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PREDICTORS OF RECURRENCE IN PRIMARY HYPERPARATHYROIDISM: AN ANALYSIS OF 1,386 CASES

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Abstract

BACKGROUND—Intraoperative parathyroid hormone (IoPTH) monitoring has enabled surgeons to perform minimally invasive parathyroidectomy (MIP). Yet, the long-term durability of this approach has recently been questioned. The purpose of this study was to determine if operative approach independently influenced recurrence and to identify perioperative predictors of recurrence.

STUDY DESIGN—A retrospective review was performed and cases of initial neck surgery for non-familial primary hyperparathyroidism were selected for analysis. Cases were classified as either open (OP) when both sides of the neck were explored or MIP when only one side was explored. Kaplan-Meier estimates were plotted for disease-free survival, and a Cox proportional hazards model was developed to evaluate factors associated with recurrence for both the entire cohort and the MIP subset. Further comparisons were made between those who recurred and those who did not recur.

RESULTS—In the last 10-year period, 1,368 parathyroid operations for primary hyperparathyroidism were performed at our institution. 1,006 were MIP while 380 were OP. There were no differences in recurrence between the MIP and OP groups (2.5% vs. 2.1%, $p = 0.68$), and the operative approach (MIP vs. OP) did not independently predict recurrent disease in our multivariate analysis. The percentage decrease in IoPTH was protective against recurrence for both the entire cohort (HR 0.96, 95% C.I. 0.93 – 0.99, $p = 0.03$) and the MIP subset. A higher postoperative PTH also independently predicted disease recurrence.

CONCLUSIONS—Operative approach does not independently predict recurrent hyperparathyroidism. The percentage decrease in IoPTH is one of many adjuncts the surgeon can utilize to determine which patients are best served by bilateral exploration while the postoperative PTH can guide follow-up after parathyroidectomy.

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Introduction

Primary hyperparathyroidism (PHPT) affects about 100,000 people in the United States each year (1). The disease manifests with hypercalcemia driven by hypersecretion of parathyroid hormone by one or more parathyroid glands. In 80% of patients, a single parathyroid adenoma is responsible. PHPT presents with a variable range of symptoms from bone and joint pain to kidney stones, fatigue, and depression (1–3). Surgery remains the only curative treatment for PHPT with long-term success rates exceeding 95% (2–4).

The development of intraoperative parathyroid hormone (IoPTH) monitoring and improvements in preoperative localization techniques enabled surgeons to offer patients a minimally invasive parathyroidectomy (MIP) (5–8). Using this technique, the surgeon localizes the suspected adenoma preoperatively and resects it through a smaller incision with less dissection compared to open parathyroidectomy (OP). MIP offers the potential benefits of improved cosmesis, less pain, a shorter operation, decreased length of stay, and fewer complications (9). Related to these studies, MIP improves quality of life measures in both short and long-term follow-up compared to patients undergoing OP (10). Finally, MIP has been shown to be cost-effective compared to OP (9).

Despite the initial enthusiasm and widespread use of MIP, more recent data suggests that this approach may miss dormant multigland disease, putting patients treated with MIP at risk for later recurrences (11–13). In a prospective study where patients were subjected to bilateral exploration following MIP, Siperstein and colleagues found that localizing studies (ultrasound and sestamibi scans) combined with IoPTH failed to identify multigland disease in 16% of patients as determined by the gross appearance of the glands when patients were subjected to bilateral exploration regardless of IoPTH results (11). In this study, Siperstein et al. did not report long-term cure rates with this approach (12). We have previously reported that although there is no statistical difference when comparing cure rates in patients treated with MIP vs. OP for single gland disease. However, MIP appeared less durable beyond five years follow-up although there was no statistical difference when comparing disease-free survival curves (14). These findings have led some to abandon MIP altogether (11, 15). However, some large series found that MIP is just as durable or even more durable than OP (16, 17).

Routine bilateral exploration is not without its own risks. Bilateral exploration puts both recurrent laryngeal nerves at risk and may slightly increase the hematoma and hypocalcemia rates. A randomized prospective study from Sweden demonstrated that compared to MIP, OP was associated with more symptomatic hypocalcemia as measured by calcium consumption (18). Several large series, however, have demonstrated that these complication rates are quite low, and the hypocalcemia often resolves (19, 20).

To balance the risks of recurrence and complications from additional exploration, several tools exist to help surgeons decide which patients are at risk for multigland disease (21, 22). These scoring systems utilize either pre- or intraoperative variables to help the surgeon select which patients are likely to have multigland disease and will benefit from OP (21–23). Such tools, however, do not evaluate the association between operative approach and

recurrence in multivariate fashion. Despite improvements in preoperative localization, refinement of IoPTH protocols, and intraoperative decision making tools, the recurrence rate after the initial surgery for PHPT remains between two and three percent (14, 16, 17).

The purpose of this study was to determine if the operative approach (MIP vs. OP) influenced disease recurrence and to identify perioperative variables that predict recurrence in PHPT. This study builds on our previous work by evaluating operative approach within a multivariate model that accounts for follow-up time.

Methods

We conducted a retrospective review of a prospectively collected parathyroid database. Cases of PHPT between 2001 and 2011 were selected for further analysis. Familial disease (named, inherited syndromes such as multiple endocrine neoplasia or hyperparathyroidism-jaw tumor syndrome), 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 the University of Wisconsin, almost all patients with biochemical evidence of PHPT are evaluated with sestamibi scan and some patients also undergo neck ultrasound. Preoperative localization was considered positive when the radiologist, nuclear medicine specialist, or surgeon interpreted preoperative imaging studies as localizing a single focus consistent with a parathyroid adenoma. Radioguidance and IoPTH were employed for localization and to guide the extent of exploration as previously described (24). Whenever any localization study is positive, patients are offered MIP, but intraoperative findings and IoPTH determine the extent of exploration. At our institution, 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 that side appeared normal intraoperatively (conversion to OP), or 3) the surgeon decided a priori to perform a bilateral exploration due to patient factors such as a strong family history or discordant imaging. By excluding patients with named familial syndromes, the latter situation is quite rare in this cohort. Our approach is to offer all patients with *any* positive imaging an MIP, and the extent of operation (conversion) is guided by IoPTH, intraoperative findings, and gamma probe counts. Since retrospectively determining which patients were designated as MIP vs. OP preoperatively would only introduce bias, we analyzed the two groups based on the actual treatments received, and not intention to treat.

Preoperative patient characteristics and lab values were recorded. Operative findings including labs and gland weights were also tabulated. The percentage decrease in IoPTH was calculated from the baseline (pre-incision) and the level that ended the operation. Operative findings were classified as either a single adenoma when one enlarged gland was identified or multigland disease when more than one gland was identified (double adenomas or hyperplasia).

Our parathyroid database is maintained with each patient's most recent calcium and PTH values. Postoperative PTH and calcium are drawn one to two weeks after surgery and then again at 6 months. Follow-up labs beyond 6 months are captured whenever feasible. Outcomes were categorized as persistence or recurrence. Persistence was an elevated calcium within six months of the initial operation. Recurrence was defined as an elevated calcium beyond six months postoperatively, with calcium greater than our laboratory's upper limit of normal (>10.2 mg/dL) representing recurrence. PTH levels were also obtained in conjunction with calcium in determining recurrence or persistence at the surgeon's discretion.

Comparisons were made with the student's t-test, Chi-squared test, or the Wilcoxon rank-sum test where appropriate. The minimum p value approach was used to determine the optimal threshold of postoperative PTH and percentage decrease in IoPTH for predicting recurrence. The minimum p-value approach, or alternatively, the maximum statistic approach estimates an optimal threshold for a single continuous covariate using a series of two-sample tests for the multiple possible candidate dichotomizations of the continuous variable. The optimal cutpoint is the candidate dichotomization with the smallest p value after adjustment for multiple comparisons (25). Threshold values were rounded to the nearest whole number for simplicity. Kaplan-Meier disease-free survival estimates were plotted, and multivariate analysis for disease recurrence was performed using the Cox proportional hazards model. Statistical analysis was performed with STATA v. 10.1 software (StataCorp, College Station, TX). $P<0.05$ was considered significant.

Results

Preoperative Characteristics

There were 1,386 patients who presented for the initial surgical treatment of PHPT at our institution between March 1, 2001 and September 1, 2011.

The preoperative patient characteristics are shown in Table 1. The mean age of these patients was 61 years old and 78% were female. Mean preoperative calcium and PTH were 11.0 ± 0.9 mg/dL and 123.8 ± 33.9 pg/mL, respectively (Table 1). 657 patients had preoperative bone scans, and the mean bone mineral density T score was -1.9 (Table 1). Renal function as measured by creatinine was preserved in this cohort of patients since the mean creatinine was 1.0 mg/dL (Table 1). Only 3.5% of patients had a family history of hyperparathyroidism (Table 1).

Intraoperative Findings

77.5% of the entire cohort had a positive sestamibi, and 1,006 patients (72.6%) were treated with MIP, meaning only one side of the neck was explored. At operation, 1,114 patients (80.6%) were found to have a single adenoma. The mean gland weight was 671.8 mg and the mean percentage drop in IoPTH was 65%. Parathyroids were found in ectopic locations (thymus, carotid sheath, upper mediastinum, retroesophageal, or intrathyroidal) in 207 patients (18.6%). The majority of ectopic glands were found in the thymus (66.7%), and

18.4% were intrathyroidal, 14.5% were retroesophageal, 4.8% were within the carotid sheath, and 3.9% were in the upper mediastinum.

Outcomes

Median follow-up time was 9.2 months with a maximum of 116.6 months (inter-quartile range 13.96). 71.1% of patients had a follow-up time greater than 6 months.

A total of 40 patients (2.8%) experienced either persistent or recurrent disease; 29 were in the MIP group, and 11 in the OP group ($p = 0.99$, Table 2). There was no statistical difference in terms of persistent disease or recurrent disease when comparing OP to MIP (Table 2). The disease recurrence rate was 2.5% in the MIP group and 2.1% in the OP group ($p = 0.68$, Table 2).

To further characterize the time pattern of disease recurrence, we plotted Kaplan-Meier disease-free survival estimates for the MIP and OP groups (Figure 1). Most of the recurrences occurred beyond 40 months follow-up (Figure 1). Although there was no statistical difference between the MIP and OP disease-free survival curves, MIP did separate from OP at later (>40 months) time points (Figure 1).

Predictors of Recurrence in Parathyroid Surgery

Although there was no statistical difference in recurrence rates between MIP and OP, we sought to determine if the operative approach (MIP vs. OP) influenced disease recurrence when controlling for all other perioperative variables because of the recent controversy regarding long-term durability of MIP (11, 12, 14, 15). In our multivariate analysis of the entire cohort ($n = 1,386$), performance of MIP did not independently predict recurrence when controlling for other factors (HR 1.93, 95% C.I. 0.50 – 7.45, $p = 0.34$, Table 3). A greater percentage decrease in IoPTH was protective against recurrence (HR 0.96, 95% C.I. 0.93 – 0.99, $p = 0.03$) while a higher postoperative (1–2 weeks) PTH was significantly associated with recurrence (HR 1.03, 95% C.I. 1.02 – 1.05, $p < 0.01$, Table 3). Age, gender, preoperative PTH level, non-localizing sestamibi scan, and the number of glands removed were also included in the multivariate model but did not independently predict recurrence (Table 3).

Postoperative Labs and Recurrence

To better characterize postoperative labs, we compared postoperative (1–2 week) PTH and calcium between those patients who recurred and those who did not recur. While there was no difference in the postoperative calcium levels (9.52 vs. 9.42, $p = 0.83$, Figure 2), those patients who recurred had a higher postoperative PTH compared to those patients who did not recur (64.30 vs. 45.26, $p < 0.01$, Figure 2).

The optimal threshold for predicting disease recurrence was a postoperative PTH level of 48. 80% of all patients who recurred had a postoperative PTH level greater than 48 pg/mL. Therefore, the sensitivity of the threshold postoperative PTH of 48 pg/mL is 80% while the specificity is 57%. The positive predictive value is 6%, but the negative predictive value is 99%.

Fate of Patients with Recurrent Hyperparathyroidism

To better understand the pattern and fate of patients with disease recurrence, we further analyzed the subset of patients who suffered recurrent hyperparathyroidism. Of those that recurred, the median number of glands removed at the initial operation was 1 for the MIP and 2 for the OP group ($p < 0.01$, Table 4). There was no difference in the time to recurrence when comparing patients treated with MIP versus OP (17.7 vs. 19.5 months, $p = 0.56$, Table 4). Of the patients who recurred, 84% of patients treated with MIP were re-operated on and 62.5% of patients treated with OP got a re-operation (Table 4). All of these patients had normal calcium and PTH at last follow-up after the removal of one additional gland at re-operation (Table 4).

Predictors of Recurrence after MIP

Given that the recent controversy regarding the long-term durability of MIP, we next performed a multivariate analysis on just the subset of patients treated with MIP to identify pre and intra-operative factors contributing to recurrence in those treated with this approach. Similar to the analysis of the entire cohort, the analysis of the MIP subgroup ($n = 1,006$) revealed that a greater percentage decrease in IoPTH was protective against recurrence after MIP (HR 0.95, 95% C.I. 0.91 – 0.99, $p = 0.01$, Table 5). Age, a non-localizing sestamibi, preoperative PTH, and the weight of the gland excised were not significantly associated with recurrence (Table 5).

Since the percentage drop in IoPTH was the only significant factor predicting recurrence after MIP in the multivariate analysis, we compared this value between those who recurred and those who did not. Patients who suffered a recurrence had a mean drop in IoPTH that was significantly less than those patients who did not recur (59.98% vs. 65.80% $p = 0.01$, Figure 3). Next, the optimal threshold of percentage decrease in IoPTH was calculated using the minimum p value approach. A percentage decrease in IoPTH of 63% proved the best division between those who recurred and those who did not recur. However, the sensitivity and specificity for this threshold in predicting recurrence was 72.7% and 54.8%, respectively. The positive predictive value was 3.8% and the negative predictive value was 98.8%. That is, only 3.8% of all patients whose percentage decrease in IoPTH was less than 63% suffered a recurrence.

Discussion

In this comprehensive examination of recurrence after initial surgical treatment of primary hyperparathyroidism, we found that operative approach did not independently predict recurrent hyperparathyroidism. Plots of the Kaplan-Meier disease-free estimates revealed no statistical difference between MIP and OP (Figure 1). This pattern remains consistent with our earlier study in which we directly compared the durability of MIP to OP for patients with single adenomas (14). The rates of recurrence reported here are consistent with recurrence rates reported in the literature (4, 26). Udelsman and colleagues reported a lower recurrence rate ($< 1\%$) in a similar number of patients treated with MIP (17), however patients were analyzed with intention to treat, such that conversions to bilateral exploration

were analyzed in the MIP group. Here, we analyzed patients according to the actual treatment received.

Recently, some authors have called for an abandonment of MIP in favor of OP. 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 (11). Here, recurrence rates are much smaller than this predicted recurrence rate, but we do not know the number of patients with additional morphologically abnormal glands left in the neck. Norman et al. found that recurrence was more likely in MIP compared to bilateral explorations (15). Their approach, however, does not utilize IoPTH.

Such claims served as the impetus for this study, as we aimed to determine if operative approach contributes to disease recurrence. When analyzed in a time-dependent, multivariate fashion, MIP with the use of IoPTH did *not* independently predict recurrent hyperparathyroidism (Table 3). The number of glands excised was included in this model, but it also fails to independently predict recurrence. This speaks against removal of more parathyroid tissue as protective against recurrence.

While many blame IoPTH for failure after MIP, the data presented here underscores the importance of IoPTH. A greater percentage decrease in IoPTH was the only factor protective against recurrence in our multivariate analysis for the entire cohort and for patients treated with MIP (Tables 3 and 5). Within the MIP subset, we found that those who recurred had a mean percentage drop of 60% while those who did not recur had a greater percentage decrease of 65% ($p = 0.02$, Figure 3). These data do not necessarily require a more strict IoPTH requirement than the commonly used 50% drop. Since our calculated cutpoint of 63% had a poor positive predictive value of only 3.8%, and would surely prompt further exploration in a large number of patients who ultimately would not recur. On the other hand, the negative predictive value is quite high (99%), so a very high percentage decrease in IoPTH ($> 63\%$) should be re-assuring. Instead of changing the IoPTH criteria, the percentage decrease is one of many pieces of data the surgeon should use to decide whether to terminate the operation or undertake bilateral exploration. Surgeon experience and judgment obviously plays a significant role in the decision to end the operation or undertake further exploration.

The other significant factor associated with recurrence identified by our multivariate analysis was the postoperative (1–2 weeks) PTH level (Table 3). Although this was not a strong association, a higher postoperative PTH was significantly associated with recurrence. Normocalcemic elevations in PTH after parathyroidectomy have been well studied with a reported incidence of 12 to 43% of cases (27–31). Authors who have studied this phenomenon state that multiple factors likely contribute to elevated PTH after parathyroidectomy but warn that this may indicate autonomous PTH secretion, or recurrent disease (28, 31, 32). The results reported here are consistent with those findings. Such patients may require shorter interval follow-up to detect and treat recurrence. Aside from

recurrence, multiple factors contribute to PTH levels, and it is difficult to interpret the PTH level in isolation, without calcium and Vitamin D data.

Previous analyses of failure after MIP cite the surgeon's inability to locate the causative adenoma (33) or the inability of IoPTH to detect multigland disease as factors contributing to operative failure (11, 15, 34). In this study, we focused on recurrent disease rather than persistence. Therefore, the analysis presented here is not directly comparable to studies where the outcome was more immediate operative failures (21, 26, 21, 35). The analysis of patients who recurred revealed that there was no difference in the timing of recurrence between those treated with MIP or OP, and the average time to recurrence occurred between 17 and 19 months postoperatively (Table 4). Therefore, if MIP truly misses morphologically abnormal glands, it takes more than 17 months for these glands to become biochemically apparent. In other words, recurrences appeared as metachronous presentation of multigland disease

The non-significant variables in our multivariate analyses are also revealing. The percentage decrease in IoPTH was significantly associated with recurrence (Tables 3 and 5). However, imaging, biochemical severity of disease, or gland weight could not independently predict recurrence after MIP (Tables 3 and 5). These disease characteristics are traditionally cited factors for 1) selecting patients for MIP and 2) predicting success of a focused approach (21, 36). For example, Kebebew developed a scoring system for predicting which patients are likely to have single gland disease. Patients with single adenomas were more likely to have higher preoperative calcium, PTH, and positive ultrasound and sestamibi studies. Concordant imaging studies also significantly increased the likelihood of a single gland (21). In contrast to the present study, the outcome in this study and others like it was the immediate operative findings and not long-term recurrence rates. In addition, our analysis was performed using the Cox proportional hazards model and not logistic regression. Therefore, these scoring systems are helpful within the operating room, but cannot be directly compared to the results presented here. Our methods account for follow-up time and adjust for multiple patient and disease-related variables. Factors such as gland weight, preoperative PTH level, or localization studies predict the ability to perform MIP with short-term success, but do not independently predict long-term outcomes.

This study has several limitations. As mentioned, the retrospective nature makes it difficult to draw conclusions about treatment differences between OP and MIP. In order to strictly define the two groups retrospectively, we defined MIP as a unilateral exploration, and this may include some patients where another ipsilateral gland was also visualized, but we did not capture this data. Since the groups were defined by the treatment received rather than preoperative designation, some confounding by indication may exist, but hopefully this is minimized by our exclusion criteria. This study cannot answer the question regarding morphologically abnormal but biochemically dormant glands as suggested by other investigators. Although the median follow-up time of 9.2 months with a maximum of 117 months exceeds that of many studies reporting long-term outcomes in primary hyperparathyroidism, this is likely not sufficient time to truly detect all recurrences. The denominator for later time points becomes quite small (Figure 1). With longer follow-up

time and the accrual of more patients, we will be able to make more definitive statements about the long-term durability of operative approach.

Despite these limitations, this large retrospective series indicates that operative approach alone does not independently predict recurrence. A greater percentage decrease in IoPTH was protective while a higher postoperative PTH was predictive of recurrence. In primary hyperparathyroidism, it remains unlikely that any single factor can predict whom MIP best serves, who will recur, or why they recur. Here we provide additional information the surgeon can incorporate into his/her clinical decision making process both during and after the operation.

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Figure 1. Kaplan-Meier Disease-Free Survival Estimates

Kaplan-Meier estimates for recurrent hyperparathyroidism are plotted for patients treated with open (black line) and MIP (gray line). Recurrence was defined as hypercalcemia beyond 6 months follow-up.

Figure 2. Postoperative Calcium and PTH Levels

Calcium and PTH levels are drawn at 1–2 weeks postoperatively. The data are represented as the means with error bars representing the standard deviations.

Figure 3. Percentage Drop in IoPTH in Patients Treated with MIP

Data are represented as the mean percentage decrease in IoPTH that ended the operation.

Error bars indicate the standard deviations.

TABLE 1

Preoperative Patient Characteristics (n = 1,386)

Variable	Mean $\pm$ SD
Age (years)	61 $\pm$ 14
Female	1074 (77.5)
Ca (mg/dL)	11.0 $\pm$ 0.9
PTH (pg/mL)	123.8 $\pm$ 33.9
BMD T score	-1.9 $\pm$ 1.9
Creatinine (mg/dL)	1.0 $\pm$ 0.7
Family history	49 (3.5)

SD = standard deviation, *Ca* = calcium, *PTH* = parathyroid hormone, *BMD* = bone mineral density
Continuous variables are represented as the mean $\pm$ standard deviation unless otherwise indicated.
Numbers in parentheses are percentages.

TABLE 2

Outcomes

Variable	MIP (n = 1,006)	OPEN (n = 380)	p value
Total Failures	29 (2.9)	11 (2.9)	0.99
Persistent	4 (0.4)	3 (0.8)	0.40
Recurrent	25 (2.5)	8 (2.1)	0.68

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

MIP = minimally invasive parathyroidectomy

TABLE 3

Multivariate Cox Proportional Hazards Model for Disease Recurrence (n = 1,386)

Variable	HR	95% CI	p value
Age	0.99	0.96 – 1.01	0.31
Female gender	0.72	0.26 – 1.99	0.52
Preoperative PTH	0.99	0.99 – 1.00	0.20
MIP	1.93	0.50 – 7.45	0.34
Sestamibi non-localizing	2.04	0.82 – 5.04	0.12
% Decrease in IoPTH	0.96	0.93 – 0.99	0.03
Postoperative PTH	1.03	1.02 – 1.05	< 0.01
# Glands removed	1.05	0.47 – 2.35	0.91

HR = hazard ratio, *CI* = confidence interval, *PTH* = parathyroid hormone, *MIP* = minimally invasive parathyroidectomy, *IoPTH* = intraoperative parathyroid hormone. Statistically significant variables are in **bold** print.

TABLE 4

Fate of Patients who Recurred

Variable	MIP (n = 25)	OPEN (n = 8)	p value
Median # glands removed	1	2	< 0.01
Time to recurrence (months)	28.1 ± 7.1	27.2 ± 12.7	0.56
Re-operation	21 (84.0)	5 (62.5)	0.32
Cured	21 (84.0)	5 (62.5)	0.32

Data are represented as the number of patients in each category with the percentage in parentheses with the exception of time to recurrence which is expressed as the mean time to recurrence ± the standard deviation.

MIP = minimally invasive parathyroidectomy

TABLE 5

Multivariate Cox Proportional Hazards Model for Disease Recurrence in MIP (n = 1,006)

Variable	HR	95% CI	p value
Age	1.00	0.97 – 1.03	0.80
Sestamibi non-localizing	2.04	0.68 – 6.15	0.21
Preoperative PTH	1.00	1.00 – 1.00	0.61
% Decrease in IoPTH	0.95	0.91 – 0.99	0.01
Gland weight	1.00	1.00 – 1.00	0.52

HR = hazard ratio, *CI* = confidence interval, *PTH* = parathyroid hormone, *IoPTH* = intraoperative parathyroid hormone. Statistically significant variables are in **bold** print.