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Outcomes after Subtotal Parathyroidectomy for Primary Hyperparathyroidism due to Hyperplasia: Significance of Whole vs. Partial Gland Remnant

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Abstract

Introduction—Primary hyperparathyroidism (PHPT) due to multi-gland hyperplasia is managed by subtotal parathyroidectomy (sPTX), with a partial gland left in situ. However, smaller, hyperplastic glands may be encountered intra-operatively, and it is unclear if leaving an intact gland is an equivalent alternative. This study evaluates the rates of permanent hypoparathyroidism and cure of PHPT patients with 4-gland hyperplasia that were left with either a whole gland remnant (WGR) or partial gland remnant (PGR) after sPTX.

Methods—We reviewed the outcomes of PHPT patients with hyperplasia who underwent sPTX at an academic institution. Surgeon intra-operative judgment determined remnant size (WGR vs. PGR).

Results—Between 2002 and 2013, 172 patients underwent sPTX for PHPT. 108 patients (62.8%) had a WGR. 64 (37.2%) had a PGR. Mean age was 60 years ± 14. 82.6% were female. Cases with positive family history for PHPT were more likely to have a PGR (12.5% vs. 3.7%, p=0.03). Patients had similar pre-operative and post- operative labs. Individuals with PGR tended to have larger glands encountered by surgeons intra- operatively (525 mg± 1308 vs. 280 mg± 341, p=0.02). One patient with WGR developed permanent hypocalcemia. Overall cure rate was 97.1%. A mean 29 months± 28.7 follow up revealed a recurrence rate of 5.2%. Disease persistence and recurrence rates were similar in patients.

Conclusion—PHPT due to hyperplasia is managed by sPTX, leaving WGR without increased rates of disease persistence/recurrence. Patients without family history for hyperparathyroidism and those with smaller glands may be the best candidates for this approach.

Introduction

Primary hyperparathyroidism (PHPT) due to multi-gland hyperplasia occurs in 8 to 15% of patients[1-4]. Classically, this has been managed by subtotal parathyroidectomy, leaving a

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viable fragment of parathyroid tissue roughly the size of normal parathyroid gland (<50 mg)[5]. Familial types of PHPT are managed by either subtotal parathyroidectomy or total parathyroidectomy with auto-transplantation parathyroid tissue[6-8]. Between these two different methods of parathyroidectomy, a subtotal resection is more commonly utilized due to comparable rates of disease persistence and/or recurrence, and a lower risk of post-operative hypoparathyroidism[4,7,9-10]. Resection of less than three hyperplastic glands, in cases with familial types of PHPT, is reported to result in strikingly high rates of persistence and recurrence (15%- 50% in different studies), and therefore, is not advised[6-7,10].

The risk of persistence and recurrence must be balanced with the risk of post-operative hypocalcemia, as the surgeon decides how much parathyroid tissue must be resected for each individual patient. Conceptually, the more parathyroid tissue removed at time of surgery, the higher the risk of post-operative hypoparathyroidism and hypocalcemia. Hence, total parathyroidectomy is more often complicated by post-operative hypocalcemia than when subtotal parathyroidectomy is performed[4,7]. When looking at all patients undergoing parathyroidectomy for PHPT, the rate of post-operative permanent hypoparathyroidism is reported to be only 0- 0.5 %, but increases dramatically to 10-15% in those patients requiring a subtotal resection[4,11]. Regardless of extent of resection, transient hypocalcemia occurs up to 35% after parathyroidectomy for PHPT[12]. Many providers attempt to avoid this complication by the routine use of post-operative calcium and vitamin D supplementation[12-13]. Post- operative hypocalcemia can also be influenced by a myriad of other factors, regardless of the type of surgery, and is not solely the result of hypoparathyroidism[3,14-17].

The aim of this study was to compare rates of symptomatic hypoparathyroidism (transient and permanent), as well as rates of disease persistence and recurrence, after subtotal parathyroidectomy with a whole gland remnant (WGR) versus as partial gland remnant (PGR) for PHPT. The study hypothesis was that patients with a WGR have lower rates of hypoparathyroidism, but at the expense of higher rates of disease persistence and recurrence when compared to patients with a PGR at time of subtotal parathyroidectomy for PHPT due to multigland hyperplasia.

Method

After IRB approval, a retrospective review was performed on a prospective database of patients with PHPT. Inclusion criteria required the patient to have four gland hyperplasia encountered at time of surgery, managed with a subtotal parathyroidectomy. Patients converted to bilateral exploration from a minimally invasive, direct approach were included if four gland hyperplasia was encountered. Patients with a previous parathyroidectomy for primary hyperparathyroidism, those undergoing a total parathyroidectomy ± autotransplant, patients with secondary or tertiary hyperparathyroidism, or cases with less than 6 months follow-up were excluded. Patient who had normocalcemic PHPT (serum PTH ≥62 pg/ml and calcium ≤10.2 mg/dl) or those who had inappropriately normal parathyroid levels in the presence of hypercalcemia (calcium >10.2 mg/dl) were considered to have mild PHPT.

All patients underwent bilateral exploration with subtotal parathyroidectomy. The parathyroid gland selected as the remnant was either left intact or resected down to the rough equivalent of a normal gland (<50mg) based on surgeon judgment and visual inspection of the glands[5]. The most normal appearing gland was generally selected for the remnant. If all glands were equivalent in appearance, a lower gland was preferred as a remnant for ease of access in the future should re-operation be necessary. All cases relied on intraoperative parathyroid hormone (ioPTH) monitoring, with a pre-incision baseline, and levels checked at 5, 10 and 15 minutes following resection of the final offending gland[2]. IoPTH was not used to influence decision making regarding WGR versus PGR, but rather to confirm all hyperfunctioning parathyroid tissue was removed. The weight of the largest resected adenoma was recorded. A majority of the specimen was sent for cryopreservation. Post-operative supplementation included 1000 mg of calcium carbonate three times a day, and patients are instructed to take the daily recommended dose of Vitamin D (600-800 international units). Patients experiencing symptoms of numbness or tingling are instructed to take an additional 2000 mg of calcium carbonate every 30 minutes as needed. Patients who experience failure to respond to oral calcium, are instructed to call the surgical clinic for further instruction.

Patients were classified based on the type of parathyroid gland remnant: WGR or a PGR. Serum calcium and PTH levels were evaluated at 1-2 weeks, and again at 6 months, after surgery. Additional serum calcium measurements were performed in the presence of signs and symptoms of hypocalcemia which did not respond to oral calcium supplementation. Transient hypocalcemia was defined as low post- operative serum calcium (<8 mg/dL) or PTH (<10 pg/ mL) levels and concomitant presence of classic sign and symptoms of hypocalcemia, paresthesia (numbness and tingling) which occurred within the first few days to weeks after surgery, out to 6 months. Patients who required calcitriol to resolve symptoms of hypocalcemia, or to maintain serum calcium ≥8 mg/dL, within the first 6 months of surgery were also considered to have transient hypocalcemia. Patients requiring more than 6 months of calcium and calcitriol supplementation to maintain serum calcium ≥ 8 mg/ dL with a serum PTH < 10 pg/ mL were defined as experiencing permanent hypoparathyroidism[18]. Disease persistence was defined as hypercalcemia within 6 months of surgery. Normocalcemia for 6 months after surgery defined cure. Recurrent disease was defined as hypercalcemia occurring more than 6 month after the surgery.

Statistical analysis was performed by using IBM SPSS Statistics version 21. Independent sample t-test was used to compare continuous variables. Categorical variables were compared using chi-square and Fisher's exact test as appropriate. P- value ≤0.05 was considered significant. Data are expressed as mean ± standard deviation, unless otherwise stated.

Results

Between 2002 and 2013, 172 patients underwent subtotal parathyroidectomy for PHPT due to parathyroid hyperplasia. Mean age was 60 years ± 14 and 82.6% of patients were female. 10 patients (7%) had a family history for PHPT. All patients underwent bilateral exploration with ioPTH monitoring. Forty seven patients (27.3%) experienced transient hypocalcemia

following the operation. During a mean follow up period of 29 months± 28.7, only 1 patient (0.6%) experienced permanent hypoparathyroidism. PHPT was cured in 97.1% of patients following subtotal parathyroidectomy, leaving 2.9% of patients with persistent disease (n=5). Overall recurrence rate was noted to be 5.2% (n=9).

Partial gland remnant vs. whole gland remnant

Subtotal parathyroidectomy with WGR was performed on 108 patients (62.8%), while 64 patients (37.2%) were left with a PGR (Table 1). Patient age and gender distribution were similar between the remnant groupings. Cases with PGR were more likely to have a positive family history for hyperparathyroidism compared to those with WGR (12.5% vs. 1.9%, p= 0.006). Patients had similar pre-operative serum calcium, PTH, phosphate, creatinine, alkaline phosphatase and vitamin D levels. Pre-operative bone mineral densitometry (BMD) revealed no difference in t-score.

Intraoperatively, patients selected for PGR had larger dominant glands (525 mg± 1308 vs. 280 mg± 341, p=0.02) (Table 2). Serum calcium and parathyroid hormone measurements were comparable at time of first post-operative visit (p=0.38 and 0.41, respectively). Patients with PGR or WGR had similar rates of post-operative transient hypocalcemia and permanent hypoparathyroidism (p= 0.86 and 0.44 accordingly). Disease persistence occurred in 3 patients (2.8%) with WGR and in 2 patients (3.1%) with PGR (p= 1). Six patients (5.6%) with WGR and 3 (4.7%) with PGR experienced recurrent disease during the follow up (p= 0.75). Follow up duration was similar among groups (p= 0.67). Only one patient developed permanent hypoparathyroidism. The patient underwent subtotal parathyroidectomy with a WGR.

Transient post-operative hypocalcemia

Of 47 patients diagnosed with post-operative transient hypocalcemia, 30 individuals (63.8%) had WGR whereas 17 patients (36.2%) had PGR (p= 0.86) (Table 3). PGR patients who experienced post-operative hypocalcemia were noted to have a greater incidence of mild PHPT (18% vs. 0 for WGR, p=0.04) and a greater incidence of preoperative kidney stones (18% vs. 0 for WGR, p=0.02). Comparing those patients who experienced post-operative transient hypocalcemia versus those who had normal post-operative serum calcium levels, demographics, pre- operative and post-operative lab values, and the rates of disease persistence and recurrence were similar (Table 4). However, patients experiencing transient hypocalcemia after parathyroidectomy were less likely to have mild PHPT (34% vs. 57.6%, p= 0.006), and had larger resected glands during the operation (530 mg± 1491 vs. 311 mg± 371, P= 0.048).

Positive family history for primary hyperparathyroidism

A sub-analysis was performed on the 10 patients with a positive family history for PHPT. 3 patients had MEN 1 (Multiple Endocrine Neoplasia) syndrome, 2 of whom were left with PGR following subtotal parathyroidectomy. Six patients were noted to have a first degree family member with a diagnosis of PHPT, and one patient had a distant relative with PHPT. Of all the patients with a known family history of PHPT, 2 patients were left with a WGR,

while the remaining 8 patients had PGR. None of the patients with positive family history for PHPT had disease persistence or recurrence during the mean follow up of 18 month± 15.

Discussion

According to the data presented in this retrospective study, no significant difference in patient outcome was found between those patients selected for WGR or PGR after subtotal parathyroidectomy for PHPT due to hyperplasia. This study did not demonstrate any difference in the rates of transient hypocalcemia, permanent hypoparathyroidism, disease persistence or recurrence. A positive family history for PHPT and larger glands encountered at time of surgery were the only differences noted between the patients selected for PGR versus WGR. Patients who experienced symptomatic post-operative transient hypocalcemia had larger parathyroid glands resected during the operation.

The overall rate of post-operative transient hypocalcemia in the study cohort of 27.3% is comparable to the reported prevalence (15-30%) in PHPT patients. Previous studies have explained numerous etiologies for this occurrence. It is more probable for patients with post-operative transient hypocalcemia to have lower pre-operative serum phosphate levels[16]. Pre-operative normal serum calcium level and PTH ≥25 pg/mL, are also introduced as determinants for post-operative transient hypocaclcemia[17]. Previous studies have described that post-operative transient hypocalcemia is more common in older patients, those with pre-operative history of hypertension and cases who were on calcium lowering agents preoperatively[3,14]. Hungry bone syndrome, which is characterized by avid bone uptake of serum calcium after surgery, is also an important factor in developing transient hypocalcemia and may even become more pronounced secondary to supressed function of residual glands[19-20]. Bilateral exploration, which may disturb blood supply of the remnant gland, is also known as a predisposing factor for post-operative transient hypocalcemia[16,21]. Of note, all the mentioned determinants had been evaluated in PHPT patients in general. In contrast, the data presented within this study is the result of selectively studying patients with PHPT due to multigland hyperplasia.

In this specific subset of patients, larger glands found at time of surgery were associated with post-operative hypocalcemia. The impact of resected gland weight on serum calcium level was previously evaluated in patients with PHPT[12,19,22-23]. Patients with larger glands resected at the time of operation were proposed to have higher rate of post-operative transient hypocalcemia which is similar to findings presented in this study[19,22]. Compromise of the blood supply following a partial resection may account for post-operative transient hypocalcemia in patients undergoing subtotal parathyroidectomy with PGR[19]. Symptoms from this could be minimized by routine post-operative treatment of patients with calcium and/or vitamin D supplementation. In contrast with larger gland size, patients with mild PHPT were less likely to experience post-operative transient hypocalcemia.

The absence of a sufficiently functioning parathyroid gland following parathyroidectomy is almost always the cause of permanent hypoparathyroidism[4]. The prevalence of permanent hypoparathyroidism in PHPT patients undergoing parathyroidectomy is reported to be less than 0.5%, and the rate of 0.6% presented within our study population is similar[11]. Women,

older patients, and those with less parathyroid gland remnant following parathyroidectomy are proposed to be at increased risk of post-operative permanent hypoparathyroidism[4,15]. Although this complication was expected to occur among patients with PGR, the only case of permanent hypoparathyroidism in the presented study happened to undergo subtotal parathyroidectomy with WGR. However, due to the very low overall rate of post-operative permanent hypoparathyroidism amongst the study cohort, it is difficult to draw any conclusions as to factors associated with this complication.

PHPT patients undergoing subtotal parathyroidectomy as the procedure of choice for treatment of multi gland hyperplasia have either a whole, or a partial gland remnant. Disease persistence or recurrence has not been previously compared in patients who underwent subtotal parathyroidectomy with PGR versus WGR. In the data presented above, follow up of patients for almost 2 and a half years after subtotal parathyroidectomy revealed similar risk of disease persistence and recurrence regardless of remnant size. Therefore, partial resection of the remnant parathyroid gland and its related complications, such as devascularisation of the gland and subsequent hypoparathyroidism, could be avoided in patients with smaller parathyroid glands; especially if they undergo subtotal parathyroidectomy in the hands of a low volume surgeon [4,24]. The overall cure rate of 97.1% in the study cohort is comparable to reported cure rate of bilateral exploration (>95%) in patients with primary hyperparathyroidism[25].

As this study represents a retrospective review of a prospectively maintained database, it has inherent limitations. No set protocol exists to determine which patient is selected for WGR versus PGR; the decision was solely based on surgeon judgement. While this study can provide insight into variables influencing surgeon decision making (family history, gland size), it cannot account for, or identify, all possible factors. This study was conducted at a high volume endocrine surgery practice, in which surgeon experience may also influence our findings, which may not be reproducible at lower volume centers. Additionally, given the low rates of disease persistence, recurrence and permanent hypoparathyroidism, it is possible that a type II error may occur. Further study with larger populations would be needed to clarify this. The designation of a positive family history within this population includes MEN 1 syndromes, as well as other familial forms of PHPT. This creates a heterogeneous group with in the family history category, each with varying degrees of concern for disease persistence and recurrence.

Conclusion

Selected patients with PHPT due to hyperplasia can be safely managed with subtotal parathyroidectomy with an intact gland left as remnant but without increased rates of disease persistence or recurrence. Patients with sporadic PHPT, and those with smaller diseased glands may be the best candidates for this approach. Risk of both transient hypocalcemia, and of permanent hypoparathyroidism is equivalent between the approaches when patients are appropriately selected.

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Table 1

Patient demographic and pre-operative lab values. Data expressed as number (percentage) or mean ± standard deviation.

		Whole gland remnant	Partial gland remnant	P- value
N		108 (62.8%)	64 (37.2%)	
Age (years)		61 ± 13.2	57 ± 15.2	0.28
Female Gender		89 (82.4%)	53 (82.8%)	0.95
Mild Hyperparathyroidism		57 (52.8%)	31 (48.4%)	0.58
Family History		2 (1.9%)	8 (12.5%)	**0.006**
Kidney Stones		4 (3.7%)	4 (6.2%)	0.44
Pre- Op	**Calcium (mg/dl)**	10.6 ± 0.7	10.8 ± 0.8	0.53
	PTH (ng/ml)	89 ± 50	92 ± 55	0.81
	Phosphate (mg/dl)	3.1 ± 0.7	3.1 ± 0.6	0.07
	Creatinine (mg/dl)	1.13 ± 0.74	1.11 ± 0.84	0.89
	Alkaline Phosphate (U/L)	93 ± 45	96 ± 29	0.13
	Vitamin D (ng/ml)	36 ± 14	38 ± 16	0.4
	BMD (T-Score)	-2 ± 1.13	-1.8 ± 1.5	0.05

Pre- Op, pre- operative; PTH, parathyroid hormone; BMD, bone mineral density

Table 2

Patient post-operative lab values and complications. Data expressed as number (percentage) or mean ± standard deviation.

		Whole gland remnant	Partial gland remnant	P- value
N		108 (62.8%)	64 (37.2%)	
Gland Weight (mg)		280 ± 341	525 ± 1308	**0.02**
Calcium (mg/ dl)		9.2 ± 0.96	9.3 ± 0.87	0.91
PTH (pg/ ml)		43 ± 30	36 ± 28	0.51
Transient Hypocalcemia		30 (27.8%)	17 (26.6%)	0.86
Permanent Hypoparathyroidism		1 (0.9%)	0 (0%)	0.44
Disease	**Persistence**	3 (2.8%)	2 (3.1%)	1
	Recurrence	6 (5.6%)	3 (4.7%)	1
Time of Follow Up		30 ± 27	27 ± 31	0.67

PTH, parathyroid hormone

Table 3

Distribution of patients experiencing symptomatic transient hypocalcemia based on the gland remnant size. Data expressed as number (percentage) or mean ± standard deviation.

		Whole gland remnant	Partial gland remnant	P- value
N		30	17	0.86
Age (years)		58 ± 15	54 ± 16	0.83
Female Gender		25 (83.3)	16 (94.1%)	0.29
Mild Hyperparathyroidism		0 (0%)	3 (17.6%)	**0.04**
Kidney Stones		0 (0%)	3 (17.6%)	**0.02**
Pre-Op	**Calcium (mg/dl)**	10.5 ± 0.71	10.6 ± 0.81	0.4
	PTH (ng/dl)	101 ± 52	111 ± 59	0.57
Post-Op	**Calcium (mg/dl)**	8.6 ± 1.1	8.7 ± 1	0.97
	PTH (ng/dl)	30 ± 23	32 ± 30	0.63
Persistence		0 (0%)	0 (0%)	1
Recurrence		0 (0%)	1 (5.9%)	0.18

Pre- Op, pre- operative; PTH, parathyroid hormone; Post- Op, Post- operative

Table 4

Comparison between patients with transient hypocalcemia and those without transient hypocalcemia. Data expressed as number (percentage) or mean ± standard deviation.

	Patients with Transient Hypocalcemia	Patients without Transient Hypocalcemia	P- value
N	47	125	
Age (years)	56 ± 15	61 ± 13	0.48
Female Gender	41 (87.2%)	101 (80.8%)	0.32
Mild Hyperparathyroidism	16 (34%)	72 (57.6%)	**0.006**
History of Hypertension	25 (53.2%)	81 (64.8%)	0.16
Family History	1 (2.1%)	9 (7.2%)	0.21
Gland Weight (mg)	530 ± 1491	311 ± 371	**0.05**
Persistence	0 (0%)	5 (4%)	0.16
Recurrence	1 (2.1%)	8 (6.4%)	0.26