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Tertiary hyperparathyroidism: Is less than a subtotal resection ever appropriate? A study of long-term outcomes

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Abstract

Background—Our aim was to examine the outcomes of patients with tertiary hyperparathyroidism (3-HPT) who had limited resection of one or two parathyroids.

Methods—We reviewed 140 patients with 3-HPT who underwent parathyroidectomy (PTX) at a single institution. Patients were analyzed according to their operation—limited PTX vs. subtotal or total PTX.

Results—The limited PTX group consisted of 29 patients who underwent resection of one (n=12) or two (n=17) parathyroids. The other 111 patients had subtotal (n=104), total (n=3), and/or reoperative PTX (n=12). The mean follow-up was 79 ± 5 months. Eucalcemia was achieved in 94% of the cases. All patients with persistent (n=2) hypercalcemia underwent subtotal PTX ($P=NS$ vs. limited PTX). In a logistic regression model, the extent of operation was not associated with the development of recurrent disease. Additionally, the incidence of permanent hypocalcemia was 7% after subtotal or total PTX versus 0% following limited resection ($P=NS$).

Conclusions—Long-term outcomes in patients with 3-HPT appear to be similar following appropriate limited resection of one or two parathyroid glands compared to subtotal or total PTX. Therefore, a strategy of limited parathyroid resection seems appropriate for patients with 3-HPT when the disease is limited to one or two glands.

Tertiary hyperparathyroidism (3-HPT) most commonly refers to the persistent over-secretion of parathyroid hormone (PTH) after renal transplantation in patients with secondary hyperparathyroidism (2-HPT). The majority of patients with 2-HPT have resolution of their parathyroid disease following the restoration of renal function. However, up to 8% of patients with 2-HPT continue to have autonomous PTH secretion after transplant which can lead to osteopenia, pathologic fractures, renal calculi, and mental status changes as well as decreased graft function (1–5). Surgical correction of 3-HPT is indicated if hypersecretion of PTH and hypercalcemia persist for more than one year following renal allograft reception or if hypercalcemia is symptomatic or severe. Parathyroidectomy (PTX) is considered to be the only curative treatment for patients with 3-HPT and should be performed with a bilateral neck exploration and examination of all parathyroid glands (6).

The majority of patients with 3-HPT have multiple hyperplastic glands and, therefore, should undergo a subtotal PTX or total PTX with forearm implantation of a parathyroid remnant (1, 2,6–9). However, a subset of patients with 3-HPT has disease due to one or two enlarged parathyroids (1–3,5–7,10,11). Reports of increased rates of recurrence in patients who undergo

limited PTX of only one or two parathyroids have led some surgeons to abandon this approach (9). The objective of this study was, therefore, to examine the outcomes after limited resection of one or two parathyroid glands in patients with 3-HPT.

METHODS

Retrospective review of all patients with 3-HPT who underwent PTX at the University of Wisconsin between January 1984 and June 2008 by 4 endocrine surgeons was performed. Patients were considered to have 3-HPT if they were previously diagnosed with 2-HPT, underwent renal transplantation, and continued to have elevated intact PTH (iPTH) levels after normalization of renal function. PTX was undertaken if patients remained hypercalcemic (serum calcium >10.2 mg/dl) for more than one year after transplant, had severe hypercalcemia (serum calcium >12 mg/dl) at any point following transplant, or were symptomatic with hypercalcemia. Each patient underwent bilateral neck exploration with identification of all parathyroid glands. In cases where enlargement of three or four glands was noted, a subtotal (3.5 gland) or total (4 gland) PTX with auto-transplantation was carried out with cryopreservation of resected tissue. These patients made up the subtotal/total PTX group. The intended parathyroid remnant size in these patients was 50 mg to 75 mg and was the same for all surgeons. A limited resection was performed when only one or two of the four visualized parathyroid glands were enlarged. In these instances, only the one or two visually enlarged parathyroids were resected. These patients became the limited PTX group for analysis. Histopathology and/or biopsy of normal parathyroids were not used to determine the type of resection to perform. A parathyroid gland was considered to be abnormally large if it was greater than approximately 50 mg in size. An attempt was made to identify all four parathyroid glands in every case. If all 4 glands were not identified, a subtotal PTX was performed of the visualized glands, if all visualized glands were abnormal. A limited PTX was performed in this instance only if all other glands appeared normal in size. Patients had a transcervical thymectomy if preoperative imaging or intraoperative radioguided localization indicated that an intrathyroid parathyroid was present, or if an inferior gland was not discovered after a thorough exploration. In later cases, intraoperative PTH (ioPTH) monitoring was used for confirmation, but was not the surgical endpoint since its utility in this patient population is not well established.

Data collected and evaluated included patient demographics, laboratory studies, operative details, and outcomes. The primary outcome used to measure success or failure after PTX was persistent or recurrent hypercalcemia. Elevated iPTH levels also were used as a secondary endpoint. The definitions of these outcome variables are summarized in Table I. For analysis of iPTH levels, patients were classified into CKD stages (1–5) by calculating their estimated creatinine clearance (eCrCl) with the Cockcroft and Gault formula which requires weight in kilograms (12). If a patient's weight was not available, the modified diet in renal disease (MDRD) equation was used to calculate the eCrCl (13). The Kidney Disease Outcome Quality Initiatives (K/DOQI) clinical practice guidelines which define a target range of iPTH for each CKD stage were then used to classify iPTH levels as elevated if the measured postoperative value was outside the recommended iPTH range (14). This adjustment of the goal postoperative iPTH level according to CKD stage was previously described by Triponez et al (9).

Institutional Review Board approval was obtained for this investigation. Statistical analysis was performed with SPSS software (version 10.0, SPSS Inc, Chicago, IL). Comparisons between limited PTX and subtotal or total PTX were performed with 2-sided, unpaired t tests and Fisher's exact where appropriate, unless otherwise noted. Continuous normally distributed demographic, laboratory, and outcome variables were correlated with Pearson correlation, while nominal and skewed data were correlated with Spearman correlation. Logistic regression with variables having a *P* value of less than 0.15 was then used to identify predictors of recurrent

hypercalcemia and recurrent iPTH elevation. Statistical significance was reached at a *P* value of less than 0.05. Data are reported as mean $\pm$ standard error (SEM).

RESULTS

We reviewed 140 patients with 3-HPT who underwent PTX (*n*=148) during the study period. The limited PTX group consisted of 29 patients who underwent resection of one (*n*=12) or two (*n*=17) parathyroid glands. The 111 patients in the subtotal or total PTX group underwent 119 surgeries: subtotal PTX (*n*=104), total PTX with autograft (*n*=3), or reoperative PTX (*n*=12). Eight patients in the subtotal or total PTX group underwent 2 operations at our hospital: 7 after an initial 3.5 gland resection and 1 after a 2.5 gland resection. Two of these 8 reoperations were performed for recurrence due to a supernumerary gland. The 4 other patients who underwent reoperative PTX had their initial surgery at outside institutions, and all underwent a previous subtotal PTX per their operative note. The mean and median duration of follow-up for the entire cohort were 78.7 and 60.4 months, respectively (range 0.1 to 22.9 years), and greater than 6 month follow-up was available after all but 12 operations (92%) (Table I). Overall, 94 patients (69%) had symptomatic 3-HPT—17 limited PTX patients (59%) and 77 subtotal or total PTX patients (70%) (*P* = 0.26).

Table II summarizes patient demographics and characteristics. The limited PTX and subtotal/total PTX patients were comparable in terms of age, gender distribution, duration of dialysis, and time since renal transplant (Table II). The two groups also had similar preoperative and follow-up serum calcium, iPTH, phosphate, and estimated creatinine clearance (eCrCl) levels (Table III). At follow-up, the serum calcium, iPTH, and eCrCl measurements were significantly lower than the respective preoperative values, while the serum phosphate levels were significantly higher (by paired *t* test; Table III). Additional analysis showed a strong direct correlation between preoperative and follow-up eCrCl (Pearson *r* = 0.66, *P* < 0.001), but no significant relationship between follow-up calcium and iPTH levels, and CKD stage.

Analysis of surgical data demonstrated that operative times were similar for the limited PTX and subtotal/total PTX patients (144 ± 7 vs 135 ± 4 mins, respectively, *P* = 0.32). Thirty-four percent of limited resection cases utilized iPTH monitoring while 51% of subtotal/total PTX cases were performed with iPTH (*P* = 0.15). The limited group also had a mean parathyroid gland weight of 951 ± 143 mg which was comparable to the mean gland weight for subtotal or total PTX patients (1114 ± 113 mg, *P* = 0.48). For all patients, preoperative iPTH levels positively correlated with gland weight suggesting that heavier gland secrete more PTH (Pearson *r* = 0.50, *P* < 0.0001). When adjusting for outliers, the groups also had average lengths of stay that were similar (2.2 ± 0.3 vs 2.2 ± 0.1 days, respectively, *P* = 0.98). In 7% of limited resection patients and 19% of subtotal/total PTX patients, ectopic parathyroid glands were discovered during surgery (*P* = 0.16). These ectopic glands were intrathyroidal (*n*=8), intrathyroidal (*n*=3), retroesophageal (*n*=3), mediastinal (*n*=2), and undescended (*n*=1). As a result of intrathyroidal or missing inferior glands, 11% and 17% of limited resection and subtotal or total resection patients, respectively, underwent concurrent thymectomy during surgery (*P* = 0.73). The incidence of permanent hypocalcemia was 0% after limited PTX compared to 7% following subtotal or total PTX (*P* = 0.36). Furthermore, after subtotal PTX, two patients had transient hoarseness and one had pneumonia. One patient suffered a permanent recurrent laryngeal nerve injury during a reoperative PTX for recurrent 3-HPT.

When examining our primary and secondary outcome variables, cases of reoperative PTX were excluded from the analyses. Those patients with available information regarding their first operation (*n*= 8) were included in the outcomes analysis. In the first 6 months after PTX, 98% of all patients (126 of 128) were eucalcemic, and 86% of all patients (95 of 111) had normal iPTH levels for their CKD stage. The 2 patients who had persistent hypercalcemia underwent

reoperative PTX with subsequent eucalcemia. After 6 months, recurrent hypercalcemia developed in 5% of all patients (7 of 128), and recurrent iPTH elevation occurred in 38% of all patients (35 of 91). Thus, 94% of all patients were eucalcemic at their most recent follow-up. The rates of all outcome variables were similar between patients who underwent limited PTX and those who had subtotal or total PTX (Table IV). Recurrent hypercalcemia in conjunction with an elevated iPTH level was observed in only 2 patients both of whom underwent initial subtotal PTX (and subsequent reoperative PTX). Table V summarizes these results by CKD stage.

Logistic regression was then used to examine predictors of recurrent hypercalcemia or recurrent iPTH elevation. Based on the significance of the correlation coefficients ($P < 0.15$), the variables that were included in the modeling of recurrent hypercalcemia included the duration of dialysis, pre-operative iPTH levels, post-operative CKD stage and creatinine level, complication occurrence, and ioPTH testing use. The type of parathyroidectomy performed (limited PTX vs. subtotal/total PTX) also was included because previous data have suggested that limited resection increases the risk of developing persistent or recurrent 3-HPT (9). None of the variables examined were significant predictors of recurrent hypercalcemia, including the extent of resection ($P = 0.58$). The most predictive variable was the occurrence of a complication which only trended toward significance as a negative predictor of recurrent hypercalcemia ($P=0.06$). We then analyzed factors predictive of the recurrent iPTH elevation, both the pre-operative iPTH level and the one-week post-operative serum calcium level were found to be predictive of iPTH recurrence ($P < 0.05$ for both). The relationship of these associations was such that a higher pre-operative iPTH or one-week post-operative serum calcium increased the odds of developing recurrent iPTH elevation. The extent of operation again was not associated with the development of recurrent iPTH elevation ($P = 0.99$).

DISCUSSION

The purpose of this study was to analyze the outcomes of patients with 3-HPT who underwent limited resection and determine whether this selective approach is ever appropriate. The results demonstrate that long-term outcomes in patients with 3-HPT are similar for those undergoing appropriate limited resection of one or two parathyroid glands compared to those undergoing subtotal or total PTX. Patients who underwent limited resection had comparable laboratory values, operative times, lengths of stay, rates of persistent and recurrent hypercalcemia, and complications.

In the present analysis, 21% of all patients underwent a limited resection for single or double gland disease as determined by visual intraoperative assessment by an experienced endocrine surgeon. Pathologic analysis of the resected specimens was not performed due to the inability to examine unresected parathyroids for comparison in limited PTX patients, and because the ability to discern an adenoma from a hyperplastic parathyroid by histopathology is somewhat ambiguous. This 21% incidence is within the range of previous reports that suggest as many as 32% of patients may have 3-HPT due to a single or double adenoma (1–3,5–7,10,11). In our previously published series, a single or double adenoma was found in 30% of cases (6). The small decrease in one or two gland disease may be due to the more recent utilization of intra-operative adjuncts such as ioPTH monitoring or radioguided probe use which provides additional information (other than size) which may influence the decision of whether or not to resect only one or two glands.

In this study, comparison of outcomes between patients who underwent limited resection and those who had subtotal or total PTX revealed that parathyroid gland weights, operative times, lengths of stay, and complication rates were similar. Interestingly, our analysis did show that increased resected gland weights were associated with higher pre-operative iPTH levels

suggesting that the amount of iPTH oversecretion is directly related to the size or density of the enlarged parathyroid. The operative times reported here were comparable to those previously published by our group (6). These similarities in operative times between the 2 groups in this study and between our current and earlier data are likely because a bilateral neck exploration was performed in all patients. When considering complications, our results confirm that an advantage of appropriate limited resection is that the risk of permanent hypocalcemia is negligible (1–4,6,7,9,10,15,16). No patients who underwent limited PTX developed permanent hypocalcemia. In addition, reoperative PTX was not required in any patients who had limited PTX, but was performed in 12 patients after subtotal PTX. Therefore, in terms of risks to the patient, appropriate limited resection in 3-HPT does not increase the risk of complications or reoperation when compared to a more traditional approach.

This investigation also examined potential predictors of recurrent hypercalcemia and recurrent iPTH elevation in an attempt to identify which patients have increased odds of developing recurrent disease. While our univariate analysis did not show that the type of resection was associated with recurrent hypercalcemia or iPTH elevation, this variable was included in both models because previous data have suggested that limited PTX increases the risk of 3-HPT recurrence (7,9,15). None of the variables examined in this study were significant predictors of recurrent hypercalcemia. The occurrence of a complication did trend toward significance, but as a negative predictor. This trend is likely because the majority of complications in this study were hypocalcemia or hypoparathyroidism which precludes the occurrence of recurrent hypercalcemia. As for predictors of recurrent iPTH elevation, both an elevated pre-operative iPTH level and a higher post-operative calcium level were significant predictors of recurrent iPTH elevation. These data suggest that patients with very high iPTH levels before PTX and higher calcium levels following PTX should be closely monitored for the recurrent iPTH elevation. Because both of these factors were analyzed as continuous variables, we were unable to determine a cut-off point beyond which recurrent iPTH elevation is significantly increased. Importantly, our data did not show that the type of PTX was associated with increased odds of developing recurrent hypercalcemia or iPTH elevation. Gilat et al. reported a similar finding that pre-transplant iPTH levels are significant predictors of persistent 3-HPT after PTX (5). Their data also indicated that duration of dialysis and post-operative renal function are important predictors of persistent 3-HPT, though our data did not confirm these results (5).

Previous series have reported that up to 29% of patients treated with subtotal or total PTX will develop persistent or recurrent 3-HPT (7,9,15). Our results are consistent with these previous series with 7% experiencing recurrent hypercalcemia and 38% recurrent iPTH elevation. However, review of the literature also suggests that as high as 91% of patients treated with a limited PTX will develop persistent or recurrent 3-HPT (7,9,15). In our series, patients who underwent a limited PTX had a much lower incidence of persistent *or* recurrent hypercalcemia or iPTH elevation than previously reported (9). In this study, the rates of persistent and recurrent hypercalcemia or iPTH elevation also were similar between the two types of operations. In addition, univariate and logistic regression analyses did not identify the extent of operation to be a significant predictor of persistent or recurrent hypercalcemia or iPTH elevation. Furthermore, all patients who underwent limited resection were eucalcemic at last follow-up. The difference in the incidence of persistent or recurrent 3-HPT in this study when compared to previous reports may be because limited resection in this study included identification of all 4 glands. In patients with hyperplasia, who undergo an inappropriate limited resection, the rate of persistent or recurrent 3-HPT should approach 100%. Therefore, careful selection of patients in whom a limited PTX is appropriate is very important.

The development of persistent or recurrent 3-HPT is often thought to be related to the function of the renal allograft. While a decline in renal function is known to occur in at least 30% of

renal transplant recipients, the CKD that develops likely results in recurrent 2-HPT which may not require reoperation (17). Thus, an elevated iPTH during follow-up may be more indicative of the redevelopment of 2-HPT from impaired renal function than true 3-HPT recurrence. Approximately 15% of patients in our series developed 2-HPT, and there were no differences between the limited PTX and the subtotal/total PTX groups. Furthermore, Table V demonstrates that recurrent iPTH elevation was not related to the CKD stage. This result also was confirmed by our univariate analysis. Our previous studies on this topic did not evaluate iPTH levels, which is one of the strengths of the current study (2,6).

With an average of over 7 years of follow-up, all 3-HPT patients treated by an appropriate limited PTX were eucalcemic and free of permanent complications. The percentage of patients who developed persistent or recurrent hypercalcemia was similar between the limited PTX and subtotal or total PTX groups. In addition, the proportion of patients who had persistent or recurrent elevated iPTH also was comparable. In a logistic regression analysis, the type of procedure performed was not a significant predictor of recurrent 3-HPT. The results of this study indicate that a strategy of limited parathyroid resection appears to be appropriate for select patients with 3-HPT when the disease is clearly due to one or two glands. When operating on these patients, bilateral neck exploration with visualization of all 4 glands should be the standard of care regardless of the underlying etiology of disease. Resection of abnormal glands should be performed, but removal of visibly normal parathyroids does not appear to be necessary when the disease appears to be limited to one or two glands.

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Table I

Definitions of Outcomes

	Laboratory Findings	Timing
Primary Outcomes		
Persistent HPT (Failure) – Persistent hypercalcemia	Ca >10.2 mg/dl	< 6 months after PTX
Recurrent HPT (Recurrence) – Recurrent hypercalcemia	Ca >10.2 mg/dl	> 6 months after PTX*
Secondary Outcomes		
Persistent iPTH elevation	iPTH > than recommended range for CKD Stage [†]	< 6 months after PTX
Recurrent iPTH elevation	iPTH > than recommended range for CKD Stage [†]	> 6 months after PTX*

[†] See text and Table V for details.

* Recurrent hypercalcemia or iPTH elevation did not include patients with persistent hypercalcemia or iPTH elevation, respectively.

HPT, hyperparathyroidism; PTX, parathyroidectomy; iPTH, intact parathyroid hormone.

Table II

Preoperative characteristics

	Total	Limited PTX	Subtotal or Total PTX	P value
N	140	29	111	
Age (y)	49 ± 1	51 ± 2	49 ± 1	0.44
Gender (% female)	50	55	49	0.60
Duration of dialysis (y)	2.3 ± 0.3	1.7 ± 0.3	2.5 ± 0.4	0.11
Time from transplant to PTX (m)	28 ± 4	20 ± 4	31 ± 5	0.06

Data shown as mean ± SEM. *PTX*, parathyroidectomy.

Table III

Preoperative and follow-up laboratory values

	Total	Limited PTX (n=29)	Subtotal or Total PTX (n=111)	P value
Pre-op calcium (mg/dL)	11.1 ± 0.1	11.3 ± 0.2	11.2 ± 0.1	0.46
Follow-up calcium *	9.1 ± 0.1	9.2 ± 0.1	9.1 ± 0.1	0.77
Pre-op iPTH (pg/mL)	457 ± 61	350 ± 83	481 ± 72	0.41
Follow-up iPTH *	106 ± 13	138 ± 27	110 ± 22	0.12
Pre-op eCrCl (mL/min)	67 ± 3	59 ± 7	68 ± 3	0.43
Follow-up eCrCl *	60 ± 3	46 ± 4	57 ± 4	0.95
Pre-op phosphate (mg/dL)	2.6 ± 0.1	2.4 ± 0.1	2.6 ± 0.1	0.15
Follow-up phosphate *	3.8 ± 0.1	3.7 ± 0.2	3.8 ± 0.1	0.93

Data shown as mean ± SEM. *PTX*, parathyroidectomy; *eCrCl*, estimated creatinine; *iPTH*, intact parathyroid hormone.

* $P < 0.01$ vs Pre-op values by 2-sided paired t test.

Table IV

Outcomes following parathyroidectomy

	Limited PTX % (n/total)	Subtotal or Total PTX % (n/total)	P value
Failure (%)	<u>0 (0/29)</u>	<u>2 (2/111)</u>	1.00
Recurrence (%)	<u>0 (0/26)</u>	<u>7 (7/101)</u>	0.34
Persistent iPTH elevation (%)	<u>29 (6/21)</u>	<u>11 (10/90)</u>	0.08
Recurrent iPTH elevation > 6 mos (%)	<u>43 (6/14)</u>	<u>38 (29/77)</u>	0.77
Follow-up (m)	84 ± 13	78 ± 6	0.63

Data shown as mean ± SEM. *PTX*, parathyroidectomy; *eCrCl*, estimated creatinine; *iPTH*, intact parathyroid hormone.

Table V

Outcomes following parathyroidectomy

CKD Stage	eCrCl	Target iPTH [†]	Ca n	Recurrent Hypercalcemia (n [%])	iPTH n	Recurrent iPTH elevation (n [%])
1	≥ 90	Normal	15	--	10	3 (30)
2	60 – 89	Normal	27	--	21	10 (48)
3	30 – 59	35 – 70	47	5 (11)	38	16 (42)
4	15 – 29	70 – 110	16	--	13	4 (31)
5	<15 or dialysis	150 – 300	11	2 (18)	7	1 (14)

Data shown as mean ± SEM.

[†]Target iPTH range as recommended by the National Kidney Foundation, KDOQI guidelines (ref 14). CKD, chronic kidney disease; PTX, parathyroidectomy; eCrCl, estimated creatinine clearance; iPTH, intact parathyroid hormone; Ca, calcium.