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Challenges and pitfalls in the management of persistent primary hyperparathyroidism, a case series

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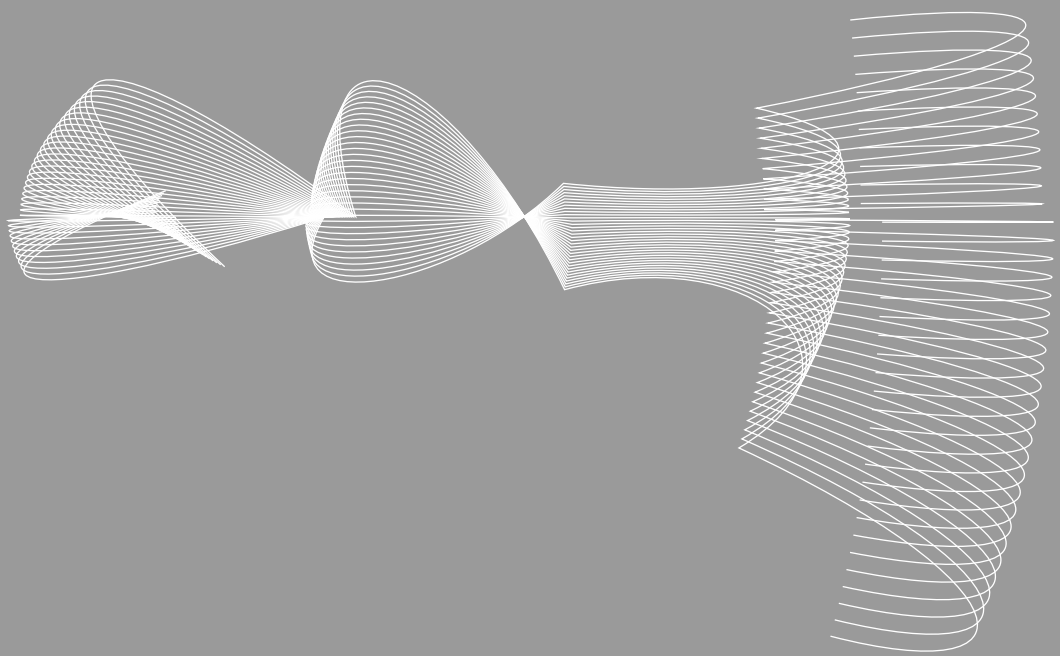

ABSTRACT

Background: Persistent hyperparathyroidism is rare after surgery for sporadic hyperparathyroidism, occurring in only 0-6% of cases. The management of these patients is complex, with a generally poor cure rate despite repeated surgery. The aim of our study was to identify the challenges and pitfalls encountered in the complex management of patients with persistent hyperparathyroidism after initial parathyroidectomy.

Methods: Using Leiden University Medical Centre hospital records, we identified 20 patients with sporadic primary hyperparathyroidism who had undergone 33 revision surgeries for persistent hyperparathyroidism. Patients with a *MEN-1, MEN-2* or *CASR* mutation or carcinoma were excluded. Clinical, operative and histology data were collected for the period covering the course of the disease.

Results: The most common causes of persistent hyperparathyroidism were a missed ectopic gland at initial surgery (33%) and missed multiglandular disease (15%). Parathyromatosis was documented in 9% of patients. Pre-operative localisation studies had poor sensitivity: ultrasound 18%, Tc99m-MIBI-SPECT 25%, CT 30%, MRI 20%. In contrast, selective venous sampling for PTH had a sensitivity of 50% and a specificity of 89%. The decrease in intraoperative PTH was significantly less marked in patients in whom hyperparathyroidism persisted compared to those who achieved cure (63 ± 26 vs. 89 ± 11%, P=0.003). The risk of complications increased with each subsequent surgery: 20% after first, 50% after 2nd and 67% after 3rd surgery.

Conclusion: Persistent PHPT represents a significant management challenge largely due to the poor predictive value of pre-operative localisation studies and to the risk of complications, which increases with each subsequent revision surgery.

INTRODUCTION

In primary hyperparathyroidism (PHPT) cure is reported in 93 to 100% of cases after parathyroidectomy, also when a minimally invasive approach is opted for (1-4). Removal of all hyperactive parathyroid tissue is of significant clinical relevance, since patients who achieve cure show significant post-operative increase in bone mass (5,6), no recurrence of nephrolithiasis (5,6) and improvement in various parameters of quality of life (7,8).

Persistent hyperparathyroidism is defined as residual biochemical features of hyperparathyroidism in the form of increased serum calcium and PTH concentrations documented directly post-operatively or within the first 6 months after removal of one or more hyperactive parathyroid glands at initial surgery and persisting thereafter (4). Persistent PHPT is most commonly due to a pathological gland missed at initial surgery, which is often small (<1.5 cm) and hyperplastic in nature (9,10), or rarely due to parathyromatosis from gland spillage during previous surgery (11). It is of note that the diagnosis of persistent hyperparathyroidism may be overlooked or delayed after parathyroidectomy, particularly in the case of multiple gland disease due to transient normalization of serum calcium and PTH concentrations due to suppression of the activity of smaller glands by the dominant first resected large gland. Pathological small parathyroid glands may indeed take up to 6 months to recover and become hyperactive in their own right (4).

Initial bilateral neck exploration or the more limited surgical approaches are associated with very few complications in the hands of experienced surgeons (12,13). In contrast, re-exploration for persistent hyperparathyroidism is associated with a 3-fold increase in morbidity due to scarring and disruption of the normal patterns of drainage due to previous surgery (14,15). In this case, pre-operative localisation studies are imperative in order to reduce operating time and the risk of complications. However, the value of standard localisation studies has been shown to be significantly curtailed in patients with persistent PHPT, predominantly because of the high frequency of hyperplastic, ectopically located and small sized

parathyroid glands (16-18). Management of patients with persistent hyperparathyroidism represents therefore a recurring challenge.

The aim of our study was to evaluate the demographic, clinical, biochemical, operative and pathology data of a series of patients with persistent hyperparathyroidism who had had one or more revision surgeries after initial parathyroidectomy, identifying in the process the challenges and pitfalls encountered in their complex management.

PATIENTS AND METHODS

Study population

Using our hospital records, we identified 20 patients who had undergone a total of 33 revision surgeries for persistent PHPT in the Leiden University Medical Center. Eighteen of the 20 patients (90%) had had their initial parathyroidectomy at another hospital. All revision surgeries were undertaken by two surgeons with considerable experience in endocrine surgery. Patients with a *MEN-1*, *MEN-2* or *CASR* mutation were not included in the study.

Methods

All available demographic data, clinical data, data on pre-operative localisation studies, operative data, including data on intra-operative PTH measurements, pre- and post-operative laboratory data and histopathological data were obtained from the patients' hospital records.

All pre-operative localisation studies, including Tc99m-MIBI-SPECT and selective venous sampling for PTH (SVS), followed by CT-scan to confirm localisations suggested by Tc99m-MIBI-SPECT or SVS, were reviewed and analysed as previously reported (19,20).

Bilateral neck exploration consisted of visualization of all four parathyroid glands, leading to either excision of a single enlarged parathyroid gland, or to subtotal or total parathyroidectomy with auto-transplantation if more than one parathyroid gland was found to be enlarged. If no parathyroid glands could be

visualized or no enlarged gland was found, the surgeon proceeded to dissection of the ipsilateral anterior compartment extending from the level of the hyoid bone superiorly to the suprasternal notch inferiorly and to a hemithyroidectomy on the side of the missing parathyroid. Less invasive neck exploration was only undertaken in patients with positive preoperative localisation studies and was guided by intra-operative PTH (IOPTH) monitoring in the majority op patients. IOPTH monitoring consisted of two initial baseline PTH measurements with an interval of 15-20 minutes, followed by 5 measurements at 3-minute intervals after excision of the pathological parathyroid(s). Surgery was considered successful if IOPTH decreased by more than 50% within 7 minutes of excision of a pathological parathyroid gland(s).

Histological preparations obtained at surgery conducted in our hospital (including all last revision surgeries) were independently reviewed by an experienced pathologist. A diagnosis of sporadic parathyroid adenoma was based on the presence of a benign encapsulated neoplasm mostly consisting of one cell type with an adjacent rim of normal glandular tissue, usually involving a single gland (21). A diagnosis of parathyroid hyperplasia was based on an absolute increase in parathyroid parenchymal cell mass resulting from proliferation of a mixture of the different parathyroid cells, present in multiple parathyroid glands in the absence of a known stimulus for PTH hypersecretion such as renal failure or vitamin D deficiency (21).

Laboratory data on serum calcium and PTH concentrations as measured more than 6 months post-operatively were used to indicate cure or persistence of hyperparathyroidism.

Statistical analysis

Statistical analysis was performed using the SPSS 16 software (SPSS inc., Chicago, IL, USA). Results are expressed as mean ± SD unless otherwise stated. Chi-square test and Student's *t*-test were used as appropriate for categorical variables and continuous variables. A probability level of random difference of $P<0.05$ was considered to be significant.

Ethical consideration

The methods used in this study were part of the clinical routine work-up of patients undergoing revision surgery in our hospital. The study was approved by the Local Ethics Committee of the Leiden University Medical Center and all patients consented to the use of their data.

RESULTS

The study population consisted of 20 patients, 4 male and 16 female, with an established diagnosis of PHPT, which persisted for a mean of 5 ± 7 years (range 0-24) after initial parathyroidectomy (PTx). Duration since first presentation with clinical and biochemical features of hyperparathyroidism was 12 ± 9 years (range 2-35) and all patients had had at least 1 revision surgery (range 1-5).

Findings before initial surgery

Nine of the 20 patients (45%) presented with nephrolithiasis, two with height loss because of documented vertebral fractures, two with generalized bone and muscle pain, one with polyuria and polydipsia, one with severe weight loss and in one patient the diagnosis was made during a hospital admission for acute pancreatitis. In the last 4 cases, the diagnosis was established by the incidental finding of hypercalcemia on general medical screening in 3 cases, and in the process of an endocrine work-up for thyroid disease in the last case.

At the time of diagnosis, only 1 of the 20 patients was asymptomatic. Although symptoms related to hypercalcemia such as polyuria, polydipsia and constipation were present in only 5 patients (25%), 47% had non-specific symptoms such as muscle or bone pain and tiredness was reported by 41% of patients (Table 1).

Mean preoperative serum calcium concentration was 2.86 ± 0.21 mmol/L and mean PTH level was 13 ± 6 pmol/L. Renal impairment (creatinine clearance <60 ml/min) was documented in 25% of patients.

At presentation, renal stones were documented on ultrasound of the kidneys in 58% of patients and 29% had osteoporosis on Dual energy X-ray absorptiometry

(DXA). Six of the 20 patients (30%) had parathyroid localisation studies before initial PTx, using a Tc99m-MIBI-SPECT scan and/or an ultrasound scan of the neck.

Eleven of the 20 patients (55%) had initially undergone bilateral neck exploration, 25% had unilateral neck exploration and the type of surgery was not specified in 4 cases. Initial surgery was guided by intra-operative PTH (IOPTH) monitoring in only 2 patients (13%). In 3 of 20 patients (15%) surgery was combined with a hemithyroidectomy, because of pre-operatively identified thyroid pathology in 1 patient and because of a negative bilateral neck exploration which raised suspicion of an intrathyroidal parathyroid gland in the other 2 patients. In both cases an intrathyroidal pathological parathyroid gland was indeed found and removed. In one of the 20 patients (5%) surgery was combined with a total thymectomy, because of a negative bilateral neck exploration with suspicion of an intrathymic parathyroid gland, although no pathological gland was found at this location (Table 1).

A single adenoma was removed at surgery in 9 of 20 patients (45%), an ectopic pathological parathyroid gland in 2 cases, one or more hyperplastic glands were removed in one case and no pathological glands were found in 8 cases.

Surgery was complicated by recurrent laryngeal nerve paralysis in 2 cases, in one of which it was transient, and by cellulitis of the neck in one case.

Findings at revision surgery

Prior to first revision surgery, 6 of the 20 patients (30%) had symptoms of hypercalcemia such as polyuria, polydipsia and constipation, 30% had symptoms of muscle or bone pain and 40% complained of tiredness. Prior to second revision surgery, polyuria and polydipsia was reported by 1 of 8 patients, constipation by 1 of 8 patients, muscle or bone pain by 1 of 8 patients and tiredness by 3 of 8 patients. Renal impairment (creatinine clearance of <60ml/min) was documented in 3 of 15 patients (20%) prior to first revision surgery and in 1 of 7 patients (14%) prior to second revision surgery. Ultrasound of the kidneys was performed in 18 of 20

Table 1. Demographic, operative and pathology data in 20 patients with persistent PHPT following surgery

	Prior to initial PTx (n=20)	At second PTx (n=20)	At third PTx (n=8)
Gender (Men:Women)	4:16	4:16	2:6
Age (years)	52 ± 12 (35-70)	57 ± 11 (36-71)	57 ± 11 (36-72)
Biochemistry prior to initial surgery			
s-calcium (mmol/L)	2.86 ± 0.21	2.73 ± 0.16	2.94 ± 0.29
PTH (pmol/L)	13 ± 6	17 ± 6	18 ± 13
phosphate (mmol/L)	0.77 ± 0.14	0.84 ± 0.14	0.90 ± 0.26
alkaline phosphatase	181 ± 176	98 ± 43	140 ± 79
creatinine clearance (ml/min)	66 ± 15	68 ± 16	75 ± 18
u-calcium (mmol/24 hours)	11.0 ± 6.5	11.2 ± 7.2	14.3 ± 8.1
Clinical presentation			
Polyuria & polydipsia	4/17 (24%)	3/18 (17%)	1/7 (14%)
Constipation	1/17 (6%)	3/18 (17%)	1/7 (14%)
Tiredness	7/17 (41%)	8/18 (44%)	3/7 (43%)
Muscle or bone pain	8/17 (47%)	6/18 (33%)	1/7 (14%)
Complications			
Renal impairment	3/12 (25%)	3/15 (20%)	1/7(14%)
Nephrolithiasis/Nephrocalcinosis	11/19 (58%)	8/18 (44%)	4/7 (57%)
Osteoporosis	2/7 (29%)	5/9 (56%)	3/6 (50%)
Fractures	0/20	1/18 (6%)	0/7
Type of surgery			
Bilateral neck exploration	11/16 (69%)	12/18 (67%)	5/8 (63%)
Unilateral neck exploration	5/16 (31%)	4/18 (22%)	3/8 (38%)
Sternotomy alone or combined	0/16	2/18 (11%)	1/8 (13%)
Combined with thyroidectomy	3/16 (19%)	5/18 (28%)	1/8 (13%)
Combined with thymectomy	1/16 (6%)	2/18 (11%)	3/8 (38%)
Use of IOPTH monitoring	2/16 (13%)	8/18 (44%)	6/8 (75%)
No data available	4//20	2/20	0/8
Pathology			
Adenoma	10/19 (53%)	8/20 (40%)	2/8 (25%)
Hyperplasia	2/19 (11%)	5/20 (25%)	5/8 (63%)
No pathological glands found	7/19 (37%)	7/20 (35%)	1/8(12%)
Outcome of surgery			
Cure	0/20	8/20 (40%)	4/8 (50%)
Persistence	20/20 (100%)	12/20 (60%)	4/8 (50%)

s: serum, u: urine, IOPTH: Intra-operative PTH measurement

patients (90%) before first revision surgery and nephrolithiasis was demonstrated in 8 (44%), all of whom also had evidence for nephrolithiasis before initial surgery. Ultrasound data were available in 7 of 8 patients (88%) before second revision surgery and demonstrated persistent nephrolithiasis in 4 patients (57%). One patient had developed this complication de novo after persistence of PHPT for 30 years after failed revision surgery.

BMD measurements were available in 9 of 20 patients (45%) who underwent first revision surgery, and demonstrated osteoporosis in 5 (55%), osteopenia in 3 (33%) and a normal BMD in 1 case. Prior to second revision surgery BMD was measured in 6 of 8 patients (75%) and demonstrated osteoporosis in 3 (50%) and osteopenia in the other 3 (50%). Only one postmenopausal patient sustained a fracture of the wrist, prior to first revision surgery. None of the patients had sustained a clinical vertebral fracture at any time since diagnosis.

The 20 patients underwent a total of 33 revision surgeries. Twenty of the 33 revision surgeries were bilateral neck explorations (61%), 9 (27%) were unilateral neck explorations, a sternotomy was performed in 2 cases and the type of surgery was not specified in the last 2 cases. Surgery was combined with a hemithyroidectomy in 8 of the 33 cases (24%) and in 6 of 33 cases (18%) with a thymectomy. The decision to perform a hemithyroidectomy was based on the intra-operative finding of an intrathyroidal node in 3 cases, negative bilateral neck exploration with suspicion of an intrathyroidal parathyroid gland in 4 cases, and the incidental finding of a small papillary thyroid carcinoma in one case.

Nineteen of the 33 revision surgeries (58%) were guided by IOPTH measurements. A decrease in PTH levels of more than 50% was observed in all 10 patients who achieved cure after revision surgery, but also in 7 of the 9 patients who had persistence of PHPT after revision surgery. However, the decrease in PTH levels was significantly greater in patients who achieved cure after revision surgery compared to patients with persistence after revision surgery (89 ± 11% *vs.* 63 ± 26%, P=0.003; Figure 1). A decrease in PTH concentration of more than 50% was also reached faster, albeit not significantly, in patients who achieved cure after

revision surgery compared to patients with persistence of HPTH after revision surgery (6 ± 4 minute vs. 10 ± 7 minutes, *P*=0.09).

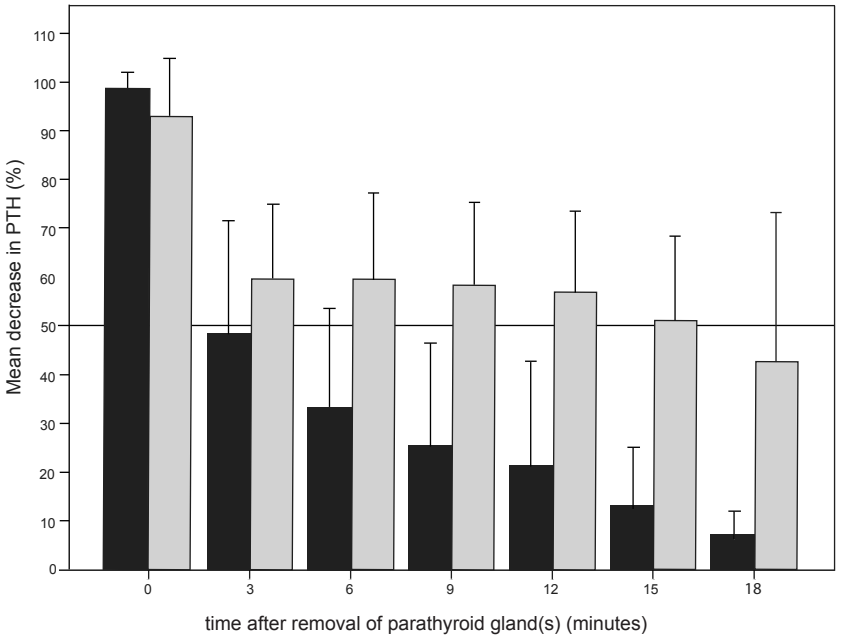

Figure 1: IOPTH measurement during revision surgery in patients with persistent PHPT who were cured post-operatively (black bars) compared to those in whom hyperparathyroidism persisted post-operatively (gray bars).

Four of the 20 first revision surgeries (20%) were associated with complications: fever (n=1), hypoparathyroidism (n=1), infected hematoma (n=1) and recurrent laryngeal nerve paralysis (n=1) (Figure 2). Four of the 8 second revision surgeries (50%) were associated with one or more complications; recurrent laryngeal nerve paralysis (n=1), transient recurrent laryngeal nerve paralysis (n=1), hungry bone syndrome (n=1) and hypoparathyroidism (n=1). Two of 3 third revision surgeries (67%) were complicated by a wound infection. The patient who also underwent fourth and fifth revision surgery had an uncomplicated fourth revision surgery, but the fifth revision surgery was complicated by permanent unilateral recurrent laryngeal nerve paralysis.

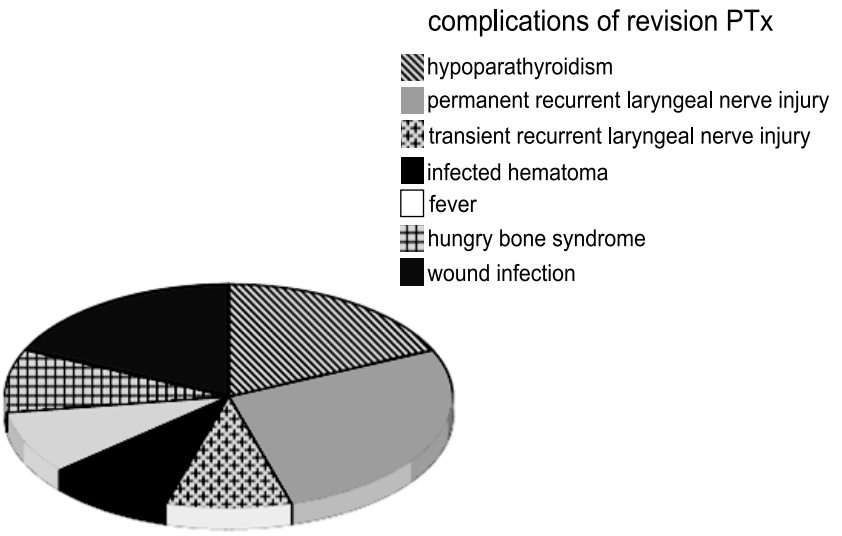

Figure 2: Complications documented after 33 revision surgeries in patients with persistent PHPT.

At first revision surgery a single and first adenoma was removed in 5 cases (25%), a second adenoma in 3 cases (15%), one or more hyperplastic parathyroid glands in 5 cases (25%) and no pathological parathyroid tissue was found in 7 cases (35%) (Figure 3). At second revision surgery a single and first adenoma was removed in 1 case (13%), one or more hyperplastic glands in 5 cases (63%), and seeded cell aggregations from parathyromatosis in 2 cases (25%). At third revision surgery one or more hyperplastic glands were removed in 1 case and cell aggregations from parathyromatosis in 2 cases. One patient also underwent a fourth and fifth revision surgery, during which remnants of hyperplastic autotransplantated parathyroid tissue and cell aggregations from parathyromatosis were respectively excised.

After first revision surgery 8 of 20 patients (40%) were cured and 12 of 20 patients (60%) had persistence of PHPT (Figure 3). Eight of the 12 patients who

were not cured by first revision surgery underwent a second revision surgery. Surgery was not undertaken in the other 4 patients, because of mild asymptomatic hyperparathyroidism in 2 cases, reluctance of 1 patient to undergo further surgery because of recurrent laryngeal nerve paralysis at previous surgery, and in the last patient surgery was not advocated because of 2 negative bilateral neck explorations and persistently negative localisation studies except for SVS, which suggested a mediastinal localisation of hyperactive parathyroid tissue, although this was not confirmed by CT-scan of the region. After second revision surgery 4 of 8 patients were cured (50%) and 4 of 8 patients (50%) had persistence of PHPT. Three of the 4 patients with persistence of PHPT went on to have a third revision surgery exclusively on the basis of a positive PTH sampling, with otherwise negative localisation studies, which failed to result in cure in all 3 cases. Only 1 of these 3 patients underwent a fourth and fifth revision surgery, neither of which again resulted in cure. These last three patients are currently being treated with the calcimimetic cinacalcet and an oral bisphosphonate with reasonable control of serum calcium and PTH concentrations and no further bone loss.

Pathology of excised hyperactive parathyroid tissue in persistent PHPT

At revision surgery, an adenoma was found in 9 of 33 revision surgeries (27%), which was a single adenoma in 6 cases (ectopic n=4, intrathyroidal n=1, normal anatomical location n=1), and a second adenoma in 3 cases (normal anatomical location n=2, intrathyroidal n=1).

A hyperplastic gland was found in 10 of 33 revision surgeries (30%), in the context of a missed multiglandular disease (MGD) in 5 cases, an ectopically located gland in 3 cases and an intrathyroidally located gland in 2 cases. In one patient the autotransplanted parathyroid tissue that was implanted in the sternocleidomastoid muscle had become hyperplastic, also showing invasive growth in the muscle, for which the patient had to undergo 2 explorations to remove all identifiable hyperplastic parathyroid tissue.

Ectopic parathyroid glands (n=7) were found in the thymus (n=3), mediastinum (n=1), caudally in the neck ventral to the trachea (n=1), caudally in the neck near the

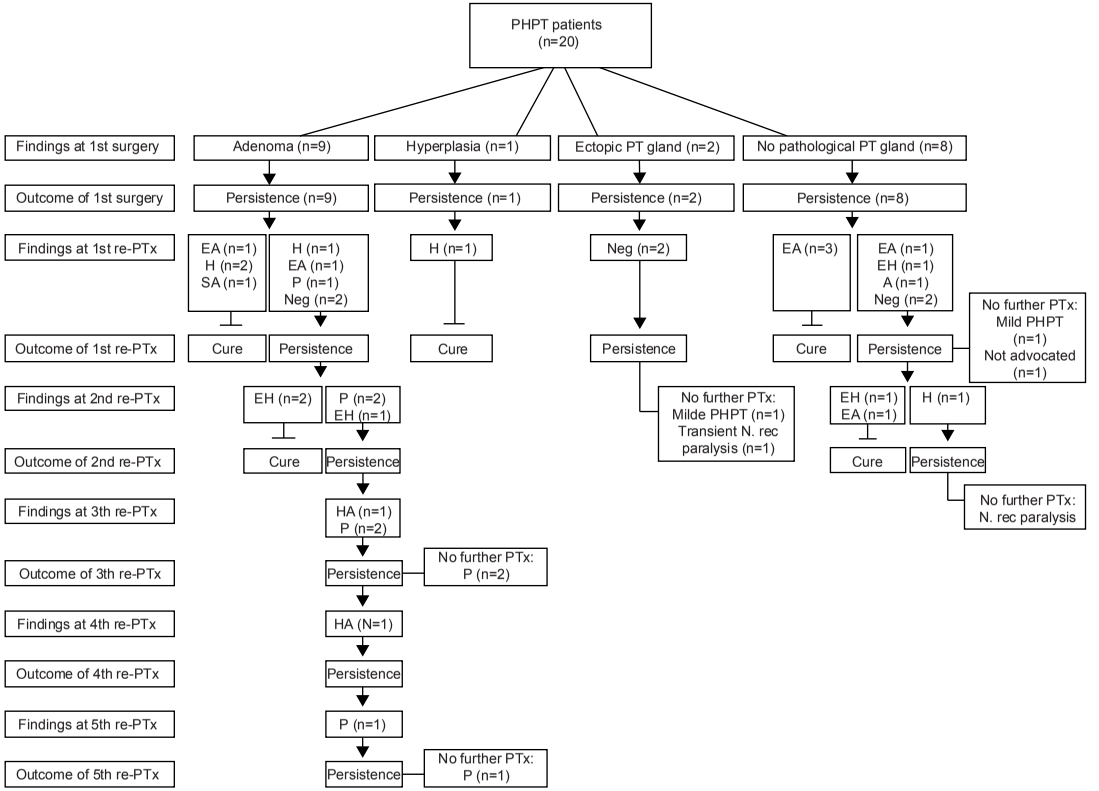

Figure 3: Flowchart of findings at revision surgery and outcome of the surgical intervention in the 20 patients with persistent PHPT after initial surgery.

aortic arch (n=1), and high on the left side of the neck on the prevertebral fascia (n=1).

Spillage of hyperactive parathyroid tissue leading to parathyromatosis occurred during initial surgery in 1 patient, during first revision surgery in 1 patient and during fourth revision surgery in 1 patient. Hyperparathyroidism persisted in these 3 patients despite a total of 6 revision surgeries.

Table 2. Predictive value of localisation studies prior to revision surgery

	Sensitivity	Specificity	PPV	NPV
Tc99m-MIBI-SPECT (*n*=35)	25%	96%	60%	83%
Ultrasound of the neck (*n*=16)	18%		29%	
CT-scan (*n*=11)	30	81%	30%	81%
MRI-scan (*n*=7)	20%	100%	50%	80%
Selective venous sampling for PTH (n=14)	50%	89%	50%	85%

PPV: Positive predictive value, NPV: Negative predictive value

Predictive value of pre-operative localisation studies in persistent PHPT

One or more localisation studies were performed prior to 27 of 33 revision surgeries compared to only 6 of 20 performed prior to initial surgeries. An ultrasound of the neck (US) was performed prior to 6 of 20 initial surgeries (30%) and prior to 10 of 33 revision surgeries (30%). US had a sensitivity of 67% prior to initial surgery and of 18% prior to revision surgery. Tc99m-MIBI-SPECT was performed prior to 5 of 20 initial surgeries (25%) and prior to 26 of 33 revision surgeries (79%). Tc99m-MIBI-SPECT failed to localise hyperactive parathyroid glands in the 5 patients in whom it was performed prior to initial surgery, and had a localising sensitivity of only 25% prior to revision surgery. A CT scan was performed in only 1 of the 20 patients before initial surgery and prior to 10 of 33 revision surgeries (30%), in which case it was mainly performed to confirm localisation suggested by Tc99m-MIBI-SPECT, SVS or both. CT scan had a general sensitivity of 30% (Table 2). An MRI scan was performed before 1 of the 20 initial surgeries and prior to 6 of 33 revision surgeries. MRI scan had a general sensitivity of 20%. Selective venous sampling (SVS) for PTH was not performed before initial surgery but SVS data

were available prior to 15 of the 33 revision surgeries and had a localisation sensitivity of 50% (Table 2).

DISCUSSION

Data from our case series of 20 patients with persistent PHPT suggest that their management is complex and associated with a number of pitfalls. The most common causes of persistent HPTH were a missed ectopic gland at initial surgery (33%) and missed multiglandular disease (15%). The more challenging surgical complication of parathyromatosis was observed in 9% of patients. Pre-operative localisation studies had poor sensitivity: US 18%, Tc99m-MIBI-SPECT 25%, CT 30%, MRI 20%. In contrast, selective venous sampling for PTH had a sensitivity of 50% and a specificity of 89%, although it failed to accurately localise hyperactive tissue in 43% of patients. The decrease in intraoperative PTH was significantly less marked in patients in whom hyperparathyroidism persisted compared to those who achieved cure (63 ± 26 vs. 89 ± 11%, P=0.003). The risk of complications, particularly that of recurrent laryngeal nerve palsy, increased with each subsequent surgery: 20% after first, 50% after 2nd and 67% after 3rd surgery.

In primary hyperparathyroidism, surgery is the treatment of choice resulting in cure in the vast majority of patients. We have previously demonstrated that the most commonly encountered sporadic hyperparathyroidism does not recur if cure is established 6 months after parathyroidectomy (4). The prevalence of persistent hyperparathyroidism is thus low, with only a small number of patients demonstrating persistence of clinical and biochemical features of hyperparathyroidism after initial surgery.

The main challenge in the management of persistent PHPT lies in the decreasing value of localisation studies after initial and each subsequent revision surgery. Tc99m-MIBI-SPECT has a lower predictive value in patients with persistent PHPT, likely to be due to disturbance in local vascular supply by previous surgery, but also due to differences in gland pathology and size in persistent hyperparathyroidism, ultimately affecting radiopharmaceutical uptake. It is of interest that Tc99m-MIBI-

SPECT performed prior to initial surgery failed to identify hyperactive parathyroid glands in 5 patients in whom hyperparathyroidism subsequently persisted, although this observation could not be confirmed in the remaining 15 patients with persistent PHPT, who did not have this localisation study before initial surgery. Although SVS is positive in all patients with persistent PHPT, this localisation study cannot accurately localise hyperactive parathyroid glands, as it reflects drainage of the hyperactive parathyroid gland rather than its actual anatomical localisation, and drainage pattern is further confounded by disturbance in local vascular supply as a result of previous surgery.

Although pre-operative localisation studies are important to guide the surgeon and decrease operating time, knowledge of anatomy and embryology of the parathyroid glands is also important to successfully locate previously missed hyperactive parathyroid glands. This is particularly so as ectopic parathyroid glands are found in 23-77% of cases of persistent hyperparathyroidism (14,22-27). In keeping with previous observations (22-27), our case series confirms that the thymus is one of the most frequent sites of ectopic parathyroid glands (43%), followed by the mediastinum (14%), ventral to the trachea (14%) and on the prevertebral fascia (14%). Other locations of hyperactive parathyroid glands are the tracheoesophageal groove (2.6-33%), para- or retroesophageal area (1.8-21.4%), carotid sheath (0.6-14.3%), carotid bifurcation (8.3%), aortopulmonary window (1.3-6.3%), and parapharyngeal area (0.6-8.4%) (22-27).

Data on the use of IOPTH measurement during revision surgery for persistent PHPT are somewhat conflicting. Some studies thus report a sensitivity of 94-100% (24,26,28), whereas data have also been reported on misleading decreases in PTH levels of 50-60% during IOPTH measurements (25). Although we show that 78% of patients with persistent PHPT have a positive IOPTH measurement at revision surgery according to the “Miami criteria” (a drop in PTH levels of more than 50%) (29,30), we and others (25,28) demonstrate that patients who achieve cure after revision surgery have a greater and more rapid decrease in PTH levels during IOPTH measurement compared to patients with persistent PHPT after revision surgery. These findings suggest that in patients with persistent PHPT, IOPTH

measurements may be more valuable in predicting cure when stricter cut-off values than the ones suggested by the "Miami criteria" are used.

In keeping with previous reports (22-24,26-28), the overall complication rate at first revision surgery was 20% in our case series. As expected, the overall complication rate significantly increased at second and third revision surgery (50 and 67%, respectively). The most common complications reported by us and others are hypoparathyroidism (2.6-12.9%) and recurrent laryngeal nerve injury leading to transient (2.3-13.5%) or permanent paralysis (0.08-25%) (22-28).

A rare but challenging complication of parathyroid surgery is the development of parathyromatosis, which is characterized by intraoperative rupture of a hyperactive parathyroid gland which leads to seeding of parathyroid tissue in and around the site from which the ruptured gland is removed. In contrast to previously published data (11), we observe in our case series that parathyromatosis leading to persistent hyperparathyroidism occurred in only 1 case during initial surgery and in 2 cases during revision surgery. In these cases, cure could not be achieved by surgery, despite repeated removal of small aggregates of hyperactive parathyroid tissue. In these cases patients have been shown to benefit from treatment with the calcimimetic cinacalcet, with reasonable control of the biochemical features and complications of hyperparathyroidism. Long-term studies are required to establish the efficacy and safety of these agents in recalcitrant persistent hyperparathyroidism.

Our findings from this case series indicate that the management of patients with persistent PHPT is complex and challenging. When initial surgery fails to achieve cure, each reoperation jeopardizes the ability of localisation studies to accurately localise residual hyperactive parathyroid glands and increases the risk of complications in its own right because of distortion and scarring of surgical planes as a result of previous interventions. In these patients, re-operation should be carefully planned and attempts at surgery strongly discouraged if a clear localisation of hyperactive tissue is not secured pre-operatively. The availability of calcimimetics allows a more conservative approach in the management of these patients. This is particularly if parathyromatosis is strongly suspected, and at least

until such time as the hyperactive tissue may have grown sufficiently to be adequately localised, which may take several years, as parathyroid cell growth and proliferation is slow. Whether calcimimetic agents, which have been shown to suppress proliferation of parathyroid cells *in vitro* and in animal studies (31-34), may have a similar effect in patients with persistent PHPT remains to be established. Further studies using cinacalcet in the long-term are required in patients with persistent hyperparathyroidism to explore this issue.

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