PAPER

Primary Hyperparathyroidism Surgical Management Since the Introduction of Minimally Invasive Parathyroidectomy

Mayo Clinic Experience

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Hypothesis: Minimally invasive parathyroidectomy (MIP) for primary hyperparathyroidism (HPT) has equal cure and recurrence rates as standard cervical exploration. Changes in the management of primary HPT have occurred since introducing MIP including localization, anesthesia, intraoperative parathyroid hormone monitoring, and indications for parathyroidectomy.

Design: Cohort analysis of 1361 consecutive patients with primary HPT operated on at the Mayo Clinic, Rochester, Minn, from June 1998 through March 2004. Mean follow-up, 25 months.

Setting: Tertiary referral center.

Patients: One thousand three hundred sixty-one patients operated on for primary HPT, excluding 160 patients who were reoperated on.

Intervention: Standard cervical exploration MIP.

Main Outcome Measures: Cure, recurrence, localization, anesthesia, hospitalization, intraoperative parathyroid hormone level monitoring, contraindications to MIP, surgical indications, assessment of osteoporosis and osteopenia, postoperative patient assessment of general patient health, and operative satisfaction.

Results: Cure of primary HPT for both conventional exploration and MIP was 97%; only 1 patient who underwent MIP had a potential recurrence. Imaging sensitivity and positive predictive values were as follows: sestamibi scintigraphy, 86% and 93%; ultrasonography, 61% and 87%, respectively. Usage of general vs local anesthesia with intravenous sedation was 46% and 49%, respectively, in patients w ho underwent MIP; 46% were dismissed as outpatients, 49% had single-night stays. The accuracy of intraoperative parathyroid hormone level monitoring was as follows: 98% (8% had true-negative results); the frequency of multiple gland disease was 13%. Accounting for causes precluding MIP, an estimated 60% to 70% of all patients would be eligible for MIP. By preoperative assessment, 79% had osteoporosis-osteopenia; 58% with postoperative bone mineral density measurements were improved. More than 85% were satisfied with the results of their operation.

Conclusion: With high-quality localization and intraoperative parathyroid hormone level monitoring, MIP can be performed with equal cure rates as standard cervical exploration, with no present evidence of delayed recurrence.

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SINCE THE RECOMMENDATIONS of the National Institutes of Health (NIH) Consensus Conference on asymptomatic primary hyperparathyroidism (HPT) were published in 1991[1] (**Table 1**), considerable new information has been published regarding symptoms of HPT,[2,3] the disease influence on bone remodeling,[4] and the marked improvements in both of these aspects following successful parathyroidectomy. Additionally, the dramatic sweeping changes spurred by minimally invasive techniques across all surgical disciplines fueled by extraordinarily rapid and widespread dissemination of information easily accessible via the Internet have driven new surgical approaches for parathyroidectomy. Incorporation of advances and refinements in technology, particularly in preoperative localization with sestamibi scintigraphy and intraoperative parathyroid hormone (IOPTH) level monitoring, has facilitated minimally invasive parathyroidectomy (MIP). Appropriately, many questions and concerns have been raised about such a drastic departure from the

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success of standard open, bilateral neck exploration: in excess of a 95% cure rate; rates of 1% or less for both hypoparathyroidism and recurrent laryngeal nerve paralysis; usually 1 night of hospitalization; and infrequent use of preoperative localization.[5]

Review of overall, unselected, consecutive clinical series of patients is valuable to establish true outcome assessments. We reviewed the data for all patients who were operated on who had primary HPT for benign disease since MIP was introduced at the Mayo Clinic, Rochester, Minn, in June 1998 through March 2004. The objectives of this study were to assess cure of conventional parathyroidectomy and MIP in initial cervical explorations; recurrence of HPT, especially for MIP; anesthetic methods and length of hospitalization; localization with sestamibi scintiscan and cervical ultrasonography; reasons precluding use of MIP; use and value of IOPTH level monitoring; bone fragility including preoperative frequency of osteoporosis and osteopenia and postoperative changes in bone mineral density (BMD); indications for parathyroidectomy according to the revised NIH criteria from 2002[6] (Table 1); and the patients' perception of well-being preoperatively vs postoperatively and their satisfaction with the operation.

Table 1. National Institutes of Health Consensus Conference on Hyperparathyroidism 1991 and 2002 Recommendations for Surgery

1991 Recommendations
Typical bone, renal, gastrointestinal, or neuromuscular symptoms; life-threatening hypercalcemia
Calcium level >11.4-12.0 mg/dL (>2.9-3.0 mmol/L)
Urine calcium level >400 mg/d (10 mmol/d); renal stones
BMD 2 SDs<age, sex-matched controls (*z* score)
Reduced creatinine clearance ≥30%
Age <50 y
Patient request; adequate follow-up unlikely
2002 Additional Recommendations*
Calcium level >1 mg/dL (0.25 mmol/L) above normal for each laboratory (Mayo Clinic: >11.1 mg/dL [2.78 mmol/L])
BMD T score≤–2.5 at any site (WHO definition of osteoporosis)

Abbreviations: BMD, bone mineral density; WHO, World Health Organization.
*All of the 1991 recommendations with these changes.

METHODS

DEMOGRAPHICS

A total of 1532 operations were performed on 1521 consecutive patients with benign primary HPT from June 1998 through March 2004 at the Mayo Clinic. We have excluded the 160 reexplorations after unsuccessful initial operation for HPT (although patients who had undergone prior thyroidectomy or neck surgery for other reasons were included) leaving 1361 patients who form the basis of this institutional review board–approved study. Patients with secondary, tertiary, or malignant HPT were excluded, as were those who refused participation in clinical studies (n=20).

OPERATIVE PROCEDURE

Patients were included as having an MIP if their incision was 4 cm or less and they had a focused approach based on preoperative localization. The type of anesthesia (local anesthesia combined with intravenous [IV] sedation or general anesthesia), use of IOPTH level monitoring, and length of hospitalization did not influence categorization. Patients considered "converted to standard exploration" included conversion to a general anesthetic, extending the incision, and undergoing a bilateral cervical exploration. For purposes of assessing success of the procedure, they were included in the conventional, standard exploration group.

LOCALIZATION

Sestamibi scintigraphy was performed utilizing a double-isotope technique using technetium sestamibi (approximately 22.0 mCi [81 MBq]) with computer subtraction of iodine I 123 thyroid scan (1.0 mCi [37 MBq]), incorporating right and left oblique views and single-photon emission computed tomography images. High-resolution, real-time ultrasonography (US) was performed with 10- to 13-MHz scanners equipped with color Doppler imaging. All images were interpreted by the assigned nuclear medicine specialists and radiologists who performed the scans.

Retrospective assessment of these scans was made in the same way that surgical success would be determined—as follows:

True-positive (TP) result: A single abnormality on the same side as a single enlarged parathyroid gland was found at surgical exploration, and the patient was cured. No attempt was made to differentiate between superior or inferior glands for this assessment. For multiple gland disease (MGD), if the scan showed 2 or more abnormalities either on one or both sides of the neck and if there were 2 or more enlarged glands at the time of surgical exploration, this was counted as a TP result.

False-positive (FP) result: An abnormality identified by the imaging physician either on a side of the neck on which no enlarged gland was found at the time of surgical exploration, or 2 abnormalities on the same side with only 1 enlarged gland at the time of surgical exploration, and the patient was cured with excision of only a single gland.

False-negative (FN) result: An enlarged gland was found at surgical exploration on a side where no abnormality was identified by scan; a second enlarged gland was found on the same side at surgical exploration when only a single abnormality was identified by scan; a single enlarged gland was found both by scan and at surgical exploration but the patient was not cured (implying an additional abnormal gland must exist).

Sensitivity = TP Result/(TP Result + FN Result)

Positive Predictive Value (PPV) = TP Result/(TP Result + FP Result)

REASONS FOR NOT PERFORMING MIP

Retrospective assessment was conducted to determine what factors precluded using an MIP approach. These were grouped in the following categories:

- Parathyroid-related such as familial HPT, multiple endocrine neoplasia syndrome, or preoperative concern of parathyroid carcinoma.
- Localization issues including more than 1 abnormality identified implying MGD; inadequate or conflicting localization.
- Combined operations on other parts of the body requiring general anesthesia where MIP seemed to offer no advantage.
- Combined with thyroid resection.

• Neck reoperations principally due to prior thyroidectomy.
• Conversions from MIP to standard surgical exploration.
• Miscellaneous causes such as morbid obesity and claustrophobia.

When none of the above reasons could be found to account for a standard open approach rather than MIP, this was labeled "no apparent reason."

IOPTH MONITORING

The IOPTH measurements were usually performed by sampling 3 mL from the ipsilateral internal jugular vein as a baseline after surgical exposure was performed but prior to excision of the enlarged gland. Five- and 10-minute postexcision samples were also obtained. The PTH level was determined using an instrument located in the surgical area. (DPC Immulite 100; Diamond Diagnostics, Halliston, Mass) Assessment of the IOPTH values was as follows:

TP result: The postexcision values had declined at least 50% and usually near or within normal limits from the preexcision value after excision of the enlarged gland(s), and the patient was cured postoperatively.

TN result: The postexcision values did not decline by 50% and either the patient was not cured or further excision of additional enlarged glands led to a cure.

FP result: The postexcision values declined by at least 50% and the patient was not cured.

FN result: The postexcision values did not decline by 50% but no additional enlarged glands were excised and the patient was cured.

In addition to sensitivity and PPV, the following were determined:

$$\text{Specificity} = \text{TN Result}/(\text{TN Result} + \text{FP Result})$$

$$\text{Negative Predictive Value} = \text{TN}/(\text{TN Result} + \text{FN Result})$$

$$\text{Accuracy} = (\text{TP Result} + \text{TN Result})/(\text{TP Result} + \text{TN Result} + \text{FP Result} + \text{FN Result})$$

BMD ASSESSMENT

Osteoporosis was defined as a T score of −2.5 or less and osteopenia referred to a T score between −1 and −2.5.[7] This information could be gleaned from either Mayo Clinic or outside institution BMD measurements of the lumbar spine, femoral neck, or forearm.

FOLLOW-UP

Follow-up information was obtained from Mayo Clinic records, patient correspondence, or a follow-up survey that determined the serum calcium level; assessment of the patient's general health since parathyroidectomy: much better, somewhat better, no difference, somewhat worse, or much worse; satisfaction with the operation: very satisfied, somewhat satisfied, neutral, somewhat dissatisfied, or very dissatisfied; and BMD: improved, same, or worse.

RESULTS

DEMOGRAPHICS

Of 1361 patients, 998 (73%) were female and 363 (27%) were male. Mean age was 62 years (age range, 11-89 years). Mean biochemical values were as follows: serum calcium, 10.9 mg/dL (2.73 mmol/L) (reference range, 8.9-10.1 mg/dL [2.23-2.53 mmol/L]); phosphate, 2.9 mg/dL (reference range, 2.5-4.5 mg/dL), PTH, 97 pg/mL [10.2 pmol/L]) (reference range, 9-50 pg/mL [15.3 pmol/L]), and 24-hour urine calcium, 278 mg. The serum calcium level was 10.9 mg/dL (2.73 mmol/L) or lower in 849 patients (62%); phosphate level, 4.0 mg/dL or lower in only 39 patients (3%); urine calcium level, 400 mg or higher in 159 patients (12%); and the PTH level was strictly within the normal limits in 201 patients (15%).

OPERATIVE PROCEDURE, CURE AND RECURRENCE, ANESTHESIA, HOSPITALIZATION, PATHOLOGIC FEATURES

The conventional standard surgical exploration was performed on 734 patients (54%), 601 (44%) had MIP, and 26 (2%) had conversion of MIP to standard exploration. A total of 41 patients (3%) had persistent HPT after their initial exploration, 26 (3%) of whom underwent standard exploration, and 15 (3%) had MIP. Therefore, the cure rate for the entire series as well as for each subgroup of standard exploration and MIP was 97%. All 4 of us carried out 99% of the parathyroidectomy procedures.

Follow-up calcium level information was obtained on 932 patients (72%), with a mean of 25 months (range, 1-74 months). Of 759 patients (56%) with a minimum of 6 months of follow-up, 4 patients have reportedly redeveloped hypercalcemia. One is a patient who seemed to have a mediastinal adenoma devascularized at the initial operation (a reoperation following prior thyroidectomy). One has mild recurrent hypercalcemia in the setting of multiple endocrine neoplasia type 1 syndrome. A third had a reoperation after prior thyroidectomy, with a single gland localized by imaging which was resected with the IOPTH monitoring dropping less than 50% but still above the normal range at 10 minutes. The immediate postoperative calcium level was 9.5 mg/dL (2.38 mmol/L), and although on the follow-up survey the calcium level assessment was "abnormal," the actual value was unknown. The fourth patient had MGD with 2 glands removed, the other 2 appeared normal at the initial standard cervical exploration. The fifth and only patient with apparent redevelopment of hypercalcemia following MIP with an intraoperative TP result on IOPTH level monitoring responded on the survey that the calcium level was "abnormal," but the actual level was unknown.

All of the conventional standard cervical explorations were carried out under general anesthesia. Of the MIPs, 338 (56%) used general anesthesia and 263 (44%) were performed under local anesthesia with IV sedation. The mean hospitalization for the entire series was 1 day with 22%, 65%, and 13% dismissed as outpatients after 1 day and after longer than 1 day, respectively. Of the patients with MIP, 279 (46%) were treated as outpatients whereas 295 (49%) and 27 (5%), respectively, were dismissed at 24 hours and after longer than 1 day. The choice of anesthetic management was clearly influenced by the surgeon involved, as 2 of the surgeons used general anesthesia in 100% and 90% whereas the other 2 surgeons each averaged about 80% local anesthesia with

Table 2. Localization Results for Sestamibi Scintigraphic Scan and High-Resolution Ultrasonography

Variable	No. (%)	Sensitivity, %	PPV, %
Sestamibi scan			
TP result	886 (81.4)	86	93
FP result	62 (5.7)		
FN result	140 (12.9)		
Total	**1088**		
Ultrasonography			
TP result	230 (55.7)	61	87
FP result	35 (8.5)		
FN result	148 (35.8)		
Total	**413**		

Abbreviations: FN, false-negative; FP, false-positive; PPV, positive predictive value; TP, true-positive.

IV sedation. These latter patients were almost uniformly dismissed as outpatients.

Multiple gland disease was found in 174 patients (13%). The median weight of the largest resected parathyroid gland was 420 mg (largest, 21 170 mg) for all 1361 patients; 360 mg for those who underwent standard cervical exploration and 480 mg for the MIP. For patients with MGD, the median weight for the second largest gland was 150 mg.

LOCALIZATION

Some form of localization was undertaken in all but 130 patients (10%) (**Table 2**). The sensitivity and PPV for sestamibi scintigraphy were 86% and 93%, respectively, whereas the similar results for ultrasonography were 61% and 87%, respectively.

REASONS FOR NOT PERFORMING MIP

Of 758 conventional standard explorations, 527 (70%) had a readily apparent cause precluding a minimally invasive approach (**Table 3**). An additional 231 patients (30%) had no apparent reason for selecting the standard exploration, but included some who were identified as either patient or surgeon "preference." These patients would still have been technically eligible for MIP. In 1998 when MIP was first introduced in our practice, only 23% of all patients with HTP underwent MIP (**Table 4**). This corresponds to 38% of the patients who were eligible for MIP (those without the aforementioned causes precluding standard exploration). In contrast, 58% of all patients who underwent parathyroidectomy, and 88% of those eligible underwent MIP in the first 3 months of 2004. From this analysis, we would conclude that a maximum of approximately 60% to 70% of patients undergoing initial cervical exploration for primary HPT in our practice could undergo MIP.

IOPTH LEVEL MONITORING

The IOPTH level monitoring was used in 681 (50%) of the patients with the following results: FN, 13 patients (2%); FP, 4 (1%); TP, 611 (90%); TN, 53 (8%); sensitivity, 98%; specificity, 93%; PPV, 99%; negative predictive value (NPV), 80%; and accuracy, 98%.

Table 3. Reasons for Not Performing Minimally Invasive Parathyroidectomy

Cause	No. of Patients	% of Total Conventional Operations
Parathyroid related	43	6
Localization problems	214	28
Combined procedures	54	7
Thyroid resections	109	14
Reoperations (not for HPT)	75	10
Conversions	23	3
Miscellaneous	9	1
Conventional operations		
With cause	527	70
Without cause	231	30
Total No. of Conventional Operations	**758**	**100**

Abbreviation: HPT, hyperparathyroidism.

Table 4. Total Number of Parathyroidectomy Operations, Percentage of Total Undergoing Minimally Invasive Parathyroidectomy (MIP), and Percentage of Patients Eligible to Undergoing MIP

Year	Total No. of Yearly Parathyroidectomies	% of MIPs	% of Patients Eligible to Undergo MIP
1998*	146	23	38
1999	218	43	67
2000	211	45	79
2001	227	44	73
2002	242	50	80
2003	255	48	83
2004*	61	58	88

*Indicates partial year.

BONE FRAGILITY

Information regarding BMD was available in 1024 patients of whom 211 (21%) were normal, osteopenia was found in 421 (41%), and osteoporosis in 392 (38%). Testing was performed at Mayo Clinic in 668 patients (66%) and by outside studies in 343 (34%). The specific sites from which the BMD was determined were known in 846 patients and included the lumbar spine in 381 (45%), the hip in 397 (47%), and the forearm in 68 (8%). Postoperative assessment of the BMD was available in 266 patients and was improved in 155 (58%), unchanged in 70 (26%), and worse in 41 (16%).

INDICATIONS FOR PARATHYROIDECTOMY ACCORDING TO 2002 NIH CRITERIA

The updated 2002 NIH recommendations (Table 1) for parathyroidectomy may be applied to our 1361 patients. Sequentially subtracting those with renal stones (329 patients), a urine calcium level greater than 400 mg/dL (>100 mmol/L) (113), osteoporosis (259), a se-

rum calcium level of 1 mg/dL (0.25 mmol/L) or higher above the normal values for Mayo Clinic would be 11.1 mg/dL or higher (≥2.78 mmol/L) (214), and being younger than 50 years (80), there would be 191 patients (14% of the original series) remaining. Further excluding patients with osteopenia (175 patients) or women at or beyond menopause, age 50 years (134 patients) when they sustain accelerated bone loss due to lack of estrogen, only 57 patients (4.2%) would remain without an obvious indication for parathyroidectomy.

PATIENT SELF-ASSESSMENT OF HEALTH SINCE PARATHYROIDECTOMY AND OPERATIVE SATISFACTION

The postoperative survey letters provided self-assessment regarding general patient health after parathyroidectomy in 737 patients. Fifty-eight percent of the patients felt either much better (268 patients [36%]) or somewhat better (163 [22%]); 275 (37%) thought there was essentially no change, and only 25 (3%) felt somewhat worse or much worse (6 patients [1%]). Of the 57 patients who did not have clear indication for parathyroidectomy by the 2002 NIH criteria noted earlier, 34 returned the follow-up survey, and 10 (27%) felt much better, 6 (16%) felt somewhat better, 17 (46%) detected no change, and only 1 (3%) felt somewhat worse. In response to the survey question regarding operative satisfaction, 557 (75%) were very satisfied, 78 (10%) were somewhat satisfied, 44 (6%) were neutral, 21 (3%) were somewhat dissatified, and 46 (6%) were very dissatisfied.

COMMENT

For decades bilateral cervical exploration has been accepted as the gold standard treatment for primary HPT, and rightfully so. Cure rates of 95% or higher were regularly achieved by experienced endocrine surgeons[5,8] with vanishingly rare complications of permanent recurrent laryngeal nerve paralysis or hypoparathyroidism. Except for the rare case of parathyroid carcinoma, however, the predominant reason for routine bilateral 4-gland exploration was to identify and treat MGD. Rather incredibly, current controversy about minimally invasive techniques continues to focus on this issue. Preoperative localization and IOPTH level monitoring represent attempts to answer this question. Unilateral cervical exploration to excise a single parathyroid adenoma is not new. In the early 1980s, Tibblin et al[9] justified unilateral exploration with intraoperative oil red O staining to exclude MGD. A selective scan-directed unilateral approach achieved 100% success by Russell et al[10] in 1990. These reports were greeted with skepticism at best and labeled as irresponsible renegade surgery by some. Remarkably, in less than a decade, a nearly complete reversal in attitude occurred as interest in the minimally invasive approach exploded on the scene. This was coincident with several factors: (1) improving preoperative localization, (2) refinement of IOPTH level monitoring, (3) piqued, almost frenzied patient interest in *any* surgical technique that could be converted to minimally invasive, and (4) direct Internet surgical marketing that could be accessed by patients around the world with just a few personal computer mouse clicks, yet perceived by surgeons as a threat to the entire practice and credibility of standard parathyroidectomy. While some surgeons have reported near-perfect cure rates with shorter operative times and hospitalization as well as reduced costs,[11-13] there are strong opponents who even currently conclude, "A bilateral approach offers the best opportunity for the long-term cure of primary hyperparathyroidism."[14(p872)]

The early postoperative cure rate was 97% for our entire series, those operated on using standard bilateral exploration, and in patients who underwent MIP. The majority of our patients would be considered as having mild HPT because the mean elevation of the serum calcium level was less than 1 mg/dL (0.25 mmol/L) above our normal range and the median weight of the excised adenomas was only 420 mg. In reviewing the failures, no single dominant cause was identified, and these results compare favorably with published reports over the last 25 years.

We found MGD in 13% of our patients which has not appreciably changed since the 1980s. As noted earlier, the frequency of true MGD is pivotal to the success or failure of MIP and to the very acceptance or rejection of a focused approach. The frequency of MGD in recent reports from highly respected endocrine surgeons has been reported as 21%,[15] 20%,[16] and even 31%[14] contrasted to less than 5%[17] in a series of MIP guided by IOPTH level monitoring. This discrepancy has underscored the need for longer follow-up specifically to uncover the persistent or recurrent HPT that should emerge from the additional enlarged glands that were a part of an original MGD. To date, we have virtually no evidence of such recurrent HPT in our patients.

For patients who underwent MIP under local anesthesia with IV sedation, nearly all have been comfortable throughout the procedure, and no patient was converted to a general anesthetic based on surgical pain. However, these patients were selected both by their personal willingness and the motivation of the surgeon. Because of the obvious selection bias, no valid comparisons can be drawn between the 2 different anesthetic methods. Similarly, the time to dismissal, whether as an outpatient or overnight hospitalization, reflects the influence of a number of variables. In concert with others' experience, MIP with local anesthesia and IV sedation using propofol facilitates prompt recovery and dismissal, and enthusiastic patient approval.

Our assessment of localization techniques on one hand required of the test the same level of success as is expected of the surgeon, namely, to be considered a TP result, and that not only must an enlarged gland be identified but the patient must be cured as well. Therefore, if 1 enlarged gland was identified by scan but 2 glands were necessarily excised to cure the patient, the imaging test was labeled as a FN result (much the same as the operation would be deemed a failure if 1 enlarged gland were removed but the patient remained hypercalcemic postoperatively). However, more leniently, the localization technique only needed to identify 2 enlarged glands to be considered a TP result for MGD even if 3 or 4 were enlarged. Ultrasonography is the most noninvasive, least expensive preoperative localization technique. It is anatomically precise and capable of identifying 95% of adenomas weighing in excess of 1000 mg. Thy-

roid pathology can be well imaged and discriminated from enlarged parathyroid glands most of the time. However, US is capable of identifying fewer than 50% of adenomas weighing less than 200 mg, and by far the most limiting factor for US localization is its extreme dependence on the skill of the operator. Technetium Tc 99m–labeled sestamibi scintigraphic scans were introduced in 1989 by Coakley et al[18] and with the addition of oblique views perhaps supplemented by single-photon emission tomographic images, this has become the widely accepted imaging test of choice. The generally reported overall sensitivity is 75% to 80%[19] but drops consistently to 60% to 66% when identifying MGD.[20-22] In our series, MGD was predicted in only 59% of our technetium Tc 99m sestamibi scintigraphic scans and 29% of our US examinations. We have markedly increased our use of sestamibi scans and greatly reduced the use of US in patients with primary HPT. The decline in sensitivity and use of US undoubtedly stems from an ever-increasing number of radiologists with variable expertise who are assigned to the US area. In contrast, interpretation of sestamibi images seems less critically dependent on the experience of the nuclear medicine physician. Moreover, there are no blind spots for sestamibi images whereas bone and air obscure US images.

Whereas in 1998 the frequency of MIP was rather low in our practice, this represented initial significant reluctance to adopt this technique in favor of a successful, safe, comfortable, tried-and-true standard exploration. Multiple unanswered questions were suddenly confronted, such as the value and necessity of the gamma probe, IOPTH level monitoring (its cost and availability), the ongoing role of pathology, the critical reliance on image localization, and the choice of anesthesia and the uncertainties of local anesthesia in this setting. As many of these questions were addressed if not fully answered and the sheer mechanisms of the processes were put into place, the use of MIP increased. There continue to be many contraindications to MIP, constituting an estimated 30% to 40% of our initial cervical explorations for HPT, but at present, nearly all of those patients eligible for MIP have their parathyroidectomy performed in that manner. We still prefer standard exploration for patients who have undergone prior thyroidectomy or require combined thyroidectomy with parathyroidectomy. In addition, we are quite willing to combine parathyroidectomy with other operations to permit a single anesthetic.

We have been impressed with the extreme accuracy of IOPTH level monitoring. Curley et al[23] described a 2-site immunochemiluminometric technique and importantly verified the approximate 3- to 5-minute half-life of PTH. A year later, IOPTH level monitoring was successfully used in 12 patients with only a 15-minute turnaround time.[24] Even though greater than 90% of the time it simply verifies cure of the patient that would have been anticipated by removing a single adenoma localized by scan, this technique also offers considerable reassurance preoperatively to the patient. The frustration of converting an MIP to a standard exploration and extending the length of the operation needlessly caused by the uncommon FN IOPTH level monitoring result is more than counterbalanced by the valuable 8% TN results that prevent an operative failure. We have not encountered the 15% late failure rate that would have been predicted by a combination of MGD and failed IOPTH level monitoring predicted by the study by Siperstein et al,[14] or the 75% FP result decrease in the IOPTH level monitoring that Clerici et al[16] reported in MGD. Our results would support the reassuring data reported by Sidhu et al[25] that with a mean follow-up of almost 5 years, none of their 181 patients cured in early follow-up had developed recurrent hypercalcemia.

Perhaps of even greater importance than the introduction of MIP, but less well appreciated because of its silent nature, is the impact of successful parathyroidectomy on osteoporosis. An estimated 30% to 50% of American women will experience a fracture over their lifetime, with considerable attendant morbidity and mortality. More than 50% of postmenopausal women are thought to be osteopenic by T score, and nearly $14 billion in medical costs per year are attributed to osteoporosis. The 2002 NIH consensus report recognized the significant benefits of PTH for HPT in osteoporotic women that have been convincingly demonstrated in a number of reports. Within 2 weeks after parathyroidectomy, sensitive methods for measuring bone turnover demonstrate enhanced bone formation. The bone remodeling sequence is uncoupled allowing more rapid BMD increases in trabecular (spine) and combined trabecular and cortical (femoral neck) bone. The remodeling space is normalized and resorption lacunae are gradually filled in. Remarkably, 79% of the patients in our series who were tested using BMD met criteria for osteopenia or osteoporosis. While only a fraction of the patients have been retested, nearly 60% have BMD evidence of improvement following parathyroidectomy.

The 1991 NIH Consensus Conference Statement stated, "All primary HPT patients should be considered candidates for surgery."[1(p594)] Perhaps receiving more notoriety was the statement that followed, "Some uncomplicated asymptomatic patients, however, may be considered for judicious non-surgical medical monitoring."[1(p593)] The focus of the entire proceedings was on the asymptomatic patient, with the clear implication that a large proportion of patients with primary HPT would not meet the objective criteria for parathyroidectomy. We were interested in what proportion of our patients met the NIH criteria for parathyroidectomy. Recognizing that a BMD T score of −1.5 is sufficiently severe to recommend antiresorptive drug therapy, and one of the conclusions of the 10-year study on HPT and the bone by Silverberg et al[4] was that PTH was especially suitable for patients with diminished BMD such as postmenopausal women, we added these 2 criteria as indications for parathyroidectomy. Therefore, abiding strictly by the objective, updated 2002 NIH Consensus Conference criteria for parathyroidectomy to which were added the criteria of osteopenia or postmenopausal women, we sequentially subtracted patients who met these criteria and of the original 1361 patients, only 57, or less than 5% of the total, failed to meet objective criteria. Even without the sophisticated measures of subtle general symptoms or those directly related to HPT that others have published,[26,27] the perception by nearly half of the remaining surveyed patients was that they were improved by parathyroidectomy. Only a single patient failed to meet objective criteria for parathyroidectomy and felt somewhat worse after the operation.

Overall satisfaction with the operation was expressed by 85% of our patients. Of the 9% who were dis-

satisfied, no central theme could be discerned. As might be expected, some of the patients who remained hypercalcemic were dissatisfied. Others were not happy that some of their unpleasant preoperative symptoms were not relieved, and some expressed displeasure with the perioperative process.

In our practice we would estimate that approximately 60% to 70% of patients with primary HPT undergoing initial cervical exploration would be eligible for MIP. Especially for patients with primary HPT who have mild disease, MIP is crucially dependent on high-quality preoperative imaging preferably using technetium Tc 99m–sestamibi scintigraphy, including expert interpretation. Whereas in less than 10% of patients does IOPTH level monitoring actually alter the standard exploration and prevent failure in MIP, the reassurance seems highly appreciated by both surgeon and patient. Moreover, the reliable accuracy of IOPTH level monitoring during MIP should allow equivalent or superior success to standard exploration in appropriately selected patients. The combination of sestamibi and IOPTH monitoring seems to sufficiently identify MGD so as to prevent subsequent recurrent hypercalcemia. The choice of anesthesia can be tailored to the patient's wishes, but local anesthesia with IV sedation facilitates outpatient discharge and avoids some of the unpleasant adverse effects of general anesthesia. The value of PTH in patients with osteoporosis or osteopenia to improve BMD is extensively documented in the literature, and our results lend further support. Recognizing this, adding to the NIH indications for PTH osteopenia and postmenopausal women who are at high risk for bone fragility, fewer than 5% of our patients lacked a specific objective surgical criterion. To the degree that MIP is perceived by patients, internists, and/or endocrinologists as advantageous and thereby stimulates increased or earlier surgical referral of patients with HPT, it will be beneficial. Overall, our assessment is that MIP represents a step, but not a quantum leap, forward.

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DISCUSSION

Richard Prinz, MD, Chicago, Ill: Let me compliment the Mayo Clinic group on an excellent review of current surgical therapy of primary HPT. It is a remarkable feat to perform more than 1500 parathyroidectomies in the short period of this study and it is just as remarkable a feat to analyze all of their data. There is a wealth of information in this paper and I would recommend it to anyone who is interested in this disease. The results are outstanding and confirm that MIP is here to stay. I have a number of questions.

First, have the authors looked at postoperative PTH values in their patients? In our experience, 20% to 30% of normocalcemic patients will still have an elevated PTH level. Most of these

will normalize their PTH level over time but not all. I worry that some of these will have over time recurrent disease.

Second, I know the decision to use general vs local anesthesia with sedation was primarily made by the surgeon's preference but were there any patient factors that were important in this decision? In other words, what patients are not good candidates for local anesthesia with sedation?

Minimally invasive parathyroidectomy depends on accurate localization. Both US and sestamibi scanning were used in your series. I got the impression that your group is relying more on sestamibi scanning and less on US. Ultrasonography also gives the surgeon more valuable anatomical information than sestamibi scanning. Since obtaining an office US machine, I have found it to be quite a reliable means to localize abnormal parathyroid glands. I think an interested surgeon is better at this procedure than the pool of radiologists who are assigned to do it. Ultrasonography also gives the surgeon more valuable anatomical information than sestamibi scanning. Why was there no localization in 130 patients in your series and did any of these patients undergo MIP?

It seems that not all eligible patients for MIP are undergoing the procedure. Can you explain why not?

Also, are there some patients with potential reasons for not performing MIP who you would consider starting out with this procedure since you can always convert to a standard operation?

Like the Mayo Clinic group, I have become very dependent on IOPTH monitoring. The small number of FP test results continues to trouble me. Any thoughts on how to avoid them and do you think that the criteria of a 50% decrease is always appropriate?

Finally, cost is evermore important in health care. Have you looked to see if there is any difference in the cost of the 2 approaches to parathyroidectomy at the Mayo Clinic?

Dr Grant: Dr Prinz, regarding postoperative PTH values, we did not systematically obtain PTH values. Your point is well taken that delayed, elevated PTH values may be of concern. They may represent at least 1 of 2 possibilities: delayed recurrence, which we have not seen; or a sort of physiologic secondary HPT. That is, the calcium level is normal, but such patients may have a low vitamin D level, and with replacement calcium and vitamin D, the PTH level eventually normalizes and the patient remains eucalcemic. Regarding recommendations about local vs general anesthesia, ideally the patient is motivated and understands what will occur during the operation. Perhaps more important is a motivated surgeon. There are a few contraindications in addition to the ones noted during the presentation. Patients who have a high body mass index and the rare patient with severe claustrophobia might be better operated with a general anesthetic. Regarding localization, we use sestamibi scans predominately but not exclusively. Ultrasonography is dependent on the following 2 things: (1) the skill of the observer and (2) the size of the abnormal parathyroid gland. If it is 200 mg or smaller, there is only approximately a 50% chance of detection in our experience. If the abnormal gland is 1000 mg or larger, the success of detection is more than 95%. In addition, there are blind spots with US. It cannot see through bone or air as you know. In answer to why we did not have localization on 130 patients, those were patients who were operated on early in our series when standard surgical exploration was still the predominant method. We did not immediately convert to a standard operation on all patients with MIP. Presently, a sestamibi scan is obtained almost routinely before we even consult on the patient. If the patient meets the criteria, discussed previously, almost all are started as MIP. The IOPTH monitoring has been successful in our hands. We agree that a 50% drop is the minimum, but we would also like to see the PTH level drop into the mid to low normal range. That is not always the case and a couple examples may help illustrate our practice. With a baseline preexcision parathyroid hormone level of 35 mg/dL (3.7 pmol/L) (with our reference range being <5 mg/dL [<0.5 pmol/L]), and the postexcision levels at 5 and 10 minutes of 12 mg/dL (1.3 pmol/L) and 6 mg/dL (0.6 pmol/L), we would accept these values as evidence of cure even though the final value remains slightly above normal. However, if the baseline was 20 mg/dL (2.1 pmol/L) and the 5- and 10-minute values were 10 mg/dL (1.1 pmol/L) and 8.5 mg/dL (0.90 pmol/L), this would indicate the values had stabilized above the reference range even though the decline exceeded 50%. In this situation it would be the prerogative of the surgeon to either extend to a bilateral exploration or draw another PTH sample to help clarify the situation. Regarding cost differential—we did not perform a cost analysis on this series. Clearly, there are a number of biases in the 2 groups, and differences in the costs would be justifiably open to criticism and might lead to significant misinterpretation. Nevertheless, it would be tempting to develop these figures.

John Ryan, MD, Sioux Falls, SD: I congratulate you on this report. It is concise and very informative, typical of what comes from endocrine surgeons at Mayo Clinic. My question though is about the indications for parathyroidectomy and how they have changed. A report from your own institution some years ago I would not say advocated but reported on the safety of observation of patients with serum calcium level less than let us say 11 (1.2 mmol/L) or 11.2 mg/dL (1.2 pmol/L). Is it the realization of the importance of treating bone disease or is it the advent of this new operative technique that has changed your indications for surgery and what are the indications currently for parathyroidectomy?

Dr Grant: The indications for parathyroidectomy have included all of the recommendations outlined in the 1991 NIH Consensus Conference, but specifically also include mild symptoms. We have not really changed these other than to include patients with osteopenia or at high risk for developing it. One of the major changes over the last 10 years is our understanding of primary HPT is the realization of the benefit of parathyroidectomy for patients with bone fragility. The landmark paper by Silverberg et al[4] in the *New England Journal of Medicine* detailed the improvement in lumbar spine and femoral neck by BMD after parathyroidectomy. There have been many other convincing reports supporting this information. This has led us now to evaluate the bones with BMD in almost all patients with primary HPT. We are recognizing that bone fragility is common in these patients and parathyroidectomy can be more effective even than bisphosphonates. Bone formation can be documented as soon as 2 weeks postoperatively.

Fiemu Nwariaku, MD, Dallas, Tex: My question has to do with the IOPTH assay. As you know, many hospitals have trouble justifying the cost, not just of the machine but of the technologist's time spent in the operating room. Therefore, some surgeons in smaller hospitals have resorted to performing MIPs based on either sestamibi scans or preoperative US. So my question is, in looking through your data, could you tell what the success rates would be if you based the minimally invasive explorations solely on sestamibi scan or US?

Dr Grant: Dr van Heerden led to a protocol to address just that question. If one excludes any patient with known multiple endocrine neoplasia syndrome or familial HPT where MGD would be expected, and if there is a clear single hot spot by sestamibi scan in a first-time cervical exploration, then the frequency of IOPTH monitoring detecting MGD is less than or equal to 5%. Therefore, if these criteria are strictly followed, and IOPTH monitoring is not used, there is approximately a 5% risk of postoperative persistent HPT. In addition, at times a single hot spot by sestamibi scan is accompanied by a second minor hot spot that is usually extraneous and can be ignored with the safety backup of IOPTH monitoring. Without the use of IOPTH monitoring, however, the rate of persistent HPT would rise above 5% if these were uniformly ignored.