the thymus, 1 was intrathyroidal, and 1 was located in the paraesophageal region. Of 20 thymic glands removed, 6 (30%) were found to contain parathyroid tissue.

No clinically apparent permanent recurrent laryngeal nerve injuries were identified. One patient experienced temporary hoarseness after the second of 3 parathyroid operations, which resolved spontaneously. No other postoperative complications were identified.

**COMMENT**

This study illustrates the complexity of the surgical management of HPT in the setting of MEN1. Because surgery in patients with symptomatic or asymptomatic sporadic primary HPT is often curative, the indications for surgery are better defined and relatively well accepted. In contrast, indications for parathyroidectomy in asymptomatic patients with MEN1 and without Zollinger-Ellison syndrome (calcium can act as a secretagogue for gastrin) are less well defined. Although surgery is clearly indicated for patients with complications of hypercalcemia such as nephrolithiasis, some have suggested that surgery is not indicated in asymptomatic MEN1 patients with early HPT. Because MEN1-associated HPT occurs at an earlier age, is characterized by multigland hyperplasia, and is associated with a high rate of recurrent HPT after initial parathyroidectomy, physicians must carefully weigh the unique risks of surgery in patients with MEN1 against the potential benefits. These unique risks (relative to sporadic HPT) include persistent/recurrent HPT, the potential morbidity of multiple operations, and the risk and management challenges of postoperative hyperparathyroidism vs the potential benefits such as symptom relief and a reduced risk of progressive bone loss. Because MEN1-related HPT often occurs during the period of bone mass accretion, it also increases the relative risk of osteopenia. In fact, it has been shown that severe osteopenia can affect more than 40% of MEN1 patients with HPT, including patients with only mild, asymptomatic hypercalcemia. Despite the young median age of patients at the time of first operation in this report (32 years), those who had formal BMD testing before their initial parathyroid surgery already demonstrated significant bone loss, supporting the concern that continued observation in asymptomatic patients carries the risk of ongoing bone loss. Because surgery is the most effective strategy for preserving bone density in patients with HPT, BMD evaluation should play a significant role in the timing of parathyroid surgery in MEN1 patients. In addition, the neuropsychiatric manifestations of HPT may affect the MEN1 patient who is otherwise thought to be asymptomatic. Hyperparathyroidism is believed to affect sleep, cognition, mood, and overall quality of life. At present, there is growing support for using these symptoms to influence the timing of surgery for sporadic HPT. Although the impact of such symptoms on the timing of surgery for MEN1-associated HPT has not been well studied, it deserves consideration in the treatment of these patients.

Although it has been difficult to establish correlations between genotype and phenotype in MEN1, it is clear that mutations throughout the entire coding sequence of the MEN1 gene yield a near-absolute risk of HPT by 35 years of age. However, the age of onset and aggressiveness of HPT can vary considerably between and within MEN1 kindreds. For example, represented in the current series of patients is a kindred with a W341X (tryptophan to premature stop signal) MEN1 mutation with many affected relatives, all of whom have received a diagnosis of HPT based on clinical presentation or through family screening. One patient within this kindred underwent a total parathyroidectomy with autografts placed in the forearm and pectoralis muscle at 20 years of age. She subsequently required 3 debulking procedures involving both autograft sites during the course of 11 years to treat recurrent HPT. Therefore, when her first cousin received a diagnosis of HPT at 35 years of age, a total parathyroidectomy with forearm autografting was performed. However, the autograft was nonfunctional, and she required oral calcium and cholecalciferol therapy until she underwent successful reimplantation of cryopreserved parathyroid tissue 9 months later. Because of the difficulty in managing this second patient’s postoperative hypoparathyroidism, a third relative was treated with a subtotal parathyroidectomy (3.5-gland resection) at 35 years of age, and she remains eucalcemic after 5 years of follow-up. As exemplified by this kindred, additional genetic and/or environmental mechanisms likely play a role in the aggressiveness of HPT.

In the era of minimally invasive parathyroidectomy, the quality of preoperative imaging has greatly improved. Technetium Tc 99m sestamibi and computed tomographic (CT) imaging can identify parathyroid glands in ectopic locations. Although one could argue that preoperative localization in the MEN1 patient is unnecessary because a bilateral central compartment exploration will be performed, the presence of sestamibi localization to the anterior mediastinum will alert the surgeon to be particularly careful in the performance of a transcervical thymectomy. Similarly, CT imaging is particularly good at identifying enlarged superior parathyroid glands that have migrated into a paraesophageal location. Although such information may be of limited value to the experienced endocrine surgeon, the careful pre-
operative review of such imaging studies often focuses extra attention on the relevant surgical anatomy and aids in the development of a specific and detailed intraoperative plan. In this report, ectopic parathyroid glands were found in 8 (22%) of 37 patients. Of these, 6 were located in the thymus, 1 was intrathyroidal, and 1 was parascapheal.

In an attempt to avoid permanent hypoparathyroidism after the initial cervical operation that often occurs early in the patient’s life (median age of 32 years in the present series), we concur with previous authors that subtotal parathyroidectomy is preferred to total parathyroidectomy. However, as demonstrated in this report, reoperation is frequent in MEN1 patients. Although 27 (87%) of the 31 evaluable patients were eucalcemic after their initial parathyroid surgery, recurrent HPT occurred in 20 (64%) of 31 at a median of 4 years after their initial parathyroidectomy. Sixteen (80%) of these 20 patients have undergone a total of 24 additional parathyroid-related operations. At last follow-up (median, 4.7 years), recurrent HPT was again present in 7 (35%) of 20 patients. Therefore, at the first operation, we advocate removal of 3 of the 4 parathyroid glands and a transcervical thymectomy. The parathyroid gland of smallest size is typically left in situ. If the gland to be left in situ is not greater than 2 times normal size (7.0 x 3.0 mm; 40 mg), then it is left undisturbed; partial resection is considered for larger glands. Great care is taken when performing partial parathyroid resection so as not to seed the local region, resulting in inadvertent parathyroid autografting within the sternocleidomastoid muscle, sternothyroid muscle, or wall of the esophagus. Although such a risk may be largely theoretical, it can be minimized by gently placing a metallic clip across the parathyroid gland and dividing the gland sharply at that level. In addition, such a clip facilitates subsequent identification if reoperation is necessary.

The IOPTH assay was used as an adjunct in the surgical decision making for parathyroid gland resection in 20 operations (in 20 patients). Despite the relatively low rate of recurrent HPT after these 20 operations (10%), the true role for this technique in the surgical management of MEN1-associated HPT remains to be determined. The IOPTH assay may be of some utility in determining the need for subtotal resection of the parathyroid gland to remain in situ. However, specific recommendations for the use of this assay cannot be provided because of the limited clinical experience and the known difference in PTH kinetics in MEN1 patients. Although our data are largely anecdotal, we concur with the recent experience of Weber and colleagues, who suggested that a drop in IOPTH level to 35 pg/mL or less, or at least 90% of baseline, may be associated with postoperative eucalcemia. In general, we wait for a 20-minute postexcision PTH value after subtotal parathyroidectomy and transcervical thymectomy in contrast to 5- or 10-minute value in patients who have sporadic HPT due to a single parathyroid adenoma. In addition, in the presence of a well-vascularized single parathyroid gland remaining in situ, we would not perform a forearm autograft, even if the intraoperative PTH declines to less than 15 pg/mL (the lower limit of the reference range at our institution). Clearly surgeon experience is needed to make maximum use of available technology at the first operation, even when performing a subtotal parathyroidectomy.

The indications for reoperation are similar to the indications for initial neck exploration: the presence of symptoms, end-organ dysfunction, or a declining BMD. Preoperative localization is routine when considering a reoperation, and at our institution, we proceed with an imaging protocol consisting of a technetium Tc 99m sestamibi scan followed by cervical ultrasonography and CT or magnetic resonance imaging (MRI). If the sestamibi scan is positive, the ultrasonography and CT/MRI are focused on the area with positive sestamibi findings. We concur with the recommendation of Jaskowiak et al, who proceed with surgery if 2 or more radiographic studies provide concordant data consistent with positive localization. If localization is not successful, then selective venous sampling is performed. The decision to proceed with reoperation is based on the anticipated technical difficulty and potential morbidity of the surgery vs the morbidity of untreated HPT. If one is solely considering debulking of a forearm autograft, then the threshold to proceed with surgery is quite low. In contrast, a reoperative cervical operation would probably not be performed in a patient who was asymptomatic with mild hypercalcemia, no evidence of osteoporosis, and a presumed yet nonlocalized parathyroid gland in the neck. For example, we are currently treating a 40-year-old man with MEN1 and refractory hypercalcemia after 3 cervical operations and resection of a total of 5 parathyroid glands. Despite extensive and repeated attempts to localize the source of the elevated PTH level, including sestamibi imaging, venous sampling of the great vessels, neck and antracubital veins, ultrasonography, CT, and MRI, concordant data consistent with positive localization have not been found. The patient therefore started calcimimetic medical therapy with cinacalcet hydrochloride and is currently asymptomatic and normocalcemic.

Although there are no approved medical treatments for primary HPT, nonsurgical alternatives are desirable for high-risk or complicated patients such as the 40-year-old man just described. Estrogen therapy has been used with some evidence to suggest a modest reduction in serum calcium level and increased bone density. In addition, the bisphosphonate alendronate sodium has been shown to increase bone mass in patients with primary HPT. However, estrogen therapy and bisphosphonates do not address the elevated PTH level. More recently, a randomized, double-blinded, placebo-controlled study by Shoback et al showed that the calcimimetic agent cinacalcet normalized serum calcium levels and lowered serum levels of PTH. Twenty-two patients with primary HPT were randomized to receive twice-daily dosing of 30, 40, or 50 mg of cinacalcet hydrochloride or placebo for 15 days. Cinacalcet caused persistent normalization of serum calcium levels at all dosages. Similarly, significant reductions in PTH levels were observed at all cinacalcet dosages as compared with placebo. No significant increase in 24-hour urine calcium excretion was noted in the cinacalcet group, and there were no significant adverse events during the study. Longer-term studies to assess the ability of cinacalcet to control serum calcium and PTH levels in patients with primary HPT are ongoing.
In addition to the medical management of recurrent hypercalcemia, there has been limited published experience with percutaneous alcohol ablation of successfully localized parathyroid glands. In a study by Harman et al,25 36 patients with primary HPT underwent alcohol ablation; 22 were identified as having sporadic adenomas and 14 had multigland disease (including 5 with MEN). Indications for alcohol ablation included concomitant medical comorbidities in 23 patients, multiple previous operations in 7, and patient preference in 6. Using ultrasound guidance, 95% ethanol was injected directly into the involved parathyroid gland(s). Twenty-nine patients underwent complete and 7 underwent partial ablation. Ten patients (34%) who underwent complete ablation and 2 (29%) who underwent partial ablation had a serum calcium level within the reference range after the procedure. Temporary recurrent laryngeal nerve palsy was reported in 2 patients, and 4 patients had temporary hypocalcemia. The authors concluded that alcohol ablation should be considered for patients with excessive reoperative morbidity or medical comorbidity, particularly if partial ablation of a single remaining parathyroid gland is considered.

Twenty-five parathyroid autografts were placed in 22 of 37 patients, with function confirmed at last follow-up in 15 (94%) of 16 evaluable autografts. This experience, while anecdotal, is in contrast to the reported literature in which approximately 20% of autografts in MEN1 patients fail to function, resulting in permanent hypoparathyroidism.3,7 In the absence of bilateral antecubital PTH levels or proven hypoparathyroidism (before autograft placement), one cannot be sure that the autograft works; this is a major problem with the reported literature on this subject. Although we encountered permanent postoperative hypoparathyroidism in 4 patients, 3 became eucalcemic after reimplantation of cryopreserved parathyroid tissue. Our experience also documented a significant delay in autograft function in 2 patients in whom functional parathyroid autografts developed 2.5 and 4 years after reimplantation. The time course of recovery of 1 patient’s autograft is shown in Figure 3. This patient is a 68-year-old woman who underwent her first parathyroid operation (subtotal parathyroidectomy) in 1973. Recurrent HPT developed, and she underwent completion total parathyroidectomy with left forearm autograft and cryopreservation for recurrent hyperparathyroidism (HPT). After this operation, the patient was hypoparathyroid (serum parathyroid hormone [PTH] level, <15 pg/mL) and dependent on calcium and cholecalciferol (vitamin D) replacement therapy. Two years later, reimplantation of cryopreserved parathyroid tissue was performed. Despite a differential increase in the serum PTH level drawn from the left antecubital fossa, it was not until 4 years after autograft revision that the serum PTH level supported eucalcemia without supplemental cholecalciferol therapy.

Figure 3. Delayed recovery of autograft function in a patient with multiple endocrine neoplasia type 1 (MEN1) after completion total parathyroidectomy with left forearm autograft and cryopreservation for recurrent hyperparathyroidism (HPT). After this operation, the patient was hypoparathyroid (serum parathyroid hormone [PTH] level, <15 pg/mL) and dependent on calcium and cholecalciferol (vitamin D) replacement therapy. Two years later, reimplantation of cryopreserved parathyroid tissue was performed. Despite a differential increase in the serum PTH level drawn from the left antecubital fossa, it was not until 4 years after autograft revision that the serum PTH level supported eucalcemia without supplemental cholecalciferol therapy.

Autograft hyperfunction occurred in 3 patients, 2 of whom underwent autograft debulking ultimately resulting in eucalcemia. The reported incidence of recurrent HPT due to autonomous function of parathyroid autografts ranges from 3% to 30%.25,26 Although there are some reports of autonomously functioning autografts from normal parathyroid glands,26 most cases have occurred in patients with MEN1, familial multigland hyperplasia, or transplantation of adenomatous glands.24,25,26,30,32 This finding is not surprising given the recent evidence that parathyroid hyperplasia in MEN1 is likely driven by the humoral mitogen basic fibroblastic growth factor.33,34 Therefore, some authors have advocated transplanting smaller amounts of parathyroid tissue with cryopreservation of additional tissue in the event that the smaller grafts are not sufficient.20 Despite the potential for recurrent HPT, parathyroid autografts are the only way to avoid permanent hypoparathyroidism after a total parathyroidectomy. Furthermore, for patients in whom recurrent HPT develops from a hyperfunctioning forearm autograft, surgery is much easier than a reoperation on the neck. Our technique for debulking the forearm autograft uses intraoperative ultrasonography and the IOPTH assay. Intraoperative ultrasonography is extremely useful in creating a 3-dimensional appreciation for the autograft allowing for satisfactory debulking. The autograft is usually embedded within the brachioradialis muscle, making its dimensions difficult to appreciate in the absence of ultrasonographic evaluation. Other potential adjuncts to autograft debulking include the use of preoperative sestamibi localization and intraoperative gamma probe identification.

Although we acknowledge the known shortcomings of long-term, retrospective cohort studies, based on the findings of this review we concur with previous authors who recommend subtotal parathyroidectomy as the initial operation in MEN1 patients with primary HPT.1,5 We would not perform a forearm autograft at the initial operation, assuming a portion of 1 gland is clearly visible in situ. This avoids the complication of autograft hyperfunction and the need to determine whether recurrent HPT is secondary to the autograft in the forearm or the remaining parathyroid gland in the neck. If recurrent HPT develops after an initial subtotal parathyroidectomy, completion total parathyroidectomy is performed by removing the remaining parathyroid gland in the neck. At
that time, forearm autografting is mandatory. The decision to proceed with reoperative completion total parathyroidectomy should be made with the knowledge that some autografts will not function, resulting in permanent hypoparathyroidism and the need for long-term administration of calcium and cholecalciferol.

The controversy of subtotal vs total parathyroidectomy has received far greater attention than the indication for initial parathyroidectomy, which remains relatively poorly defined in the MEN1 patient. Careful assessment of end-organ function, especially BMD evaluation, is critically important in the decision to proceed with the initial operation as well as reoperation. In the asymptomatic patient with a mild elevation in serum calcium level (<1 mg/dL [=<0.3 mmol/L] above the upper limit of the reference range), the need for parathyroidectomy should be based on the findings from serial BMD evaluations. Our data illustrate the complexity of managing HPT in the setting of MEN1 and emphasize the need for accurate patient assessment, high-quality localization studies, and a clear surgical plan consisting of initial subtotal parathyroidectomy, transcervical thymectomy, and cryopreservation of all surgically excised parathyroid glands. If reoperative completion total parathyroidectomy is necessary, forearm autografting is performed at that time.

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REFERENCES


