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ORIGINAL ARTICLE – ENDOCRINE TUMORS

What Can We Learn from Intraoperative Parathyroid Hormone Levels that Do Not Drop Appropriately?

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ABSTRACT

Background. Parathyroidectomy remains the only definitive treatment for primary hyperparathyroidism. We studied our large series of parathyroidectomies to identify factors predictive of failure to meet intraoperative parathyroid hormone (IOPTH) monitoring criteria.

Methods. We performed a retrospective cohort review of patients who underwent initial parathyroidectomy for primary hyperparathyroidism with IOPTH monitoring. Primary outcome was intraoperative failure, defined as failure to decrease IOPTH by ≥50 % and into normal range. Univariate and multivariate analyses were performed to determine factors associated with intraoperative failure. A subset analysis evaluated 6-month outcomes.

Results. Of 2,185 subjects, 5.0 % ($n = 110$) experienced intraoperative failure. The intraoperative failure group had more multigland disease (35.2 vs. 16.6 %, $p < 0.001$) and smaller glands (1.3 vs. 1.5 cm, $p = 0.048$) compared to patients who experienced intraoperative success. On multivariate analysis, PTH level was statistically, but not clinically, significantly associated with intraoperative failure (odds ratio 1.0, 95 % confidence interval 1.000–1.003). Persistent hyperparathyroidism was identified in 2.5 % ($n = 15$) of 592 patients with ≥6 month follow-up. Median IOPTH decrease was lower in patients with persistent hyperparathyroidism (67.1 vs. 85.8 %, $p < 0.001$). IOPTH criteria were 93.7 % sensitive and 40.0 % specific for eucalcemia 6 months postoperatively. Of 15 patients with persistent hyperparathyroidism, 7 underwent reoperation with a 100 % cure rate. Reoperative diagnoses included ectopic mediastinal glands ($n = 3$), hyperplasia ($n = 3$), and missed second adenoma ($n = 1$).

Conclusions. Intraoperative failure is associated with higher rates of multigland disease and smaller parathyroid glands. Patients with persistent disease had significantly lower decreases in IOPTH, but half of patients who experienced failure by IOPTH criteria were eucalcemic 6 months postoperatively. All patients undergoing reoperation experienced successful cure.

Primary hyperparathyroidism is the most common cause of hypercalcemia. The reported incidence varies widely, from 0.4 to 21.6 cases per 100,000 adults annually.[1,2] Hyperparathyroidism disproportionately affects elderly women, in whom the incidence approaches 120 per 100,000 person-years.[3] Parathyroidectomy remains the only definitive cure.

Parathyroidectomy is a highly successful operation, with published cure rates ranging from 94 to 99 %.[4] However, for patients who are not cured, reoperation can be challenging due to postoperative scarring and distorted anatomy.[5] Compared to the approximately 1 % procedure-specific complication rate associated with initial parathyroidectomy, reoperative parathyroidectomy is associated with complication rates ranging from 27 to 54 %.[6–8] Recurrent nerve injury has been documented in 1.3–9 % of reoperative cases, with persistent hyperparathyroidism in 8–20 %, and mortality as high as 1 %.[8–11] Published cure rates after reoperative parathyroidectomy are typically lower than those for initial procedures, ranging from 83 to 96.8 % in specialized centers.[11–13] Additionally, the cost associated with reoperative parathyroidectomy is roughly twice that of initial parathyroidectomy.[14] As a result, successful initial parathyroidectomy is the safest and most cost-effective option for patients.[15]

Given the challenges surrounding reoperation after failed parathyroidectomy, we analyzed our experience to

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determine factors associated with operative failure with the goal of improving surgical outcomes. Our primary outcome measure was failure to meet intraoperative parathyroid hormone monitoring (IOPTH) criteria. To then determine the relationship between intraoperative failure and persistent hyperparathyroidism, we performed a subset analysis of 6-month outcomes. Although cure (eucalcemia 6 months postoperatively) is the true measure of a successful operation, patients who fail by IOPTH criteria are a crucial population to analyze because surgical decision-making occurs in real time. Particularly in the era of minimally invasive parathyroidectomy, the surgeon must make a decision as to whether to continue exploring. Many variables potentially factor into this decision, including preoperative imaging findings, IOPTH monitoring, frozen section analysis, and clinical judgment. However, IOPTH monitoring is the most objective and quantifiable outcome variable, and the most able to be standardized between institutions.

METHODS

After Institutional Review Board approval was obtained from the University of Pennsylvania, we performed a retrospective study of patients undergoing initial parathyroidectomy for primary hyperparathyroidism using IOPTH monitoring. Patients were identified from our prospectively maintained endocrine surgery registry (2002–2013). Patients with recurrent or persistent hyperparathyroidism, and those with secondary or tertiary hyperparathyroidism were excluded.

The primary outcome of interest was intraoperative failure, defined as failure of IOPTH to decrease by ≥50 % and into the normal range. Preexcision serum parathyroid hormone (PTH) level was drawn immediately prior to operative incision. PTH specimens were processed in the using turbo intact PTH electrochemiluminescent immunoassay and analyzed on Siemens IMMULITE1000 system (Siemens AG, Erlangen, Germany). A postexcision PTH level was drawn at the 15-minute time point. Percent change in IOPTH was calculated as: 100 %—(postexcision PTH/preexcision PTH). For patients with multigland disease, the percent change in IOPTH was calculated using the final PTH after resection of all the abnormal parathyroid glands.

Long-term outcomes were also evaluated: cure was defined as eucalcemia ≥6 months postoperatively, persistent hyperparathyroidism as hypercalcemia ≤6 months postoperatively, and recurrent hyperparathyroidism as hypercalcemia occurring after >6 months of eucalcemia postoperatively, consistent with published definitions.[9] Repeat PTH levels were not routinely obtained in patients with concern for persistent hyperparathyroidism, as elevated parathyroid hormone levels have been documented in 8–44 % of patients after therapeutic parathyroidectomy and are not associated with higher rates of operative failure.[16–18]

TABLE 1 Characteristics of 2,185 patients undergoing initial parathyroidectomy for primary hyperparathyroidism

Characteristic	Value	Reference range
Age, y, mean (standard deviation)	58.5 (13.1)	
Sex		
Female	1,682 (77.0 %)	
Male	503 (23.0 %)	
Nephrolithiasis	465 (21.3 %)	
Bone density loss	1,194 (72.5 %)	
Systemic symptoms	1,522 (69.7 %)	
Genetic syndrome		
MEN-1	9 (0.4 %)	
MEN-2	2 (0.1 %)	
Prior neck operation	42 (1.9 %)	
Serum calcium, mg/dl	10.8 (10.4–11.2)	8.9–10.3
Serum PTH, pg/ml	98.7 (74.0–134.0)	10–65
Serum creatinine, mg/dl	0.8 (0.7–1.0)	0.5–1.1

Data are presented as *n* (%) or median (interquartile range) unless otherwise indicated

PTH parathyroid hormone

Minimally invasive parathyroidectomy (MIP) was defined as a directed unilateral exploration performed through a 2–3 cm incision. Bilateral neck exploration (BNE) was defined as a bilateral exploration performed through a 3–4 cm incision. Prior neck operation was defined as any operative procedure performed via cervical incision, including thyroid resection, cervical lymph node dissection, and tracheostomy. Patients with persistent or recurrent hyperparathyroidism after prior parathyroidectomy were excluded, as noted above. Systemic symptoms included neurocognitive symptoms, constipation, abdominal and bone pain. Bone density loss was defined as osteopenia or osteoporosis, as determined by T-score on DEXA scan. On final surgical pathology, gland size and mass were evaluated for the dominant excised gland.

Descriptive statistics were performed. Univariate analysis was performed using the Chi square test, Student's *t* test, Fisher's exact test, and Wilcoxon rank-sum test, as appropriate. Preoperative covariates achieving nominal significance ($p < 0.20$) on univariate analysis were incorporated into a forward stepwise multivariate logistic regression model to identify factors independently associated with intraoperative failure by IOPTH criteria. A p value of <0.05 was considered statistically significant.

A subset analysis was performed on the cohort of patients with long-term follow-up. Due to a referral practice covering a large geographic area, follow-up data of ≥6 months was available for 27.1 % ($n = 592$) of patients. The cohort with long-term follow-up data had a higher proportion of patients with a positive family history of hyperparathyroidism, including patients with MEN (2.6 vs. 0.9 %, $p = 0.004$); there were no other significant differences between groups.

Statistical analysis was performed using STATA/IC 13.0 software (Stata Corporation, College Station, TX).

RESULTS

Of 2,185 subjects included in the study, the mean age was 58.5 ± 13.1 years (Table 1). The majority (77.0 %, $n = 1,682$) of patients were female. The median preoperative serum calcium level was 10.8 mg/dl [interquartile range (IQR) 10.4–11.2 mg/dl], and the median serum parathyroid hormone (PTH) level was 98.7 pg/ml (IQR 74.0–134.0 pg/ml).

On analysis of patients by IOPTH criteria, 5.0 % ($n = 110$) were in the intraoperative failure group (Table 2). There were no significant differences between patients who experienced intraoperative failure and patients who did not in terms of age (mean 60.0 vs. 58.5 years, $p = 0.222$), gender (78.2 vs. 76.9 % female, $p = 0.759$), or incidence of genetic syndromes (0.9 vs. 0.5 %, $p = 0.434$). Symptom profiles were similar, including nephrolithiasis (20.9 vs. 21.3 %, $p = 0.943$); bone density loss (80.0 vs. 72.2 %, $p = 0.125$); and systemic symptoms (69.1 vs. 69.8 %, $p = 0.883$), in intraoperative failure and intraoperative success groups, respectively. There was no difference in rates of preoperative localization (53.6 vs. 62.2 %, $p = 0.073$), median preoperative serum calcium (10.7 vs. 10.8 mg/dl, $p = 0.525$) or PTH levels (107.9 vs. 98.0 pg/ml, $p = 0.154$) between the intraoperative failure and intraoperative success groups. The median change in IOPTH level was 47 % in the intraoperative failure group versus 86.6 % in the intraoperative success group. Patients who experienced intraoperative failure were more likely to require BNE (75.4 vs. 59.6 %, $p = 0.001$) and had a higher proportion of multigland disease when compared to intraoperative success patients (35.2 vs. 16.6 %, $p < 0.001$), although the most common diagnosis in both groups was single adenoma (64.8 vs. 83.4 %, respectively). There was no difference between the intraoperative failure and intraoperative success groups in rates of ectopic glands found at the time of initial operation (4.6 vs. 7.5 %, $p = 0.346$). Patients in the intraoperative failure group had smaller dominant glands by size (median 1.3 vs. 1.5 cm, $p = 0.048$) but not by mass (median 298.0 vs. 395.0 mg, $p = 0.103$).

TABLE 2 Characteristics of patients undergoing initial parathyroidectomy for primary hyperparathyroidism by operative outcome

Characteristic	Failure ($n = 110$)	Success ($n = 2,075$)	p
Age, y, mean (standard deviation)	60.0 (13.4)	58.5 (13.1)	0.222
Sex			0.759
Female	86 (78.2 %)	1,596 (76.9 %)	
Male	24 (21.8 %)	479 (23.1 %)	
Nephrolithiasis	23 (20.9 %)	442 (21.3 %)	0.943
Bone density loss	64 (80.0 %)	1,130 (72.2 %)	0.125
Systemic symptoms	76 (69.1 %)	1,446 (69.8 %)	0.883
Genetic syndrome			0.434
MEN-1	1 (0.9 %)	8 (0.4 %)	
MEN-2	0 (0.0 %)	2 (0.1 %)	
Prior neck operation	3 (2.7 %)	39 (1.9 %)	0.467
Imaging			
Localized, by any imaging modality	59 (53.6 %)	1,290 (62.2 %)	0.073
Serum calcium, mg/dl	10.7 (10.2–11.2)	10.8 (10.4–11.2)	0.525
Serum PTH, pg/ml	107.9 (70.0–174.8)	98.0 (74.3–132.0)	0.154
Serum creatinine, mg/dl	0.9 (0.7–1.2)	0.8 (0.7–1.0)	0.008
Operative approach			0.001
MIP	27 (24.6 %)	838 (40.4 %)	
BNE	83 (75.4 %)	1,237 (59.6 %)	
Change in IOPTH, %	47.0 (21.6–73.9)	86.6 (79.2–91.5)	<0.001
Operative findings			<0.001
Single adenoma	59 (64.8 %)	1,716 (83.4 %)	
Multigland disease	32 (35.2 %)	342 (16.6 %)	
Ectopic gland	5 (4.6 %)	155 (7.5 %)	0.346
Gland size, cm[a]	1.3 (0.9–2.0)	1.5 (1.1–2.0)	0.048
Gland mass, mg[a]	298.0 (92.0–1,105.0)	395.0 (199.0–819.0)	0.103

Data are presented as n (%) or median (interquartile range) unless otherwise indicated

MIP minimally invasive parathyroidectomy, *BNE* bilateral neck exploration, *IOPTH* intraoperative parathyroid hormone

[a] Gland size and mass listed for dominant excised gland

Multivariate analysis was performed to identify preoperative factors associated with intraoperative failure (Table 3). Higher serum PTH level was statistically, but not clinically significant (odds ratio 1.0, 95 % confidence interval 1.000–1.003). No other factors were independently associated with intraoperative failure.

Subset analysis was performed on patients with ≥6 month follow-up, to determine what proportion of patients who experienced intraoperative failure ultimately had persistent disease. A total of 592 patients (27.1 %) had ≥6 month follow-up; the median follow-up period was

TABLE 3 Multivariate analysis of factors associated with operative failure

Factor	Odds ratio	95 % confidence interval	*p*
Bone density loss,	1.9	0.781–4.551	0.159
Serum PTH	1.0	1.000–1.003	0.015
Serum creatinine	0.8	0.207–2.911	0.708
Localization, by imaging	0.7	0.376–1.475	0.398

PTH parathyroid hormone

28 months (IQR 8–63 months). Eventual recurrence was identified in 3.2 % ($n = 19$). An additional 2.5 % ($n = 15$) had persistent hyperparathyroidism. As shown in Table 4, there were no differences between patients with persistent hyperparathyroidism and cured patients in terms of age (mean 52.5 vs. 58.7 years, $p = 0.076$), gender (66.7 vs. 77.0 % female, $p = 0.358$), successful preoperative imaging (53.3 vs. 65.3 %, $p = 0.336$), preoperative median serum calcium (11.0 vs. 10.8 mg/dl, $p = 0.206$), or PTH level (82.6 vs. 98.0 pg/ml, $p = 0.280$). Patients with persistent hyperparathyroidism underwent BNE in 73.3 % of cases, compared to 58.4 % of patients who were cured ($p = 0.297$). Of patients with persistent hyperparathyroidism who underwent MIP ($n = 27$), the majority met criteria of a $\geq$50 % decrease in IOPTH (92.6 %, $n = 25$) but had a final IOPTH level outside the normal range (85.2 %, $n = 23$). The median percent change in IOPTH was significantly lower in patients with persistent disease (67.1 vs. 85.8 %, $p < 0.001$) compared to cured patients.

Of the 42 patients with intraoperative failure in the long-term follow-up group, only 14.3 % ($n = 6$) had persistent hyperparathyroidism; only one patient (2.3 %) underwent MIP. There were no statistically significant differences between the 6 patients who ultimately had persistent

TABLE 4 Characteristics of patients undergoing initial parathyroidectomy for primary hyperparathyroidism, by 6-month outcomes

Characteristic	All patients ($n = 592$)	Persistent disease ($n = 15$)	Cure ($n = 577$)	*P*
Age, y, mean (standard deviation)	58.6 (13.5)	52.5 (16.6)	58.7 (13.4)	0.076
Sex				0.358
Female	454 (76.7 %)	10 (66.7 %)	444 (77.0 %)	
Male	138 (23.3 %)	5 (33.3 %)	133 (23.0 %)	
Nephrolithiasis	126 (21.3 %)	125 (21.7 %)	1 (6.7 %)	0.232
Bone density loss	305 (72.1 %)	7 (70.0 %)	298 (72.2 %)	0.881
Systemic symptoms	397 (67.2 %)	10 (66.7 %)	387 (67.2 %)	0.966
Genetic syndrome				1.000
MEN-1	7 (1.2 %)	0 (0.0 %)	7 (1.2 %)	
MEN-2	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
Redo neck	10 (1.7 %)	1 (6.7 %)	9 (1.6 %)	0.228
Imaging				
Localized, by any imaging modality	385 (65.0 %)	8 (53.3 %)	377 (65.3 %)	0.336
Serum calcium, mg/dl	10.8 (10.4–11.2)	11.0 (10.7–11.5)	10.8 (10.4–11.2)	0.206
Serum PTH, pg/ml	97.8 (73.0–139.1)	82.6 (54.0–114.3)	98.0 (73.0–139.1)	0.280
Serum creatinine, mg/dl	0.8 (0.7–1.0)	1.0 (0.7–1.2)	0.8 (0.7–1.0)	0.527
Operative approach				0.297
MIP	244 (41.2 %)	4 (26.7 %)	240 (41.6 %)	
BNE	348 (58.8 %)	11 (73.3 %)	337 (58.4 %)	
Change in IOPTH, %	85.6 (77.7–91.2)	67.1 (25.0–76.3)	85.8 (78.1–91.4)	<0.001
Operative findings				1.000
Single adenoma	472 (81.0 %)	8 (80.0 %)	464 (81.0 %)	
Multigland disease	111 (19.0 %)	2 (20.0 %)	109 (19.0 %)	
Ectopic gland	158 (7.3 %)	2 (13.3 %)	31 (5.4 %)	0.201
Gland size, cm[a]	1.5 (1.1–1.9)	1.3 (1.1–1.5)	1.5 (1.1–2.0)	0.400
Gland mass, mg[a]	362 (190–797)	357.8 (151.4–533.5)	362.0 (190.0–808.0)	0.534

Data are presented as *n* (%) or median (interquartile range) unless otherwise indicated

MIP minimally invasive parathyroidectomy, *BNE* bilateral neck exploration, *IOPTH* intraoperative parathyroid hormone

[a] Gland size and mass listed for dominant excised gland

TABLE 5 Characteristics of patients with persistent hyperparathyroidism

Patient no.	Sex	Age, y	IOPTH decrease, %	Operative approach	Reoperation	Reason for persistence
1	F	59	76	MIP	Yes	Missed multigland disease, subtotal parathyroidectomy performed for hyperplasia on reoperation
2	F	69	25	BNE	No	Misdiagnosis; subtotal parathyroidectomy performed, all glands normal
3	F	63	52	MIP	No	Patient lost to follow-up
4	M	60	67	BNE	Yes	Missed mediastinal adenoma; cured on sternotomy by thoracic surgery
5	M	50	67	BNE	No	Patient deferred further surgery due to metastatic bladder cancer
6	M	33	79	BNE	No	Patient lost to follow-up
7	F	55	−43[a]	BNE	Yes	Inadequate subtotal parathyroidectomy; cured on reoperation with further debulking
8	F	56	63	BNE	No	Patient lost to follow-up
9	F	60	84	MIP	Yes	Missed second adenoma in normal position; cured on reoperation
10	M	71	72	MIP	No	Patient deferred further surgery because asymptomatic
11	F	25	−132[a]	BNE	Yes	Missed mediastinal adenoma; cured on transcervical thymectomy by thoracic surgery
12	F	75	75	BNE	Yes	Missed multigland disease; subtotal parathyroidectomy performed on reoperation
13	F	32	−9[a]	BNE	Yes	Missed mediastinal adenoma; cured on transcervical thymectomy by thoracic surgery
14	M	23	68	BNE	No	Likely missed multigland disease; inherited disorder of calcium metabolism on genetic testing (first-degree relative of patient 15)
15	F	56	86	BNE	No	Subtotal parathyroidectomy performed, but hypercalcemic 6 wk after surgery; inherited disorder of calcium metabolism on genetic testing (first-degree relative of patient 14)

IOPTH intraoperative parathyroid hormone, *MIP* minimally invasive parathyroidectomy, *BNE* bilateral neck exploration

[a] IOPTH levels increased after gland manipulation, consistent with no abnormal tissue excised

hypertension and the 36 patients who were ultimately cured in terms of any of the preoperative or intraoperative variables examined. Within the intraoperative failure group, patients who had persistent hyperparathyroidism had abnormal calcium levels at 2- to 3-week postoperative follow-up, compared to the normal values in patients who were cured on long-term follow-up (median 10.3 vs. 9.3 mg/dl, $p = 0.010$).

Of the 15 patients with persistent hyperparathyroidism, 60 % ($n = 9$) originally met IOPTH criteria. Of the 6 patients who did not originally meet IOPTH criteria, 1 patient failed to drop ≥50 %, 2 patients failed to normalize IOPTH, and 3 patients failed both criteria. The sensitivity of IOPTH criteria for cure at 6 months was 93.7 %, with a specificity of 40.0 %, a positive predictive value (PPV) of 98.3 %, and a negative predictive value (NPV) of 14.3 %.

On detailed analysis of the 15 cases of persistent hyperparathyroidism, one patient was found to be misdiagnosed, and did not have primary hyperparathyroidism. Three patients were lost to follow-up, and an additional 4 patients have elected not to pursue further surgical intervention to date (Table 5). Two of these (patients 14 and 15) were first-degree relatives, and had a non-MEN inherited disorder of calcium metabolism diagnosed on postoperative genetic testing. One (patient 15) was found to be hypercalcemic 6 weeks postoperatively, despite having undergone a subtotal parathyroidectomy with an 86 % decrease of IOPTH into the normal range. The remaining 7 patients underwent reoperation with a 100 % cure rate. Of these patients, on reoperation 43 % ($n = 3$) had ectopic mediastinal glands; 14 % ($n = 1$) had a missed second adenoma in the normal position; and 43 % ($n = 3$) had hyperplasia.

DISCUSSION

In this study, we analyzed our large series of initial parathyroidectomies to identify factors associated with operative failure and persistent hyperparathyroidism. We found that patients who failed by IOPTH criteria had higher rates of multigland disease and smaller parathyroid glands. On multivariate analysis the only preoperative factor associated with intraoperative failure was serum PTH level, however with an odds ratio of one, it was not clinically significant. Nonlocalization by preoperative imaging was not associated with intraoperative failure on univariate or multivariate analysis. On subset analysis of 6-month outcomes after parathyroidectomy, the median percent change in IOPTH was significantly lower in

patients with persistent hyperparathyroidism (67.1 vs. 85.8 %). In patients who underwent reoperation, the reasons for persistent hyperparathyroidism were missed multigland disease and ectopic mediastinal adenoma; reoperation was successful in all patients.

In this investigation, we found that smaller glands and higher incidence of multigland disease were associated with failure by IOPTH criteria, but negative localization was not. Our group has previously reported a higher rate of multigland disease in patients with a ≥50 % decrease in IOPTH levels but failure to normalize IOPTH.[19] Other investigators have noted a correlation between smaller gland size and persistent disease or smaller decrease in IOPTH. One recent report found that in patients with initial resection of a parathyroid microadenoma (<200 mg), persistent disease was observed in 6.6 %, which was significantly more frequent than the 0.7 % observed in those with macroadenoma.[20] In a study of 30 patients with single adenomas, Moretz et al. reported a significant negative correlation between gland weight and the percent decrease in IOPTH.[21] Notably, although both multigland disease and smaller gland size are associated with nonlocalization by preoperative imaging, in our study cohort negative imaging was not associated with intraoperative failure on either univariate or multivariate analysis.[22–25] Nonlocalization by imaging should not influence the decision to refer patients for surgical evaluation.

On analysis of 6-month outcomes in our study cohort, we found that patients with persistent hyperparathyroidism had a significantly smaller decrease in IOPTH. Reports in the literature vary as to the relationship between IOPTH values and persistent hyperparathyroidism. One study found that patients with a final IOPTH value ≥40 pg/ml had a higher rate of persistent hyperparathyroidism (13.6 vs. 0.0 %, $p < 0.001$) when compared to patients with a final IOPTH value in the low normal range, despite a median IOPTH decrease of 74 % in the higher group.[26] In contrast, a recent study of 1,108 parathyroidectomies found no difference in rates of persistent hyperparathyroidism based upon the same IOPTH cut-off of 40 pg/ml, but a higher incidence (1.2 %) of recurrent hyperparathyroidism in patients with a high normal IOPTH compared to 0 % recurrence observed in patients with a final IOPTH <40 pg/ml.[27] Further investigation of this area is needed.

In our study population, an IOPTH decrease of ≥50 % and into the normal range had a sensitivity of 93.7 %, specificity of 40.0 %, PPV of 98.3 %, and NPV of 14.3 % for cure. Chiu et al. previously reported a sensitivity of 88 %, specificity of 22 %, PPV of 97 %, and NPV of 6 % for the same criteria.[28] The slightly better performance of these criteria in our study cohort is similar to the findings of Wharry et al. and may reflect variations in clinical practice and decision making at different institutions.[27] Notably, within the group that did not meet IOPTH criteria, none of the preoperative or intraoperative variables examined was significantly associated with persistent hyperparathyroidism. This may reflect underpowering due to small sample size, but limits the ability of this study to predict which patients who failed by IOPTH will eventually be cured based upon the information available to the surgeon at the time of surgery. However, those patients with persistent hyperparathyroidism were hypercalcemic at their postoperative clinic visit 2–3 weeks after surgery, while patients who ultimately experienced cure were normocalcemic. These data suggest that patients who have truly failed operative intervention may be identified well before the 6-month time point which is widely accepted as the definition of persistent hyperparathyroidism.

In contrast to published series of reoperative parathyroidectomies in which the most common cause of persistent hyperparathyroidism is missed single adenoma in the normal anatomic position, missed multigland disease and ectopic glands accounted for all 7 cases of persistent hyperparathyroidism in our patients who underwent reoperation.[7,10,11] This may represent the effect of surgical volume in our tertiary care center. The majority of reoperative cases are typically referred in from smaller institutions; surgeons who operate infrequently for primary hyperparathyroidism may be more likely to miss a single adenoma in the normal position. Several studies have noted lower success rates and higher complication rates in this setting, compared to high volume centers.[11,29]

In our patients with persistent hyperparathyroidism, 43 % had hyperplasia on reoperation. This is slightly higher than prior reports, in which rates of hyperplasia range from 18 to 37 %, however this may be due to small sample size.[9,10,30] An additional 43 % of our reoperative cases had ectopic mediastinal glands. Mediastinal adenomas are a well-documented cause of persistent hyperparathyroidism, and an indication for reoperation. Some authors have advocated for the use of angiographic ablation as a potential option for missed mediastinal adenomas, however this technique has only a 60 % success rate, even at specialized centers.[31] Surgical resection has a similar complication rate to angiographic ablation with more durable outcomes, and therefore should be considered the standard of care in patients who are operative candidates.

In this study, for patients who had persistent disease and underwent reoperation, the success rate was 100 %. Although historical cure rates for reoperative parathyroidectomies range from 80 to 90 %, recent studies have reported cure rates comparable to those in initial parathyroidectomies.[11–13] As preoperative imaging techniques and intraoperative adjuncts have improved, reoperative parathyroidectomy has become a safer and more successful operation, and it should be considered as a potential management option for all patients who are candidates for surgery.

This study has several limitations. Although data were collected prospectively, the analysis was performed retrospectively, and may therefore be subject to bias. A further limitation is the incomplete availability of long-term follow-up data, due to the long distance referral pattern in our institution. However, on comparison of patients based upon the availability of $\geq$ 6 month follow-up, the only significant difference was a higher incidence of positive family history in those patients with long-term follow-up. Better follow-up in this population is desirable due to the increased likelihood of recurrence.[32–34]

In summary, in this large series of parathyroidectomies, we found that failure to meet IOPTH criteria was associated with increased rates of multigland disease and smaller parathyroid glands, but not with nonlocalization by preoperative imaging. Patients with persistent disease had a significantly smaller decrease in IOPTH, but failure by IOPTH criteria was only 14 % predictive of hypercalcemia 6 month postoperatively. For patients undergoing reoperation for persistent hyperparathyroidism, missed multigland disease and ectopic mediastinal adenomas should be included in the differential diagnosis. Although potentially technically challenging, reoperation can be highly successful and should be considered for all patients.

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