

Limited Parathyroidectomy in Multiple Endocrine Neoplasia Type 1-Associated Primary Hyperparathyroidism: A Setup for Failure

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ABSTRACT

Background. Recently, some surgeons have suggested that minimally invasive parathyroidectomy guided by preoperative localizing studies of patients with multiple endocrine neoplasia type 1 (MEN1)-associated primary hyperparathyroidism (pHPT) provides an acceptable outcome while minimizing the risk of hypoparathyroidism. This study aimed to evaluate the outcome for MEN1 patients who underwent limited parathyroidectomy compared with subtotal parathyroidectomy.

Methods. The authors performed a retrospective analysis of 99 patients with MEN1-associated pHPT who underwent at least one parathyroid operation at their institution. Preoperative imaging studies, intraoperative findings, and clinical outcomes for patients were compared.

Results. A total of 99 patients underwent 146 operations. Persistent pHPT was significantly higher in patients whose initial operations involved removal of 1 or 2 glands (69 %) or 2.5 to 3 glands (20 %) compared with those who had 3.5 or more glands removed (6 %) ($P < 0.01$). Persistent pHPT occurred in 5 % of all operations that cumulatively removed 3.5 or more parathyroid glands compared with 40 % of operations that removed 3 or fewer glands ($P < 0.01$).

The single largest parathyroid gland was correctly identified preoperatively in 69 % (22/32) of the patients. However, preoperative localizing studies missed enlarged contralateral parathyroid glands in 86 % (19/22) of these patients. Preoperative localizing studies missed the largest contralateral parathyroid gland in 16 % (5/32) of the patients.

Conclusions. Limited parathyroidectomy in MEN1 is associated with a high failure rate and should not be performed. Preoperative identification of a single enlarged parathyroid gland in MEN1 is not reliable enough to justify unilateral neck exploration because additional enlarged contralateral parathyroid glands are frequently missed.

Multiple endocrine neoplasia syndrome type 1 (MEN1) is the most common cause of familial pHPT, which accounts for 1–5 % of all pHPT cases.^{1–4} An autosomal dominant hereditary disorder, MEN1 is caused by a germline mutation in the *MEN1* tumor suppressor gene, with a prevalence of two to three cases per 100,000.⁵ In MEN1 patients, pHPT is the most prevalent endocrinopathy, occurring in 80–90 % of MEN1 cases.⁶ In contrast to sporadic pHPT, MEN1-associated pHPT commonly presents with multigland parathyroid disease, with mono- or oligoclonal asymmetric and asynchronous enlargement of parathyroid glands.^{7,8} The goals of parathyroidectomy in the treatment of MEN1-associated pHPT are to provide a durable biochemical remission [eucalcemia and normal parathyroid hormone (PTH) level] and to minimize the occurrence of permanent hypoparathyroidism.

Bilateral neck exploration (BNE) with 3.5-gland subtotal parathyroidectomy and cervical thymectomy or total

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parathyroidectomy with thymectomy and parathyroid autotransplantation are the optimal treatment strategies recommended by several investigators.^{9–11} Compared with sporadic pHPT, the rates of persistent and recurrent pHPT in MEN1-associated pHPT are high, varying from 14 to 69%.^{12–16} The surgical approach for patients with sporadic pHPT has shifted in some centers to a limited parathyroidectomy (also referred to as minimally invasive or focused parathyroidectomy) due to improved accuracy of current preoperative localizing studies and intraoperative PTH monitoring to confirm biochemical cure. The focused approach for sporadic pHPT has resulted in cure rates similar to those obtained by BNE.¹⁷ However, the role of a limited parathyroidectomy for patients with MEN1-associated pHPT remains unclear.

Higher rates of persistent pHPT and shorter times to recurrence were observed in patients with MEN1-associated pHPT who underwent less than subtotal parathyroidectomy (<3 glands removed).^{10,11} However, high rates of permanent hypoparathyroidism have been reported after subtotal or total parathyroidectomy with autotransplantation (25–50%).^{12–16,18} Therefore, some surgeons have recently suggested that focused or minimally invasive parathyroidectomy, based on preoperative localizing studies provides comparable rates of eucalcemia with a lower risk of hypoparathyroidism.^{19,20} In addition, it has been suggested that the operation for recurrent disease on the contralateral side after a limited parathyroidectomy could be easier due to minimal scar tissue development because the risk of recurrent pHPT is high. Thus, this study aimed to evaluate and compare the outcomes of patients with MEN1-associated pHPT who underwent limited versus subtotal parathyroidectomy.

METHODS

We performed a retrospective analysis of 99 patients with a diagnosis of MEN1 who had undergone at least one parathyroidectomy for pHPT from December 1993 to January 2013 at the National Institutes of Health (NIH) Clinical Center. The study was approved by the Office of Human Subject Research at the NIH. All patients provided written informed consent.

The MEN1 diagnosis was made based on clinical presentations, the presence of *MEN1* germline mutation, or both.²¹ All patients underwent screening and surveillance tests for other manifestations of MEN1, per published guidelines.²²

The diagnosis of pHPT was made based on the presence of hypercalcemia (albumin-corrected total calcium, ionized calcium, or both) and inappropriately elevated intact PTH in the absence of hypocalciuria or a family history of familial hypocalciuric hypercalcemia. All preoperative

localizing studies were performed at the NIH Clinical Center under a clinical research protocol regardless of the results from the localization studies conducted at the referring institutions. Of the patients in this cohort, 50% who had prior parathyroidectomy with one or two glands removed at outside institutions were known or suspected to have MEN1 syndrome at the time of initial parathyroidectomy. The diagnosis of the remaining patients was determined after initial parathyroidectomy.

Once the diagnosis of MEN1-associated pHPT was confirmed and the patients fulfilled the indications for parathyroidectomy, preoperative neck ultrasound (US) and Tc99 m-sestamibi (MIBI) scans were recommended to all patients per clinical research protocol. Additional localizing studies were performed selectively as clinically indicated. The technical details of the localizing studies used were as previously described.^{23,24}

The MIBI scan was performed with I123 thyroid subtraction and 20 mCi of technetium Tc99 m-sestamibi. Early and delayed images of the neck and chest, including pinhole images, were obtained, followed by single-photon-emission computed tomography (CT) imaging (SPECT/CT).²⁵ The results of imaging studies available at the time of surgery were collected without additional re-review.

All the patients who underwent an initial parathyroidectomy at our institution underwent BNE and subtotal parathyroidectomy. Cervical thymectomy was performed for 87% (59/68) of the patients. Parathyroid tissue cryopreservation was performed in all cases. Intraoperative PTH assay has been used at the NIH Clinical Center since 1997.

Intraoperative diagnosis of the parathyroid gland was performed by frozen section tissue analysis. We assessed the number of parathyroid glands removed by reviewing surgical pathology reports. Limited parathyroidectomy was defined as one or two parathyroid glands removed at the initial operation.

Persistent pHPT was defined as pHPT that occurred within 6 months postoperatively and recurrent pHPT as pHPT that developed after 6 months. Permanent hypoparathyroidism was defined as low calcium and PTH levels in any patient who continued to receive calcium and/or vitamin D analogue replacements for more than 6 months postoperatively. Follow-up time longer than 6 months was available for 68.5% (100/146) of the operations. Postoperative follow-up assessment was performed by telephone contact with the patient or the referring physician or by evaluation at the NIH Clinical Center.

Fisher's exact test and the chi-square test were used to assess the differences between patient outcomes by the number of glands removed. One-way analysis of variance (ANOVA) and the Mann-Whitney *U* test were used to compare the follow-up times by the number of glands

removed. A two-tailed P value lower than 0.05 was considered statistically significant. We used persistent pHPT as the primary outcome measure in this study. Statistical analysis was performed using SPSS v16.0 for Windows (SPSS, Inc., Chicago, IL, USA).

RESULTS

A total of 99 patients underwent 146 operations at the NIH Clinical Center and outside institutions. Of these patients, 28 had two operations, 8 had three operations, and 1 had four operations for persistent or recurrent pHPT or permanent hypoparathyroidism at the NIH Clinical Center and outside institutions. At the NIH Clinical Center, 68 of the patients had their initial parathyroidectomies performed and 37 had their reoperations performed (Fig. 1). Two patients who had their initial parathyroidectomy at the NIH Clinical Center underwent three reoperations for persistent and recurrent pHPT. The first patient who had persistent pHPT was in biochemical remission for 3 years and required a third operation for recurrent pHPT.

The preoperative clinical characteristics of the patients with MEN1-associated pHPT who had initial parathyroidectomies at the NIH are summarized in Table 1. About half (54 %) of the patients had 3.5 or more parathyroid glands removed. Only one patient had more than 3.5 parathyroid glands removed, with 5 enlarged parathyroid glands identified and 4.5 glands resected. The supernumerary gland was in the thymus. The remaining patients had three or fewer glands removed because surgeons were not able to identify the missing gland or glands. The initial operation for 31 patients was performed at an outside institution (Fig. 2). The median follow-up time for this cohort was 23 months. The follow-up time did not differ based on the number of glands removed (≤ 3 vs ≥ 3.5 glands, $P = 0.11$; 1–2 vs 2.5–3 vs ≥ 3.5 glands, $P = 0.11$). Of 68 patients, 64 (94 %) who underwent an initial parathyroidectomy had at least one preoperative localizing study performed, whereas the remaining four patients had

no preoperative localizing study. The scans included US for 94 % (60/64) of the patients, MIBI for 91 % (58/64), CT for 36 % (23/64), and magnetic resonance imaging (MRI) for 19 % (12/64).

In combination, preoperative localizing studies correctly identified one enlarged gland in 32 patients, two enlarged glands in 17 patients, and three enlarged glands in 11 patients. Four enlarged glands were not identified in any patient.

Preoperative localizing studies performed for 64 patients failed to identify any enlarged glands in four patients (Fig. 2). The performance of preoperative localizing studies in detecting enlarged parathyroid glands in this cohort has been reported previously.²³ No supernumerary glands were identified by preoperative localizing studies in the patient with MEN-1-associated pHPT undergoing initial parathyroidectomy. No thymic neuroendocrine tumor was found on cervical thymectomy. Of 59 patients, 16 (27.1 %) had 18 enlarged parathyroid glands in the thymus.

Of 32 patients whose preoperative localizing studies identified one enlarged parathyroid gland before their initial parathyroidectomy, 8 (25 %) had 1 or 2 enlarged glands removed, 12 (37.5 %) had 2.5 to 3 enlarged glands removed, and 12 (37.5 %) had 3.5 or more enlarged glands removed. For 69 % (22/32) of the patients, the single largest parathyroid gland was correctly identified preoperatively. However, of the patients with the single largest gland correctly identified preoperatively, preoperative localizing studies missed enlarged contralateral parathyroid glands in 87 % (19/22) of the cases. Preoperative localizing studies did not identify the largest parathyroid gland in 10 patients, and the largest gland was found on the contralateral side in 16 % (5/32) of the patients.

We observed higher rates of persistent pHPT in patients with MEN1-associated pHPT who had 1 or 2 parathyroid glands removed at initial parathyroidectomy (69 %, 11/16) than in those who had 2.5 to 3 glands removed (19 %, 4/21) ($P < 0.01$). The rate of persistent pHPT was

FIG. 1 Flow diagram demonstrating treatment for patients with multiple endocrine neoplasia type 1 (MEN1)-associated (pHPT) in the cohort.¹ Primary hyperparathyroidism

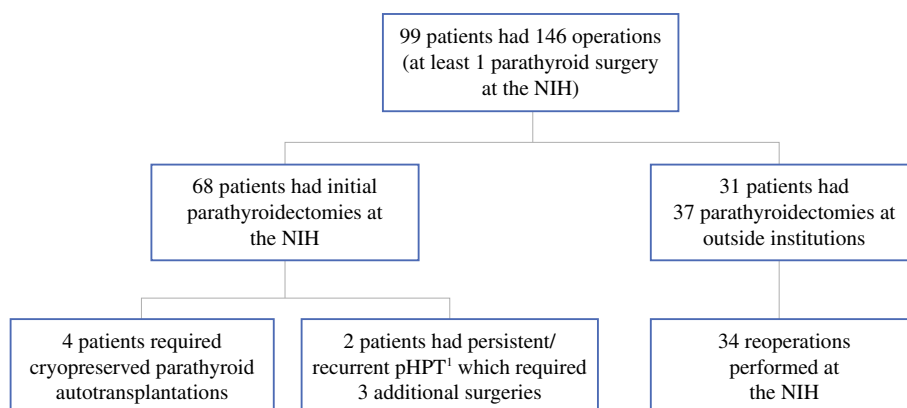


TABLE 1 Preoperative clinical characteristics by the number of parathyroid glands removed in patients with multiple endocrine neoplasia type 1 (MEN1)-associated primary hyperparathyroidism (pHPT) undergoing initial parathyroidectomy at the National Institutes of Health (NIH)

Parameters ^a	No. of parathyroid glands removed		
	≤2 (n = 10)	2.5–3 (n = 21)	≥3.5 (n = 37) ^b
Male: n (%)	4 (40)	9 (43)	20 (54)
Median age (years) range	31 (23–78)	33 (13–67)	34 (15–74)
Serum creatinine: mg/dl (RR 0.7–1.3 mg/ml)	0.8	0.9	0.8
Ionized calcium: mmol/l (RR 1.12–1.32 mmol/l)	1.50	1.56	1.55
Corrected total calcium: mg/dl (RR 8.2–10.0 mg/dl)	10.9	11.0	11.0
Phosphorous: mg/dl (RR 2.5–4.8 mg/dl)	3.0	3.3	2.9
24 h urine calcium: mg (RR 50–250 mg)	360	334	388
Mean DEXA T score ^c	–2.6	–2.0	–2.0

RR reference range, DEXA dual-energy X-ray absorptiometry

^a Biochemical parameters are presented as means

^b One patient had five enlarged parathyroid glands identified, and 4.5 glands were removed. The supernumerary gland was in the thymus

^c The lowest T scores were used

FIG. 2 Flow diagram demonstrating preoperative localizing studies of patients with multiple endocrine neoplasia type 1 (MEN1)-associated primary hyperparathyroidism (pHPT) in the cohort who underwent at least one parathyroidectomy at the National Institutes of Health (NIH)

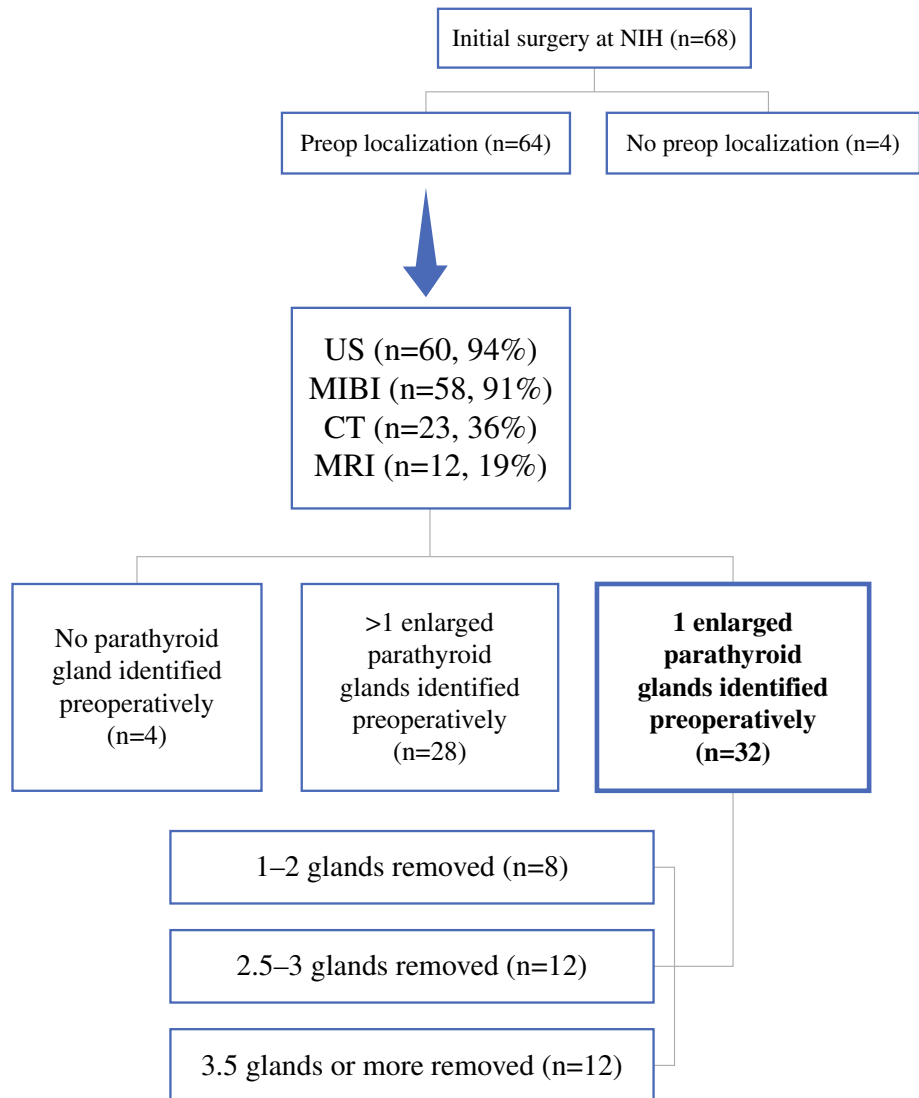


TABLE 2 Comparison of biochemical outcomes after initial parathyroidectomy performed at the National Institutes of Health (NIH) clinical center and at outside institutions by the number of glands removed

	Patients by no. of parathyroid glands removed ^a <i>n</i> (%)			Total	<i>P</i> Value
	≤2	2.5–3	≥3.5		
Outcome					
Persistent pHPT	11 (69)	4 (19)	2 (6)	17	<0.01
Recurrent pHPT	3 (18)	4 (19)	13 (42)	20	0.24
Biochemical remission ^b	2 (12)	8 (38)	14 (45)	24	0.08
Permanent hypoparathyroidism	0	5 (23.8)	2 (6.4)	7	0.04
Total	16	21	31	68	

Numbers highlighted in bold represent statistically significant *p* values

Patients with a follow-up period shorter than 6 months were not included in the outcome analysis

pHPT primary hyperparathyroidism

^a No statistically significant difference in the number of patients with insufficient follow-up was found between the groups

^b Absence of biochemical evidence of pHPT

significantly lower for the patients who underwent initial removal of 3.5 or more parathyroid glands (6 %, 2/31) than for those who had 3 or fewer glands removed (41 %, 15/37) ($P < 0.01$) (Table 2).

Of 37 reoperative parathyroidectomies performed at the NIH Clinical Center, 17 were for persistent pHPT. Two patients continued to have persistent pHPT after the second operation. Each had one gland removed during their initial parathyroidectomy, performed at outside institutions, followed by the removal of one and two glands, respectively, during a second operation for each patient, performed at the NIH. None of the ten patients who had 3.5 or more parathyroid glands cumulatively removed experienced persistent pHPT.

The rate of persistent pHPT was analyzed by the cumulative number of glands removed (including those removed before participation in our study) after each operation, and we found a significantly lower rate of persistent pHPT in the patients with 3.5 glands or more cumulatively removed (5 %, 3/55) than in those who had 2 or fewer glands removed (57 %, 12/21) ($P < 0.01$) or in those who had 2.5 to 3 glands removed (5 vs 45 %, 5/11; $P < 0.01$). The rate of persistent pHPT did not differ significantly between those who had 2 or fewer glands removed and those who had 2.5 to 3 glands removed (57 vs 45 %; $P = 0.71$).

Permanent hypoparathyroidism after the initial operation occurred for seven patients (10 %), and four patients (6 %) underwent cryopreserved parathyroid autotransplantation. Of the seven patients who experienced permanent hypoparathyroidism, two had 3.5 parathyroid glands removed and five had 2.5 to 3 glands removed. The rate of permanent hypoparathyroidism was significantly lower for the patients who had two or fewer glands removed ($P = 0.04$) (Table 1). None of the patients

experienced recurrent laryngeal nerve injury or postoperative bleeding.

DISCUSSION

The goal of parathyroidectomy for patients with MEN1-associated pHPT is to provide a durable eucalcemia with the fewest number of operations and a low rate of permanent hypoparathyroidism. With the widespread use of the focused-approach parathyroidectomy in patients with sporadic pHPT and good results, a few investigators recently have suggested that limited neck exploration and parathyroidectomy also is the optimal surgical treatment for patients with MEN1-associated pHPT.^{19,20} Of 32 patients in this study who would have been potential candidates for a limited exploration because preoperative localizing studies identified a single enlarged parathyroid gland, 86 % had additional enlarged contralateral parathyroid tumors. Of the ten remaining patients, five had their largest parathyroid gland identified intraoperatively on the contralateral side, which would have been missed if they had undergone a limited or unilateral exploration guided by preoperative localizing studies. Furthermore, the rate of persistent pHPT was significantly higher (41 %) when three or fewer glands were removed at the initial operation, compared with 3.5 or more glands removed (6 %). Both patients who continued to have persistent pHPT after their second parathyroidectomy each had one gland removed at their initial operation, suggesting that the initial single-gland removal was inadequate and may have led to failure of a second operation because reoperative parathyroidectomy often is focused on a single gland, guided by localizing studies.

The findings from our relatively large cohort support the use of subtotal parathyroidectomy for patients with MEN1-

associated pHPT who are undergoing initial parathyroidectomy due to the higher rate of persistent pHPT observed in patients from our cohort who had three or fewer glands removed. In contrast to our study, Vernick et al.¹⁹ demonstrated a remission rate in a small cohort of patients who underwent the focused-approach parathyroidectomy ($n = 19$) comparable with that for subtotal and total parathyroidectomy treatment of MEN1-associated pHPT. The use of a limited parathyroidectomy for patients with familial pHPT ($n = 34$) guided by preoperative localizing studies resulted in a rate of persistent pHPT similar to that for sporadic disease, but only five patients in this study had MEN1-associated pHPT. However, the rate of recurrent disease in the familial pHPT patients (9 %) was higher than in those with sporadic pHPT (1 %) (median follow-up period, 39 months).²⁰ The recurrence rate in our study was 21 %, comparable with the rate in other studies.^{26–28}

Although limited initial parathyroidectomy for MEN1-associated pHPT may facilitate the operation for recurrent pHPT because of minimal scar tissue development on the contralateral side, the rate of persistent pHPT after initial removal of one or two enlarged parathyroid glands in our study was unacceptably high, consistent with other series.¹¹ The results in the current study emphasize that the routine use of preoperative localizing studies provide little benefit to patients with MEN1-associated pHPT who are undergoing an initial parathyroidectomy,²³ because enlarged parathyroid glands were commonly identified on the contralateral side of the gland identified preoperatively, and the rate of persistent pHPT was significantly higher for patients who had a limited parathyroidectomy. Although the results from preoperative localizing studies do not alter the extent of the operation in most patients with MEN1-associated pHPT, we performed neck US for all patients because it facilitates the intraoperative identification of enlarged parathyroid glands and can detect ectopic parathyroid glands outside the thymus in most patients.²³

Several studies show that patients with MEN1-associated pHPT who have less than subtotal parathyroidectomy exhibit lower rates of permanent hypoparathyroidism,^{11,28,29} consistent with our series, in which permanent hypoparathyroidism did not occur in patients who had one or two glands removed. However, more than two thirds of the patients with MEN1-associated pHPT who had only a one- or two-gland parathyroidectomy experienced persistent pHPT. As expected, the patients with MEN1-associated pHPT who underwent BNE and had 2.5 or more glands removed showed a significant higher rate of permanent hypoparathyroidism than those who had two or fewer glands removed.

Because patients with MEN1-associated pHPT often require multi-gland resection, an inadequate parathyroid remnant or insufficient blood supply to the last parathyroid

gland can lead to permanent hypoparathyroidism. The rate of permanent hypoparathyroidism after an initial subtotal parathyroidectomy and cervical thymectomy in our series was low and similar to the rates in other studies.^{28,30}

Because our data suggest that a limited parathyroidectomy guided by preoperative localizing studies is associated with a high rate of persistent pHPT in patients with MEN1-associated pHPT, subtotal parathyroidectomy, cervical thymectomy, and parathyroid tissue cryopreservation, if feasible, are the procedures of choice for the treatment of these patients. These procedures provide a high rate of durable eucalcemia, with a low rate of permanent hypoparathyroidism and availability of cryopreserved parathyroid tissue for the patients who may experience permanent hypoparathyroidism. We believe parathyroidectomy for patients with MEN1-associated pHPT should be performed by experienced surgeons to minimize complications. Because parathyroid reoperation is common among patients with MEN1 and because permanent hypoparathyroidism can occur in patients who undergo a 3.5-gland parathyroidectomy, we believe that cryopreservation is necessary because 6 % of our patients received cryopreserved parathyroid autotransplantation.

We recently demonstrated that the use of intraoperative parathyroid hormone monitoring provides a positive predictive value of biochemical remission equaling the identification of three or more parathyroid glands intraoperatively but does not accurately predict postoperative hypoparathyroidism or biochemical remission.³¹ Therefore, BNE with subtotal parathyroidectomy and cervical thymectomy should be performed regardless of the intraoperative parathyroid hormone monitoring results because it would not be useful for guiding the extent of parathyroidectomy. Thus, we no longer use intraoperative parathyroid hormone to guide the extent of initial parathyroidectomy for patients with MEN1.

Our study had several limitations. The analysis was retrospective. All the patients whose initial operation was performed at our institution underwent a subtotal parathyroidectomy, but our findings emphasize that a focused-approach parathyroidectomy guided by preoperative localizing studies may miss enlarged contralateral parathyroid glands. In addition, our cohort lacked serial intraoperative PTH levels after each enlarged parathyroid gland was removed. These data would not alter the extent of surgical exploration or resection.³¹ However, they could provide better insight into the functional status of additional enlarged parathyroid glands not identified preoperatively on imaging studies. Although we could not demonstrate the functional status of enlarged contralateral parathyroid glands, the high rate of persistent pHPT among the patients who had three or fewer glands removed suggests that these glands would be hyperfunctioning.

Furthermore, the experience of surgeons outside the NIH and the rationale for the procedures were not available in most cases. Thus, we used the number of pathologically confirmed parathyroid glands removed because it was associated with outcome. Moreover, it is the only objective measure showing the extent of initial parathyroidectomy.

In summary, we showed that patients with MEN1-associated pHPT who undergo limited parathyroidectomy have a high failure rate. Thus, initial focused or limited parathyroidectomy should not be performed for these patients. Preoperative identification of a single enlarged parathyroid gland in patients with MEN1 is not sufficiently reliable to justify unilateral neck exploration because additional contralateral enlarged parathyroid glands are frequently missed.

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CONFLICT OF INTEREST There are no conflicts of interest.

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