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IS MINIMALLY INVASIVE PARATHYROIDECTOMY ASSOCIATED WITH HIGHER RECURRENCE COMPARED TO BILATERAL EXPLORATION? ANALYSIS OF OVER 1,000 CASES

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Abstract

BACKGROUND—The durability of minimally invasive parathyroidectomy (MIP) has been questioned, and some advocate for routine open parathyroidectomy (OP). This study compared outcomes between patients treated with MIP versus OP for primary hyperparathyroidism (PHPT).

METHODS—A retrospective review was performed to identify cases of PHPT with single adenomas (SA) between 2001 and 2011. Operations were classified as OP when both sides were explored. Kaplan-Meier estimates were plotted and compared by the log-rank test. $P < 0.05$ was considered significant.

RESULTS—We analyzed 1,083 cases of PHPT with SA. 928 (85.7%) were MIP and 155 (14.3%) were OP. There was no difference in the rates of persistence (0.2% MIP vs. 0% OP, $p = 0.61$) or recurrence (2.5% MIP vs. 1.9% OP, $p = 0.68$) between the two groups. However, the Kaplan-Meier estimates began to separate beyond eight years follow-up. The OP group did experience a higher incidence of transient hypocalcemia postoperatively (1.9% vs. 0.1%, $p = 0.01$).

CONCLUSIONS—MIP appears equivalent to OP in single-gland disease. While patients undergoing OP experienced more transient hypocalcemia, patients undergoing MIP appear to have a higher long-term recurrence rate. Therefore, proper patient selection and counseling of these risks is necessary for either approach.

Introduction

Primary hyperparathyroidism (PHPT) occurs at an annual incidence of approximately 100,000 patients in the United States (1). Hypersecretion of parathyroid hormone by one or more parathyroid glands disrupts bone and mineral metabolism causing a myriad of symptoms. In 80% of patients, the disease occurs in one hypersecreting gland. The remaining patients have either a double adenoma or four-gland hyperplasia (2). Surgical resection of the abnormal glands remains the only curative treatment option, and this was traditionally achieved by performing a bilateral neck exploration, or open parathyroidectomy (OP). The introduction of intraoperative parathyroid hormone (IoPTH) testing and improved

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localization studies has enabled surgeons to offer patients a minimally invasive parathyroidectomy (MIP). In this technique, the suspected single adenoma is localized preoperatively and resected through a much smaller incision with less dissection compared to OP (3).

MIP offers the potential benefits of improved cosmesis, less pain, a shorter operation, decreased length of stay, and fewer complications (3). A randomized prospective study from Sweden demonstrated that compared to OP, MIP decreased symptomatic hypocalcemia as measured by calcium consumption (4). Related to these findings, MIP improves quality of life measures in both short and long-term follow-up compared to patients undergoing OP (5). Finally, MIP has been shown to be cost-effective compared to OP (3).

Recently, some centers have abandoned MIP and returned to the OP technique, arguing that imaging studies are too inaccurate, and IoPTH fails to identify dormant multigland disease, putting patients treated with MIP at risk for future recurrence (6–8). Bilateral exploration obviously puts both recurrent laryngeal nerves at risk and may slightly increase the hematoma and hypocalcemia rates. Several large series and randomized studies, however, have demonstrated that these complication rates are negligible and the hypocalcemia often resolves (9, 10).

Despite the arguments favoring OP to avoid operative failures in MIP, there are numerous studies demonstrating a high cure rate with MIP that is equivalent or better than cure rates reported with OP (11, 12). Proponents of MIP argue that operative failure in MIP occurs when the surgeon cannot find the abnormal gland and not missed multigland disease (13).

Some patients will present with imaging or clinical characteristics suggestive of multigland disease. Still, 80% of patients will have a single adenoma, and often the preoperative imaging will suggest the location of that single gland. Amidst the controversy surrounding the success and durability of MIP, this study focused on patients with PHPT and a single adenoma, comparing outcomes between patients treated with MIP versus OP.

Methods

We conducted a retrospective review of a prospectively collected parathyroid database. Cases of PHPT with single adenomas between 2001 and 2011 were selected for further analysis. Familial disease, secondary, tertiary, or re-operative cases were excluded. We also excluded patients who underwent concomitant thyroid operation or who underwent a thoracic procedure to remove a parathyroid adenoma. At our institution, all patients with biochemical evidence of PHPT are evaluated with sestamibi scan and some patients also undergo neck ultrasound. Radioguidance and IoPTH were employed for localization and to guide the extent of exploration as previously described (14). Whenever any localization study is positive, patients are offered MIP, but intraoperative findings and IoPTH determine the extent of exploration. At the University of Wisconsin, we require a 50% drop in PTH from the peak PTH level measured at 5, 10, or 15 minutes post-excision. Operations were classified as either OP when both sides of the neck were explored whereas MIP refers to a unilateral exploration. A bilateral (OP) exploration was undertaken when 1) all imaging studies were negative, 2) preoperative imaging suggested one side, but the gland(s) on this side appeared normal intraoperatively, or 3) the surgeon decided a priori to perform a bilateral exploration due to patient factors such as a strong family history or mild disease. Preoperative patient characteristics and lab values were recorded. Operative and postoperative findings including complications were also tabulated.

Our parathyroid database is maintained with each patient's most recent calcium and PTH values. Outcomes were categorized as persistence or recurrence. Persistence was an elevated

calcium and PTH within six months of the initial operation. Recurrence was defined as an elevated calcium at or beyond six months postoperatively, with calcium greater than our laboratory's upper limit of normal (>10.2 mg/dL) representing recurrence. Single adenomas were defined as one gland resected during surgery and confirmed to be parathyroid tissue by pathology. Kaplan-Meier estimates were plotted for disease-free survival, and these curves were compared by the log-rank test.

Univariate comparisons were made with the student's t-test, Chi-squared test, or the Wilcoxon rank-sum test where appropriate. Statistical analysis was performed with STATA v. 10.1 software (StataCorp, College Station, TX). $P<0.05$ was considered significant.

Results

Patient Characteristics

There were 1,538 patients who presented for the initial surgical treatment of PHPT at our institution between March 1, 2001 and September 1, 2011. Of these, 1,083 were found to have a single adenoma, and these patients were considered for further analysis.

The preoperative patient characteristics are shown in Table 1. The mean age of these patients was 61 years old and 78% were female. 526 patients had preoperative bone scans, and the mean bone mineral density t score was -1.8 (Table 1). Only a small number of patients had a history of kidney stones, and renal function as measured by creatinine was preserved in this cohort of patients (Table 1). 29 patients had a family history of hyperparathyroidism.

Perioperative Findings

Of the 1,083 patients who presented for initial neck operations for PHPT, 928 underwent MIP and 155 had OP. We compared their perioperative findings, and the results are shown in Table 2. Patients undergoing MIP had higher preoperative calcium compared to those treated with OP (11.2 ± 0.0 vs. 10.9 ± 0.1 , $p<0.01$, Table 2). As expected, a greater proportion of patients undergoing MIP had positive sestamibi localization compared to the OP group (84% vs. 43%, $p<0.01$, Table 2). The MIP cohort also displayed a greater percentage drop in IoPTH compared to the OP group, but this group also had a higher baseline PTH (Table 2). Although there was no statistical difference in postoperative calcium between the two groups, the MIP group did have a higher postoperative PTH level (49.0 vs. 38.8, $p<0.01$, Table 2). Incorrect localization studies led to conversion from MIP to OP in 49 patients in the OP group.

Recurrence

Outcomes were classified as either persistent disease if the calcium was elevated within six months of operation or recurrence if an elevated calcium and PTH occurred after six months of the initial operation. Median follow-up time was 9.2 months (range 0 – 116.6 months).

A total of 28 patients experienced either persistent or recurrent disease; 25 were in the MIP group, and 3 in the OP group ($p = 0.58$, Table 3). Although there was no statistical difference, there were 2 cases of persistent disease in the MIP group and none in the OP group ($p = 0.61$ Table 3). Similarly, the rate of disease recurrence was 2.5% in the MIP group and 1.9% in the OP group ($p = 0.68$, Table 3).

To further characterize the patterns of disease recurrence, we compared Kaplan-Meier disease-free survival estimates for MIP vs. OP (Figure 1). Again, there was no statistical difference between the two groups ($p = 0.55$), but the curves progressively separated beyond

60 months follow-up (Figure 1). When considering the period beyond eight years alone, there was an 8.11% recurrence rate in the MIP group vs. zero in the OP group ($p = 0.48$).

Complications

Complications were classified as either permanent or transient hoarseness and hypocalcemia. The OP group experienced more permanent and transient hoarseness compared to the MIP group, but there was no statistical difference (Table 3). Compared to the MIP group, the OP did have significantly more transient hypocalcemia (1.9% vs. 0.1%, $p = 0.01$, Table 3). Neither group suffered from permanent hypocalcemia. Importantly, the OP group also had one patient requiring emergent evacuation of a hematoma, but there were none in the MIP group (Table 3). We classified all other complications into the “Other” category, and this mainly consisted of minor wound irritation, cellulitis, or seroma. Four patients experienced such issues in the MIP group, and there were none in the OP group.

Discussion

Much controversy surrounds the appropriate surgical approach to PHPT. While MIP has gained much popularity, proponents of OP cast doubt on its long-term success (6). Advocates of OP state that targeting a single gland leaves other morphologically abnormal glands behind to cause recurrence at a later date. Yet, at least 80% of all patients with PHPT will have a single adenoma responsible for their hypercalcemia (15, 16). Therefore, this calls into question the utility and risk benefit ratio for exploring both sides of the neck when such a high percentage of patients will have a single adenoma. Here, we report on the recurrence rates among those patients treated with either MIP or OP where just a single adenoma was resected. Previous studies evaluating the effectiveness of MIP have been limited by relatively low numbers and follow-up times of six months or less (17–19). Our study contains over 1,000 patients, and some patients were followed for almost 10 years, well beyond the six month time point conventionally associated with a lasting cure.

We found that MIP was equivalent to OP for both persistence and recurrence (Table 3, Figure 1). There were two cases of persistent disease among patients treated with MIP (Table 3). This means that of the patients treated with MIP for a single adenoma, only 0.2 % had missed multigland disease that became apparent within six months. That is, IoPTH falsely indicated cure at the time of surgery. This tiny percentage of persistent disease is eliminated by the OP approach since we did not have any cases of persistence in the OP group (Table 3). The overall number of failures (persistence + recurrence) was again similar between the two groups (2.7% MIP vs. 1.9% OP). A recurrence rate of 2.7% is consistent with published results using either surgical technique (6, 13, 18). Siperstein and colleagues have reported that a combination of preoperative imaging and IoPTH employed for MIP fails to identify additional morphologically abnormal glands in at least 16% of patients when they subjected everyone to a bilateral exploration after excising the targeted gland seen on preoperative imaging (6). Our recurrence rates are much smaller than this predicted failure rate, but we do not know the number of patients with additional morphologically abnormal glands left in the neck.

In one of the largest series of patients with PHPT, Udelsman and colleagues found that MIP was superior to OP due to an improved cure rate, decreased complications, and decreased costs (15). Recently, Norman et al published an even larger series, and came to the opposite conclusion, finding the failure rate with MIP unacceptably high (20). Although we utilize the radioguided probe like the Norman group, we do not biopsy the glands to determine their functional status. Instead, we utilize IoPTH, similar to Udelsman’s series. This report is unique from both of these previous studies because we only examined patients where a single gland was resected. Only after analyzing our data using Kaplan-Meier estimates, the

trend toward greater long-term recurrences in the MIP group became obvious, although the log rank test indicated no statistical difference in disease free survival functions. Without this type of time-dependent analysis, then the overall success rates and the higher complications in the OP group are similar to Dr. Udelsman's series. Hence, this is a large series that is much less heterogeneous, answers a more specific question, and the analysis is time-dependent.

If MIP truly leaves behind abnormal glands, it suggests that these glands remain biochemically dormant at the time of surgery. IoPTH relies on the physiology of PTH secretion to indicate a cure. Some authors posit that the surgeon must consider both the physiologic *and* anatomic parathyroid abnormalities to achieve the highest cure rates in PHPT (6, 20). If we try to explain our own data within this paradigm, then any "missed" glands require a lengthy period of time (years) to become physiologically active. The Kaplan-Meier plots demonstrate that MIP separates from OP with more recurrences at later time points (Figure 1). These curves begin to separate between 40 and 60 months postoperatively (Figure 1). After five years, the only recurrences occurred in the MIP group. Hence, if anatomic multigland disease exists at the time of surgery, the biochemical presentation is metachronous, and can be quite delayed.

Further examination of our Kaplan-Meier plots reveals that the MIP and OP curves progressively separated beyond 60 months (Figure 1). While there was no statistical difference, the trend suggests MIP may lack durability with long-term follow-up. Despite a total number exceeding 1,000 patients, there were relatively few patients followed for the longest time points (beyond 60 months) when the disease-free survival plots separated. As we continue to follow these patients and accrue more data, we will need to re-evaluate the long-term success of MIP.

The routine use of OP was not without risks. Significantly more transient hypocalcemia occurred in OP than MIP (Table 3). These results are consistent with other prospective and retrospective series that report a higher incidence of transient hypocalcemia in OP (4, 10, 21). Although there was no statistical significance, there were cases of bleeding and recurrent laryngeal nerve injury in the OP group and none in the MIP group (Table 3). Retrospective series also report these consequences of OP (3, 22), but randomized controlled trials found no difference between MIP and OP for serious complications like hematoma and recurrent laryngeal nerve injury (4, 9, 10). The present study is retrospective, and comparing risks between two groups that were not randomized does introduce some bias. The other reported drawbacks to the OP approach include longer incision, lengthier operative times, increased hospital stay, and costs (23, 24). Many of these concerns do not apply if the surgeon performs both OP and MIP as an outpatient procedure.

Our results are limited by the retrospective nature of this study. We feel that this specifically affected the data on transient complications. Since we offer parathyroidectomy as an outpatient procedure to the vast majority of patients, transient complications may go undetected. While we relied on laboratory values to make the diagnosis of transient hypocalcemia, there may be more patients in both groups who suffered this complication, but it was never detected because it resolved by the time labs were repeated at the postoperative visit. Despite the high volume of patients included in this study, there were relatively fewer patients with follow-up beyond 60 months when the separation in recurrence rates seemed to occur. We are fortunate to have an electronic records system and a regional presence of our hospital system that facilitates tracking calcium levels in our database. Yet, a significant number of patients are referred from other hospital systems or from out of state, which limits the follow-up beyond 6 months.

We plan to provide follow-up data as time passes and we can report on larger numbers of patients with follow-up at late time points. Although we have emphasized the trend for more late (>60 months) recurrences in the MIP group compared to OP, we do not feel this calls for abandoning the MIP approach for universal application of OP. Overall, the recurrence rates are quite low, and many patients benefit from a shorter operation, a smaller incision, and less dissection since OP is not without added risk. Because of the metachronous pattern of late recurrence in a small number of patients initially treated for a single adenoma, the real question becomes how to predict which patients will recur, and, therefore, who might benefit from OP as the initial procedure. Our group is currently identifying risk factors for recurrence to improve patient selection for either operative approach. Clearly, there are numerous patients treated with MIP who never recur. Improved selection of patients for MIP or OP can maximize the risk-benefit ratio for the most number of patients.

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Figure 1. Recurrence

Kaplan-Meier plots for recurrent hyperparathyroidism. These plots were compared by the log-rank test with the p value indicated. *OPEN* = open parathyroidectomy, *MIP* = minimally invasive parathyroidectomy.

TABLE 1

Preoperative Patient Characteristics (n = 1083)

Variable	Number (%)
Age	61 ± 14
Female	831 (78)
BMI (kg/m ²)	31.2 ± 2.8
BMD T score	−1.8 ± 1.7
Creatinine (mg/dL)	1.0 ± 0.7

BMI = body mass index, *BMD* = bone mineral density

Continuous variables are represented as the mean ± standard error of the mean unless otherwise indicated

TABLE 2**Perioperative Findings**

Variable	MIP (n = 928)	OPEN (n = 155)	p value
Preoperative Ca (mg/dL)	11.2 ± 0.0	10.9 ± 0.1	<0.01
Preoperative Phos (mg/dL)	2.8 ± 0.0	2.9 ± 0.1	0.52
Preoperative PTH (pg/ml)	131 ± 3	122 ± 12	0.26
Sestamibi localization (%)	780 (84)	67 (43)	<0.01
Gland weight (mg)	809 ± 36	804 ± 218	0.96
Ectopic location	166 (18)	37 (24)	0.08
% Decrease in IoPTH	66	62	<0.01
Postoperative Ca (mg/dL)	9.5 ± 0.1	9.4 ± 0.0	0.60
Postoperative PTH (pg/ml)	49 ± 1	39 ± 2	<0.01

Ca = calcium, *Phos* = phosphorus, *PTH* = parathyroid hormone, *IoPTH* = intraoperative PTH

Continuous variables are represented as the mean ± standard error of the mean. Categorical variables are given as the number of patients with the indicated finding and the percentage in parentheses. Gland weights shown are the heaviest gland resected.

TABLE 3

Outcomes

Variable	MIP (n = 928)	OPEN (n = 155)	p value
Total Failures	25 (2.7)	3 (1.9)	0.58
Persistent	2 (0.2)	0	0.61
Recurrent	23 (2.5)	3 (1.9)	0.68
Complications	16 (1.7)	5 (3.2)	0.21
Transient hoarseness	2 (0.2)	8 (5.2)	0.61
Permanent hoarseness	0	2 (1.3)	0.56
Transient hypocalcemia	1 (0.1)	3 (1.9)	0.01
Permanent hypocalcemia	0	0	--
Bleeding/hematoma	0	1 (0.7)	0.68
Other	4 (0.43)	0	0.41

Data are represented as the number of patients in each category with the percentage in parentheses.