



Universiteit
Leiden
The Netherlands

Primary hyperparathyroidism : challenges and pitfalls in management

Witteveen, J.E.

Citation

Witteveen, J. E. (2012, November 27). *Primary hyperparathyroidism : challenges and pitfalls in management*. Retrieved from <https://hdl.handle.net/1887/20191>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/20191>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/20191> holds various files of this Leiden University dissertation.

Author: Witteveen, Janneke Egbertine

Title: Primary hyperparathyroidism : challenges and pitfalls in management

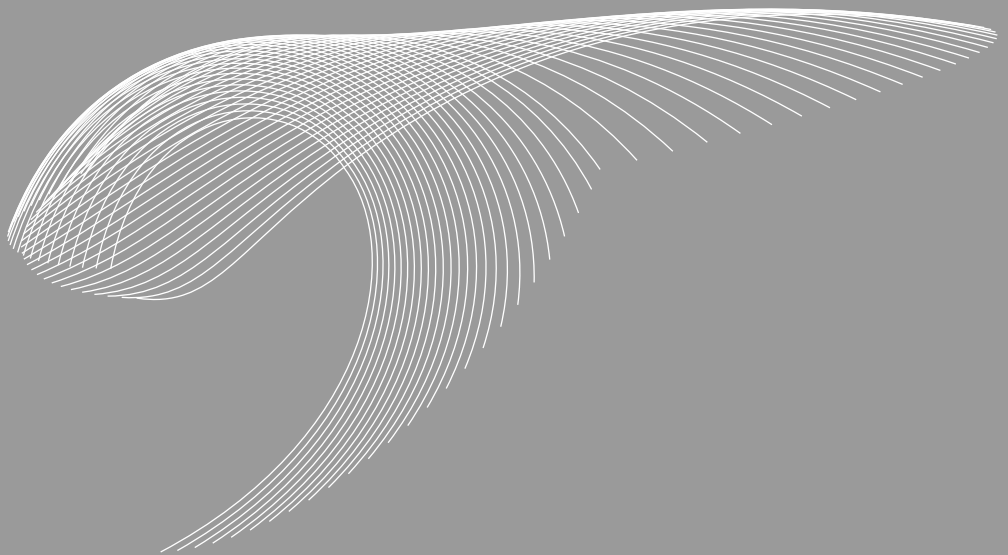
Issue Date: 2012-11-27



**No recurrence of sporadic primary
hyperparathyroidism when cure is established 6 months
after parathyroidectomy**

Janneke E. Witteveen, Job Kievit, Hans Morreau, Johannes A. Romijn,
Neveen A.T. Hamdy

European Journal of Endocrinology, 2010 Feb;162(2):399-406



ABSTRACT

Objective: Cure rate for primary hyperparathyroidism (PHPT) is reported to be 94-100% 1 year after surgery, but recent data suggest recurrence in 4% of patients 1-5 years postoperatively. The aim of our study was to establish the cure rate and its maintenance in the long-term after parathyroidectomy (PTx) in patients with sporadic primary hyperparathyroidism.

Design: Evaluation of recurrence in patients with sporadic hyperparathyroidism who underwent PTx 1-24 years prior to the study.

Patients & Methods: We identified 111 patients who underwent initial PTx between 1984 and 2008 and had no *MEN-1*, *MEN-2* or *CASR* mutation; parathyroid carcinoma; a history of lithium use; or renal failure. Thirty-eight patients were lost to follow-up or were unwilling or unable to participate in the study. Cure was defined as maintenance of normal serum calcium and parathyroid hormone concentrations 6 months after PTx.

Results: Cure was achieved in 68 of 73 patients studied (93%) and was sustained in all for 6±5 years.

Conclusion: The cure rate of sporadic PHPT after initial surgery is 93%. When cure is achieved, this is sustained in 100% of the patients for up to 24 years postoperatively. Our data suggest that closer early follow-up is advocated in all patients undergoing PTx to definitively establish cure and to provide a safety net for those with residual gland pathology. The data do not support the need for long term follow-up when cure is established 6 months after PTx.

INTRODUCTION

In primary hyperparathyroidism (PHPT), surgical removal of all pathological parathyroid glands is the only approach that provides a definitive and durable cure. Cure rate has been reported to be in the range of 94-100% for bilateral neck, as well as less invasive surgery, more than 6 months after parathyroidectomy (PTx) (1-10). Residual postoperative biochemical features of PHPT may be due to either recurrent or persistent PHPT. In a 5 year follow-up of 91 patients successfully operated for PHPT, Westerdahl *et al.* reported a recurrence rate of 4%, largely due to previously undiagnosed germline mutations in the *MEN-1* gene and consequent multiple gland pathology (11). Persistent hyperparathyroidism is usually due to a pathological parathyroid gland missed at initial surgery. Such a gland is often small, usually forming a part of unrecognized multiple gland hyperplasia (12,13). The diagnosis of persistent hyperparathyroidism may be delayed because of the initial suppression of multiple pathological glands by a dominant enlarged gland, falsely suggesting cure immediately post-operatively. These pathological glands eventually overcome their suppressed state leading to overt hyperparathyroidism.

In PHPT, the importance of achieving cure has been highlighted in a number of studies focusing on the effect of PTx on bone mineral density (BMD), nephrolithiasis and neurocognitive function (14-16). Patients who are cured show a significant post-operative increase in bone mass, with BMD remaining significantly above baseline for up to 15 years of follow-up (17). This is in contrast to BMD changes in patients treated conservatively, in whom significant cortical bone loss and increased fracture risk are observed. As reported in a number of studies, patients with nephrolithiasis at presentation demonstrate no recurrence of renal stones after successful PTx, in contrast to a 75-100% chance of recurrent nephrolithiasis if not operated (14,17). Symptomatic and also 'asymptomatic' patients undergoing PTx have been reported to experience a significant improvement in various parameters of quality of life compared to patients who had no surgery (18-22). The aim of our study was to establish the cure rate and its

maintenance in the long-term after initial PTx in patients with sporadic PHPT who underwent surgery in our hospital between 1984 and 2008.

PATIENTS AND METHODS

Study population

All patients with a diagnosis of PHPT who had a PTx in the Leiden University Medical Center (LUMC) from March 1984 to May 2008 were identified from our hospital records and were considered for study. Patients who were not initially operated in our institution and patients with parathyroid carcinoma, renal failure, or a history of lithium use were excluded from the study. Patients with a *MEN-1*, *MEN-2* or *CASR* mutation were also excluded from the final analysis, although genetic testing may have been undertaken some years after initial PTx. Details on the outcome of these 32 patients with a documented mutation are shown in Figure 1. One hundred and eleven patients with sporadic PHPT were thus eligible for the study and were recalled for a follow-up visit at the outpatient clinic of the Department of Endocrinology and Metabolic Diseases.

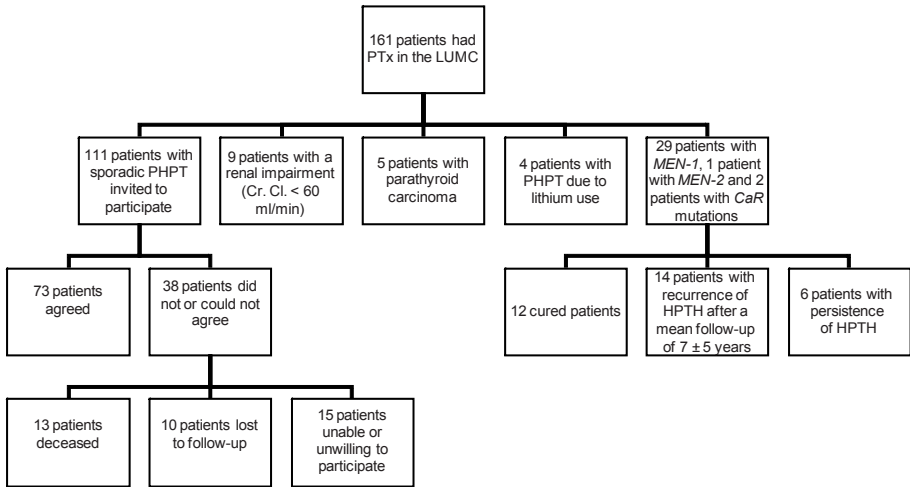


Figure 1. Study flow diagram

Methods

A detailed medical history was obtained from all patients with special emphasis on symptoms related to hypercalcaemia and non specific symptoms of hyperparathyroidism, such as tiredness, mood swings, depression, feeling irritable, being forgetful, feeling weak, bone pain, muscle weakness, constipation and polyuria/polydipsia. These symptoms represent 10 of the 13 items of the validated Pasieka's 'Parathyroid Assessment of Symptoms Score (PAS)' (21,23). Blood was collected from all patients. Operative and pathology data were obtained from patients' hospital records. Fracture history was obtained by direct questioning and was confirmed by reviewing available radiological data spanning the period before and after PTx.

Serum Biochemistry

Serum concentrations of calcium (reference range 2.15-2.55 mmol/l), albumin (reference range 34-48 g/l), phosphate (reference range 0.90-1.50 mmol/l), and creatinine (reference range 44-80 μ mol/l) were measured using semi-automated techniques. Creatinine clearance was calculated using the Cockcroft formula. Serum concentrations of intact parathyroid hormone (PTH: reference range 1.5-8 pmol/l) and 25-hydroxycholecalciferol (25 (OH) D3) (reference range 30-120 nmol/l) were measured using standard RIAs. Vitamin D status was judged to be inadequate when 25(OH)D3 concentrations were <50 nmol/l (24,25).

Radiological investigations

BMD was measured at the lumbar spine (L1-L4) and femoral neck, using dual energy X-ray absorptiometry (DXA, Hologic QDR 4500; Waltham, MA, USA), in 46 patients who had a baseline BMD measurement before PTx. World Health Organization criteria were used to define osteopenia (*T*-score between -1 and -2.5) and osteoporosis (*T*-score <-2.5) (26). Lateral X-rays of the thoracic and lumbar spine were performed in 35 patients, when medically indicated, in case of height loss or back pain, and in those who had baseline X-rays before PTx.

Fifty one patients, including those with persistent PHPT and those with a history of nephrolithiasis or nephrocalcinosis, and representing 70% of the study population, had an ultrasound of the kidneys to document the presence or absence of nephrocalcinosis and/or nephrolithiasis.

Surgical procedure

The indication criteria for surgery were based on the 1990 (27) and subsequent 2002 (28) NIH Consensus guidelines. The 1990 guidelines were broadly followed in our institution in the period preceding their publication. Before the introduction of intra-operative PTH (IOPTH) measurement in our hospital in 1997, almost all the patients underwent bilateral neck exploration with visualization of all the four parathyroid glands. This led either to the excision of a single enlarged parathyroid gland, or to subtotal or total PTx with auto transplantation if more than one parathyroid gland was found to be enlarged. If all parathyroids could not be visualized and no enlarged parathyroid was found, dissection of the ipsilateral anterior compartment extending from the level of the hyoid bone superiorly to the suprasternal notch inferiorly and hemithyroidectomy were undertaken on the side of the missing parathyroid. After standardizing the use of IOPTH, a more selective surgical approach was opted for, and less invasive neck exploration was undertaken in patients with positive preoperative localization studies. IOPTH monitoring consisted of two initial baseline measurements with an interval of 15-20 minutes, followed by five 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).

Definition of cure, persistence and recurrence of hyperparathyroidism

Successful surgery or cure was defined as normal serum calcium and PTH concentrations as measured more than 6 months after PTx. Persistence of hyperparathyroidism was defined as high serum calcium and PTH concentrations or inappropriate concentrations of one parameter with respect to the other, documented

directly post-operatively or within the first 6 months after PTx, and persisting thereafter. Recurrence of hyperparathyroidism was defined as the recurrence of elevated serum calcium and PTH concentrations after successful PTx and a period of normalization of both parameters of at least 6 months after surgery.

Statistical analysis

Statistical analysis was performed using the SPSS 16.0 for Windows (Chicago, IL, USA). Results are expressed as mean \pm S.D. unless otherwise stated. χ^2 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 significant.

The study was approved by the local ethics committee, and informed consent was obtained from all patients prior to inclusion in the study.

RESULTS

Demographic data

Seventy-three of the 111 patients who were invited to participate in the study agreed to take part. Of the remaining 38 patients, 13 had died, 10 were lost to follow-up and 15 were physically unable or unwilling to take part in the study (Figure 1).

Fifty-six women and 17 men, with a mean age of 56 ± 10 years at the time of the diagnosis were included in the study (Table 1). At the time of the first presentation, only 18 of the 73 patients (25%) were asymptomatic. Although only 7 patients had symptoms related to hypercalcemia such as polyuria, polydipsia, and constipation, nonspecific symptoms were common. Tiredness was reported in 44%, muscle or bone pain in 22%, and depressive symptoms in 16% of the patients. Twenty-seven patients (37%) had symptoms related to renal stones and six patients (8%) had sustained a documented fracture, two vertebral and four non-vertebral after some degree of trauma. Mean pre-operative serum calcium concentration was 2.76 ± 0.20 mmol/l and mean PTH level was 19.5 ± 15.7 pmol/l. Renal impairment,

as defined by a creatinine clearance of <60 ml/min, was documented in 21% of patients. Renal stones were documented on ultrasound of the kidneys in 41% of patients and 38% had BMD evidence for osteoporosis on DXA.

Sixty-three of the 73 patients (86%) had undergone parathyroid localization studies before PTx, using Tc99m-MIBI-SPECT scan and/or ultrasound scan of the neck. Forty-seven of the 73 patients (64%) had undergone bilateral neck exploration, 12% had unilateral neck exploration and 23% had a minimally invasive procedure. Surgery was guided by IOPTH monitoring in 53 patients (73%). In 14 of the 73 patients (19%), PTx was combined with a hemithyroidectomy. The decision for this procedure was based on pre-operatively identified thyroid pathology in seven patients and negative bilateral neck exploration in the other seven patients. However, an intra-thyroidal parathyroid gland was found in only 3 of the 14 patients.

Since 2001, due to the availability of IOPTH monitoring and the increased popularity of less invasive surgical procedures, the percent of bilateral neck explorations decreased from 76 to 56% and that of the more focused surgical approaches increased from 24 to 44%. Parallel to the use of less invasive surgical approaches, the use of pre-operative localization studies increased from 77 to 95% and the use of IOPTH monitoring increased from 43 to 93% (Figure 2). A single adenoma was removed at surgery in 56 of the 73 patients (77%), and one or more hyperplastic glands were removed in 16% of the cases.

Short-term follow-up, within one year of parathyroidectomy

At the time of first follow-up, within 3 months of surgery, 70 of the 73 patients (96%) had evidence for biochemical cure of hyperparathyroidism. At the time of the second post-operative follow-up, 6 months after PTx, 68 of the 73 patients (93%) had evidence for cure. Five patients (7%) demonstrated persistence of hyperparathyroidism; in two of whom this was originally overlooked because of a transient normalization of serum calcium and PTH concentrations post-operatively. In these two patients, a second laboratory measurement demonstrated elevated

Table 1. Demographic, laboratory, clinical and surgical data of patients who underwent initial surgery for sporadic primary hyperparathyroidism

	Total patients N=73	Achieved cure after initial PTx N=68	Persistence after initial PTx N=5	<i>P</i> value
Gender (men:women)	17:56	16:52	1:4	0.857
Age at diagnosis (years)	56 ± 10	56 ± 11	56 ± 6	0.910
Age at follow-up (years)	63 ± 11	63 ± 11	69 ± 5	0.199
Years after PTx	6 ± 5	6 ± 5	12 ± 5	0.013
Follow-up time after PTx (months)	39 ± 56	33 ± 50	129 ± 66	0.000
Biochemistry prior to initial surgery				
s-calcium (mmol/l)	2.76 ± 0.20	2.77 ± 0.20	2.68 ± 0.08	0.313
PTH (pmol/l)	19.5 ± 15.7	20.2 ± 16.0	9.9 ± 2.0	0.161
phosphate (mmol/l)	0.88 ± 0.18	0.89 ± 0.19	0.85 ± 0.15	0.676
Creatinine clearance (ml/min)	72 ± 14	72 ± 14	66 ± 5	0.068
u-calcium (mmol/24 h)	11.05 ± 4.80	10.96 ± 4.89	12.13 ± 3.67	0.604
Clinical presentation				
Polyuria & polydipsia	6/73 (8%)	6/68 (9%)	0/5	0.488
Constipation	1/73 (1%)	1/68 (1,5%)	0/5	0.785
Tiredness	32/73 (44%)	31/68 (46%)	1/5 (20%)	0.266
Muscle or bone pain	16/73 (22%)	15/68 (22%)	1/5 (20%)	0.914
Depressive symptoms	12/73 (16%)	12/68 (18%)	0/5	0.304
Complications				
Renal impairment	15/73 (21%)	14/68 (21%)	1/5 (20%)	0.925
Nephrolithiasis	30/73 (41%)	28/68 (41%)	2/5 (40%)	0.959
Osteoporosis	28/73 (38%)	27/68 (40%)	1/5 (20%)	0.382
Fractures	7/73 (10%)	6/68 (9%)	1/5 (20%)	0.413
Pre-operative localization studies				
US and/or MiBi-SPECT	62/73 (86%)	58/68 (85%)	4/5 (80%)	0.671
Type of surgery				
Bilateral neck exploration	47/73 (64%)	44/68 (65%)	3/5 (60%)	0.832
Unilateral neck exploration	9/73 (12%)	8/68 (12%)	1/5 (20%)	0.589
Minimally invasive	17/73 (23%)	16/68 (24%)	1/5 (20%)	0.857
Combined with thyroidectomy	14/73 (19%)	13/68 (19%)	1/5 (20%)	0.961
Combined with thymectomy	5/73 (7%)	4/68 (6%)	1/5 (20%)	0.228
Use of IOPTH monitoring	53/73 (73%)	50/68 (74%)	3/5 (60%)	0.513
Pathology				
Adenoma	56/73 (77%)	53/68 (78%)	3/5 (60%)	0.360
Hyperplasia	12/73 (16%)	11/68 (16%)	1/5 (20%)	0.824
No pathological glands found	5/73 (7%)	4/68 (6%)	1/5 (20%)	0.228

s: serum, u: urinary, renal impairment=creatinine clearance <60 ml/min

serum calcium and PTH concentrations at respectively 3 and 5 months post-operatively. There were no significant differences in demographic or biochemical data before or after PTx between patients who were cured after initial surgery and those (n=5) who demonstrated persistence of PHPT (Table 1).

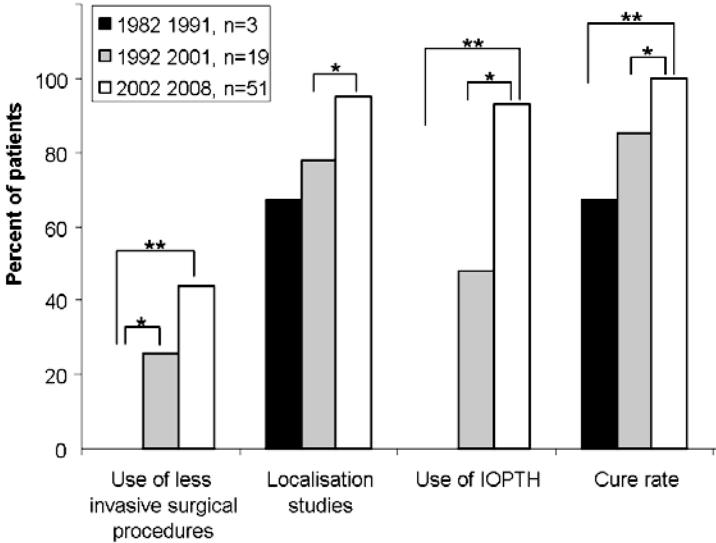


Figure 2. Pattern of change in surgical procedures, use of pre-operative localization studies and IOPTH monitoring, and cure rate over 24 years of follow-up. In the first decade of the study (1982-1991) all patients underwent bilateral neck exploration and IOPTH monitoring was not yet available. * P<0.05, ** P<0.001.

Long-term follow-up

Patients were evaluated after a mean of 6 ± 5 years and up to 24 years after PTx, with the majority of the patients (68%) being assessed more than 5 years after PTx. Median age at follow-up was 63 years compared to 55 years before PTx. Cure was sustained for the length of follow-up in all 68 patients in whom cure was established at 6 months after initial surgery. Regardless of age, 29% of the patients complained of tiredness, only two of whom were older than 70 years, 22% of muscle or bone pain, and 15% of depressive symptoms, which persisted despite complete cure. The mean corrected serum calcium concentration was 2.27 ± 0.13

mmol/l, with a mean serum PTH concentration of 4.4 ± 2.4 pmol/l. Two of the five patients with persistent HPTH had undergone successful revision surgery, resulting in cure after excision of one or more additional hyperactive parathyroid glands, one of which was situated retrosternally. The third patient is being treated conservatively because of the mild asymptomatic nature of her PHPT and the failure of localization studies to identify the site of the hyperactive gland(s). A conservative approach was also originally opted for in the fourth patient because of the mild asymptomatic nature of his persistent PHPT, but he is now scheduled for revision surgery as he demonstrated significant symptomatic and biochemical progression of his HPTH 9 years after his initial surgery (Figure 3). The fifth patient still has persistent PHPT after unsuccessful full neck and mediastinal explorations, and is being treated successfully with the calcimimetic cinacalcet.

Predictive factors for cure after parathyroidectomy

There were no significant differences in gender and age at presentation between patients who achieved and maintained cure and patients with persistence of HPTH after initial PTx (Table 1). Clinical presentation (symptomatology and skeletal and/or renal complications) was also not significantly different in patients in whom HPTH persisted post-operatively. None of the laboratory investigations, including serum calcium, PTH, phosphate, urinary calcium, and creatinine clearance, showed a significant difference between cured and noncured patients. There was also no significant difference in the availability of pre-operative localization studies, type of surgical approach, or use of IOPTH monitoring between groups. No pathological tissue was found at initial surgery in one of the five patients with persistent HPTH, but this was also the case in 4 patients who were subsequently cured. It is of note that all five patients with persistent HPTH had undergone surgery before 2001 and all had undergone localization studies in the form of ultrasound of the neck and/or Tc99m-MIBI-SPECT scan. Three of the five patients also had IOPTH monitoring (Table 2), in 2 of whom IOPTH monitoring indicated cure, with a decrease in PTH levels of 96 and 71,6% respectively after excision of a pathological parathyroid gland. In both patients, this was associated with a transient normalization of serum

calcium and PTH concentrations lasting 3 and 5 months respectively after PTx. In the third patient with persistent HPTH, only one hyperplastic gland could be identified and removed during surgery, but there was no significant decrease in IOPTH levels and hyperparathyroidism persisted post-operatively.

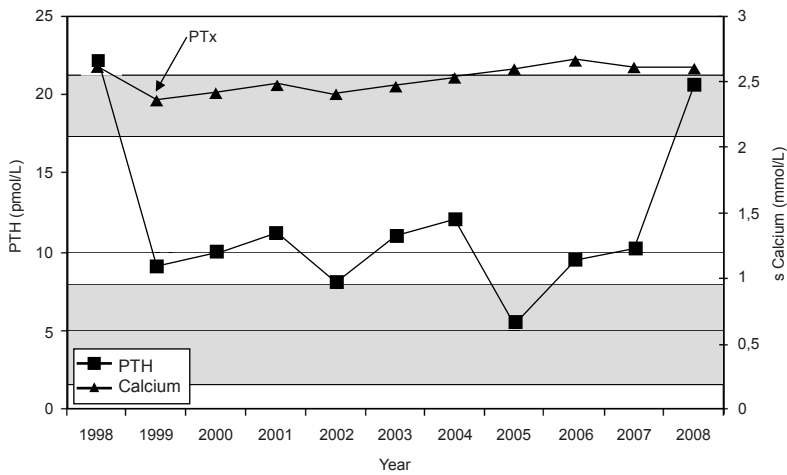


Figure 3. Serum calcium and PTH concentrations in a patient conservatively treated for mild asymptomatic persistent hyperparathyroidism after incomplete parathyroidectomy (PTx). Clear demonstration of progression of biochemical features associated with clinical manifestations of overt hyperparathyroidism 9 years after surgery, outlining the importance of long-term follow-up in these patients.

Fate of symptoms/complications of primary hyperparathyroidism after cure

After successful parathyroidectomy, none of the 68 cured patients had specific symptoms related to hypercalcaemia, particularly no polyuria and polydipsia (Figure 4). Although there was a trend towards a decrease in reported tiredness ($P=0.05$), there was no significant change in a number of other non-specific symptoms, such as depressive symptoms, muscle pain or muscle weakness after cure. The frequency of nephrolithiasis decreased significantly from 41% to 10%, ($P=0.000$). There was also a significant improvement in BMD, with only 16% of patients having evidence for osteoporosis a mean of 6 years after PTx compared to

Table 2. Surgical and pathological data of patients with sporadic primary hyperparathyroidism with persistent HPTH after initial surgery

Age at presentation (years)	Localisation studies					Pathology excised	IOPTH monitoring	Surgical procedure	Outcome of cure	Outcome of revision PTx
	Gender	US scan	MiBi-SPECT scan	Surgical procedure	IOPTH monitoring					
49	F	No	Yes, Positive	Bilateral	No	Adenoma	None	None	Persistence	
57	F	No	No	Bilateral	No	No pathology	None	None	Cured	
66	F	Yes, Positive	No	Unilateral	Yes	Adenoma	5 months	Cured		
56	M	Yes, Positive	No	Minimally invasive	Yes	Adenoma	3 months	Awaits revision PTx		
53	F	Yes, Negative	Yes, Negative	Bilateral	Yes	Hyperplasia	None	Persistence		

40% before surgery $P=0.002$). After parathyroidectomy, 4 patients, all of whom were post-menopausal women aged 59 to 78 years, sustained 4 documented fractures, one vertebral and 3 non-vertebral (2 hip fractures and 1 Colle’s fracture). 64% of patients who had renal impairment prior to PTx demonstrated a 35% improvement in their renal function after successful surgery. In the remaining patients with renal impairment at initial surgery, this remained stable in 21% and further decreased by 22% in 14% of patients who achieved and maintained cure. Renal function decreased over time of follow-up in 4 patients who had normal renal function pre-operatively.

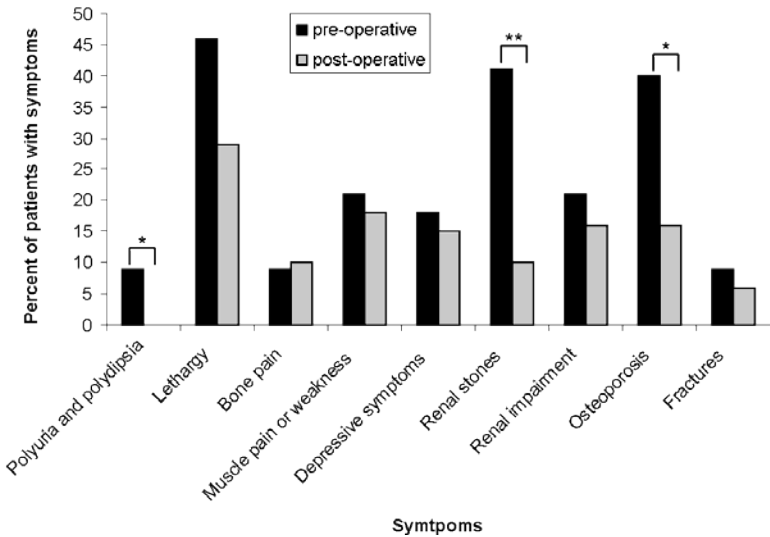


Figure 4. Change in symptomatology and in renal and skeletal complications after successful surgery for sporadic primary hyperparathyroidism, after a mean 6 years follow-up. * $P<0.05$, ** $P<0.001$.

DISCUSSION

In our population of patients with sporadic PHPT, we observed an overall cure rate of 93%, which has risen to 100% over the last 7 years with the increasing use of

pre-operative localization studies and IOPTH monitoring. We demonstrated that when cure is achieved in these patients, this is sustained in all for up to 24 years of follow-up.

Cases of ‘recurrent HPTH’ reported by Westerdahl *et al.* (11) and Hedback *et al.* (29) were shown to be due to initially unsuspected *MEN-1* or *MEN-2* mutations or due to secondary or tertiary hyperparathyroidism, all potentially associated with multiple gland disease. Data from our study, in which we excluded patients with known germ cell mutations in the *MEN-1* or *MEN-2* gene or other genes controlling parathyroid growth and PTH secretion, support the notion that ‘recurrent’ HPTH does not occur in sporadic PHPT when cure is established 6 months after PTx. This is in clear contrast to the outcome in patients with a known germ cell mutation, who were excluded from the study, in whom hyperparathyroidism recurred post-operatively in 44% of the cases (Figure 1). In this context, DNA analysis is strongly advocated in all the cases of ‘recurrent’ HPTH to assess the possible presence of a specific germ cell mutation as this holds significant clinical implications for the management of these patients.

Following adequate surgery, persistent HPTH is most commonly due to multiple gland disease with additional pathological glands often missed during initial surgery. Transient normalization of serum calcium and PTH concentrations occurs post-operatively in multiple gland disease due to the suppression of the activity of smaller glands by a dominant large gland. Pathological small parathyroid glands may take sometimes up to 6 months to recover and become hyperactive in their own right. Failing to consider this possibility may result in premature discharge of patients from follow-up because of the erroneous impression of permanent cure. This is illustrated in one of our patients with persistent HPTH, who demonstrated progression of HPTH 9 years after initial PTx. Solorzano *et al.* also showed that patients with normal calcium and inappropriately high PTH values after surgery have, in fact, persistence of HPTH which can take up to 2 years to become symptomatic (30). Follow-up is therefore strongly advocated for more than 6 months after PTx to definitively establish cure and provide a safety net for those patients with pseudo-cure, who have residual gland pathology.

In addition to the essential requirement of an experienced surgeon, pre-operative localisation studies and IOPTH monitoring appear to significantly contribute to a successful outcome of surgery. In our hands, implementation of these measures has resulted in a 100% cure rate over the last 7 years.

In contrast to the widely observed shift in clinical presentation of PHPT from a symptomatic to a largely asymptomatic one, more than 70% of our patients were symptomatic and had renal impairment, renal stones or osteoporosis with or without fractures. Our institution is a tertiary referral center treating the more severe forms of PHPT, and patients with more severe forms of the disease are thus overrepresented in our study. However, this bias also represents the strength of our study, as we do show that despite the severity of hyperparathyroidism, cure can be achieved and sustained and is associated with significant beneficial effects on kidneys and bones.

We observed a significant decrease in the frequency of nephrolithiasis, an improvement in renal function in those with pre-operative renal impairment, and a general improvement in BMD after successful surgery. Other studies have also shown this positive effect of PTx on BMD, supporting the notion that osteopenia and osteoporosis are at least partially reversible after PTx (15-17). In our study, the limited number of X-rays performed in the study population combined with the small number of fractures sustained before or after PTx precludes a meaningful analysis of an effect of PTx on fracture risk.

The retrospective nature of the analysis of changes in neurocognitive function represents a limitation of our study, particularly with a time span of up to 24 years from presentation. It was notable, however, that a high proportion of patients, who were permanently cured, still had residual nonspecific symptoms, such as tiredness and depressive symptoms. This suggests that to some extent these symptoms may have been falsely attributed to PHPT, although irreversible changes in neurocognitive function may have also occurred as a result of long-term exposure to high circulating levels of PTH.

Our findings from this study hold significant clinical implications. The absence of recurrence of sporadic PHPT, when cure is established 6 months post-

operatively, strongly suggests that long-term follow-up of these patients is not necessary. In contrast, close follow-up is advocated within the first 6 months after PTx to definitively establish cure and to provide a safety net for those with residual gland pathology.

REFERENCES

1. Chiu B, Sturgeon C, Angelos P. What is the link between nonlocalizing sestamibi scans, multigland disease, and persistent hypercalcemia? A study of 401 consecutive patients undergoing parathyroidectomy. *Surgery* 2006;140(3):418-422.
2. Calva-Cerqueira D, Smith BJ, Hostetler ML, Lal G, Menda Y, O'Dorisio TM, Howe JR. Minimally invasive parathyroidectomy and preoperative MIBI scans: correlation of gland weight and preoperative PTH. *J Am Coll Surg* 2007;205(4 Suppl):S38-S44.
3. Jones JM, Russell CF, Ferguson WR, Laird JD. Pre-operative sestamibi-technetium subtraction scintigraphy in primary hyperparathyroidism: experience with 156 consecutive patients. *Clin Radiol* 2001;56(7):556-559.
4. Palmer RM, Lokey JS. Is minimally invasive parathyroidectomy reasonable in the nonuniversity setting? *Am J Surg* 2006;192(6):865-868.
5. Bergenfelz A, Lindblom P, Tibblin S, Wester Dahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. *Ann Surg* 2002;236(5):543-551.
6. Wester Dahl J, Bergenfelz A. Sestamibi scan-directed parathyroid surgery: potentially high failure rate without measurement of intraoperative parathyroid hormone. *World J Surg* 2004;28(11):1132-1138.
7. Moka D, Voth E, Dietlein M, Larena-Avellaneda A, Schicha H. Technetium 99m-MIBI-SPECT: A highly sensitive diagnostic tool for localization of parathyroid adenomas. *Surgery* 2000;128(1):29-35.
8. Goldstein RE, Billheimer D, Martin WH, Richards K. Sestamibi scanning and minimally invasive radioguided parathyroidectomy without intraoperative parathyroid hormone measurement. *Ann Surg* 2003;237(5):722-730.
9. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. *Ann Surg* 2002;235(5):665-670.
10. Ruda JM, Hollenbeak CS, Stack BC, Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg* 2005;132(3):359-372.
11. Wester Dahl J, Bergenfelz A. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: five-year follow-up of a randomized controlled trial. *Ann Surg* 2007;246(6):976-980.
12. Carty SE, Norton JA. Management of patients with persistent or recurrent primary hyperparathyroidism. *World J Surg* 1991;15(6):716-723.
13. Alexander HR, Jr., Chen CC, Shawker T, Choyke P, Chan TJ, Chang R, Marx SJ. Role of preoperative localization and intraoperative localization maneuvers including intraoperative PTH assay determination for patients with persistent or recurrent hyperparathyroidism. *J Bone Miner Res* 2002;17 Suppl 2:N133-N140.
14. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med* 1999;341(17):1249-1255.
15. Nomura R, Sugimoto T, Tsukamoto T, Yamauchi M, Sowa H, Chen Q, Yamaguchi T et al. Marked and sustained increase in bone mineral density after parathyroidectomy in patients with primary hyperparathyroidism; a six-year longitudinal study with or without parathyroidectomy in a Japanese population. *Clin Endocrinol (Oxf)* 2004;60(3):335-342.
16. Hagstrom E, Lundgren E, Mallmin H, Rastad J, Hellman P. Positive effect of parathyroidectomy on bone mineral density in mild asymptomatic primary hyperparathyroidism. *J Intern Med* 2006;259(2):191-198.
17. Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, Udesky J et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. *J Clin Endocrinol Metab* 2008;93(9):3462-3470.
18. Talpos GB, Bone HG, III, Kleerekoper M, Phillips ER, Alam M, Honasoge M, Divine GW et al. Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey. *Surgery* 2000;128(6):1013-1020.

19. Mihai R, Sadler GP. Pasieka's parathyroid symptoms scores correlate with SF-36 scores in patients undergoing surgery for primary hyperparathyroidism. *World J Surg* 2008;32(5):807-814.
20. Coker LH, Rorie K, Cantley L, Kirkland K, Stump D, Burbank N, Tembreull T et al. Primary hyperparathyroidism, cognition, and health-related quality of life. *Ann Surg* 2005;242(5):642-650.
21. Pasieka JL, Parsons LL. Prospective surgical outcome study of relief of symptoms following surgery in patients with primary hyperparathyroidism. *World J Surg* 1998;22(6):513-518.
22. Adler JT, Sippel RS, Schaefer S, Chen H. Preserving function and quality of life after thyroid and parathyroid surgery. *Lancet Oncol* 2008;9(11):1069-1075.
23. Pasieka JL, Parsons LL, Demeure MJ, Wilson S, Malycha P, Jones J, Krzywda B. Patient-based surgical outcome tool demonstrating alleviation of symptoms following parathyroidectomy in patients with primary hyperparathyroidism. *World J Surg* 2002;26(8):942-949.
24. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357(3):266-281.
25. Roux C, Bischoff-Ferrari HA, Papapoulos SE, de Papp AE, West JA, Bouillon R. New insights into the role of vitamin D and calcium in osteoporosis management: an expert roundtable discussion. *Curr Med Res Opin* 2008;24(5):1363-1370.
26. World Health Organisation: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis., in (ed WHO Technical Report Series 843. Geneva).1994.
27. Diagnosis and management of asymptomatic primary hyperparathyroidism. National Institutes of Health Consensus Development Conference. October 29-31, 1990. Consensus Statement 1990;8(7):1-18.
28. Bilezikian JP, Potts JT, Jr., Fuleihan G, Kleerekoper M, Neer R, Peacock M, Rastad J et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. *J Clin Endocrinol Metab* 2002;87(12):5353-5361.
29. Hedback G, Oden A. Recurrence of hyperparathyroidism; a long-term follow-up after surgery for primary hyperparathyroidism. *Eur J Endocrinol* 2003;148(4):413-421.
30. Solorzano CC, Mendez W, Lew JI, Rodgers SE, Montano R, Carneiro-Pla DM, Irvin GL, III. Long-term outcome of patients with elevated parathyroid hormone levels after successful parathyroidectomy for sporadic primary hyperparathyroidism. *Arch Surg* 2008;143(7):659-663.

