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ORIGINAL SCIENTIFIC REPORT

Results of a Fifteen-Year Follow-up Program in Patients Operated with Unilateral Neck Exploration for Primary Hyperparathyroidism

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Abstract

Background Since the introduction of unilateral parathyroidectomy for primary hyperparathyroidism (pHPT) it has been debated wherever this approach is associated with greater long-term risk for recurrence compared to bilateral neck exploration.

Methods This is a prospective study based on a structured 15-year follow-up program in patients with non-hereditary, sporadic pHPT, undergoing first time surgery with unilateral or focused neck exploration (unilateral procedures), with the use of intraoperative PTH (iOPTH) between 1989 and 2010.

Results 292 patients were analyzed. The median age of the patients was 66 years [interquartile range (IQR) 57–75], and 234 (80.4 %) were female. The median preoperative level of total calcium was 2.74 mmol/L (IQR 2.63–2.85 mmol/L) and the median PTH level was 10 pmol/L (IQR 7.4–14 pmol/L). The median follow-up time was 5 years (IQR 1–10 years). Some 275 patients were followed for 1 year (94.2 %/275 person-years/5 patients deceased), 164 for 5 years (56.2 %/820 person-years/31 patients deceased), 70 for 10 years (24.0 %/700 patient-years/57 patients deceased) and 51 (17.5 %/765 patient-years/69 patients deceased) for 15 years after surgery. Three patients (1.1 %) had signs of persistent disease. One patient recurred in pHPT at 5 years postoperatively during 15 years of follow-up. Histopathology indicated solitary parathyroid adenoma at primary surgery.

Conclusion Patients with pHPT operated with unilateral procedures and iOPTH, had a low risk for long-term recurrence during a 15 years follow-up program.

Introduction

Some 30 years ago Tibblin et al. introduced unilateral parathyroidectomy in primary hyperparathyroidism (pHPT) due to single adenoma [1, 2]. This approach was initially highly controversial, due to the supposed risk for short- and long-term recurrence of pHPT [3–7]. The main advantage of a unilateral approach is that, compared to bilateral neck exploration (BNE), it is associated with a decreased risk for complications, especially early postoperative hypocalcaemia [8–12]. The validity and reliability of preoperative localization procedures has been discussed since their introduction. Even though some studies showed that sestamibi scintigraphy had unsatisfactory sensibility for detection of multiglandular disease (MGD) [6, 7, 13], several publications have proven the short-term validity of scan-directed parathyroid exploration in combination with ultrasound and/or intraoperative PTH measurements (iOPTH) [3, 14–18]. The difficulty in differentiating between parathyroid adenoma and hyperplasia based on

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histopathological features implicates the need for long postoperative follow-up and peroperative adjuncts (iOPTH) to verify successful removal of pathological parathyroid tissue and. The unilateral or focused approach for the surgical treatment of pHPT, has gained widespread acceptance during the last decades. In 2012 the Scandinavian Quality Register showed that BNE comprised only 40 % of all parathyroid operations in Sweden (http://www.thyroid-parathyroidsurgery.com/assets/Årsrapport-2014.pdf). Even if good results have been shown by a randomized trial at follow-up 5 years postoperatively [19] the long-term risk for recurrent PHPT has been debated. Recently, retrospective studies investigating long-term outcome after unilateral and bilateral exploration have been published [4, 5, 20–26] .

It was hypothesized that patients undergoing unilateral parathyroid exploration had a low long-term risk for recurrent disease. In this prospective study results from a structured 15-year follow-up program of patients operated with a unilateral or focused approach between 1989 and 2010 at a single center are reported.

Methods

Study population

Patients operated for pHPT from 1989 to 2010 were included in the study. Exclusion criteria were a family history of pHPT (MEN1, MEN2, or hereditary pHPT), reoperation for pHPT, concordant thyroid surgery and bilateral neck exploration, whether preoperatively planned or peroperatively required. All patients operated for pHPT at the department of surgery at Lund University hospital, Sweden were included in a 15-year follow-up program. The date for last follow-up was December 31, 2013. The length of follow-up was calculated as date for latest biochemical follow-up operation date. The study group consisted of patients with preoperatively localized parathyroid adenoma by (99 m)Tc Sestamibi scanning (MIBI) or by ultrasound complemented by intraoperative PTH (iOPTH). Patients with non-localized adenoma in whom iOPTH measurements confirmed successful excision of pathological parathyroid tissue after unilateral neck exploration, were also included in the study.

Follow-up program

The 15 years structured follow-up program was initiated in 1989. The program was designed to investigate the risk for long-term recurrence in patients with pHPT specifically in patients operated with a unilateral approach.

Results of pre-and postoperative variables, were registered by one of the authors in a database. Registered variables included symptoms and signs of pHPT, medical history and medication, biochemical variables including, among others, calcium and PTH levels, urinary calcium, biochemical markers for bone remodeling, vitamin D status, bone density and renal function. Parathyroid imaging, intraoperative PTH measurements, operation technique and intraoperative findings and histopathology were also recorded.

In the 15 years follow-up program all patients were followed by one of the authors. Follow-up with biochemistry were routinely conducted at 4 weeks, and at 1, 5, 10, and 15 years after surgery. At 1 year after surgery biochemistry were supplemented with investigation of bone density, renal function and Vitamin D status.

Cure was defined as calcium levels below the upper limit for normocalcemia (ionized calcium <1.35 mmol/L/ P-Calcium <2.50 mmol/L), regardless of PTH levels at 12 months after surgery. Persistent disease was defined as calcium levels above the upper limit for normocalcemia within 1 year after surgery.

Surgery

All patients underwent surgery performed under general anesthesia, either with a short anterior Kocher incision or a lateral mini-incision over the sternocleidomastoid muscle in patients operated with a focused approach.

In patients with negative preoperative localization studies, operation was performed with exploration of the left side first as previously described by the authors [27].

To verify successful removal of all pathological parathyroid tissue, intraoperative PTH measurement (iOPTH) was used, according to the MIAMI criterion as earlier described by Irvin et al. [28] e.g., a decrease to <50 % of baseline value.

Biochemical variables

Preoperative serum ionized calcium concentrations (reference range 1.15–1.35 mmol/L) were analyzed from blood samples normalized to pH 7.4 with the ion-selective electrode ABL 505 (Radiometer, Copenhagen Denmark). The method has a coefficient of variation (CV) of <1 % at an assigned value of 1.27 mmol/L. Levels of total serum calcium (reference range 2.20–2.60 mmol/L) were measured by a routine laboratory analyzer. Plasma parathyroid hormone (PTH) was analyzed by an essay for intact PTH (Hitachi Modular –E), reference range 1.6–6.9 pmol/L. The analysis has a total CV of 5 % at 100 pmol/L. On 20th

March 2000 the method was changed. The correction formula between old and new values is as follows: new value = 1.4 × old value−0.2.

High performance liquid chromatography (HPLC) was used for assessment of the level of serum 25-hydroxyvitamin D_3 [25(OH)D_3] (reference range >75 ng/L). The method concerning analyses of 25-hydroxyvitamin D_3 was changed to Nichols Advantage 25-Hydroxyvitamin D, Nichols Institute Diagnostics and all data were transformed. Glomerular filtration rate, GFR, was determined by a technique that measures renal clearance of the contrast agent iohexol. Using this method, the average value for young healthy subjects is 127 ml/min with n reduction in subjects older than 55. Thus, in 65-year-old subjects, the expected GFR would be about 80 mL/min.

Cure was defined as calcium levels below the upper limit for normocalcemia (ionized calcium <1.535 mmol/L/P-Calcium <2.50 mmol/L) at 12 months after surgery. Persistent disease was defined as calcium levels above the upper limit for normocalcemia before 1 year after surgery.

Statistics

Statistical analysis was carried out using STATA 11 StataCorp LP, 4905 Lakeway Drive College Station, Texas 77845 USA. The association between variables over time was tested with the Spearman rank correlation test. Nominal data are shown as numbers and per cent. All tests were two-sided.

Overall survival data were calculated by Kaplan–Meier survival curves.

A p value <0.05 was considered statistically significant.

Results

Preoperative status

There were 570 patients with non-hereditary pHPT undergoing first time surgery, and 292 of these patients were operated with a unilateral approach. The median age of the patients was 66 (range 22–89) years. The median level of total calcium was 2.74 mmol/L (IQR 2.63–2.85 mmol/L).

The results of preoperative localization procedures, is shown in Table 1. Sestamibi scintigraphy was used in 253 patients, indicating single gland disease (SGD) in 219 patients. Sensitivity was 87.2 % for correct prediction of adenoma side. Additional ultrasound was performed in 71 patients, predicting SGD in 61 patients. Sensitivity was 77.0 % for correct prediction of adenoma side. 36 patients had concordant, positive localization results. In 131 of 292 patients (45 %), two parathyroid glands were identified intraoperatively.

Histopathology

Histopathology report showed a solitary parathyroid adenoma in 286 patients with a median gland weight of 730 mg (range 100–9800 mg; IQR 380–1550 mg). In four patients, in whom one gland was excised, the histopathology report suggested parathyroid hyperplasia due to absence of suppressed parathyroid tissue in the specimen. None of these patients, however, showed signs of persistent or recurrent disease.

Follow-up

Results from preoperative biochemical data and follow-up, are shown in Table 2. The median follow-up time was 5 years (range 4 weeks–15 years). Eleven patients were followed for <1 year. Three of these died within the first year of follow-up. During follow-up 69 patients died (Fig. 1). Some 275 patients (94.2 %) were followed for 1 year, 164 (56.2 %) for 5 years, 70 (24.0 %) for 10 years and 51 (17.5 %) for 15 years after surgery. The reason for not taking part in the follow-up program at a particular time point included, patient refusal, medical reasons, and that the patients had moved from the catchment area of the endocrine surgical unit.

None of the patients suffered from postoperative hypocalcemia.

Persistent disease

Three patients (1.1 %) had signs of persistent disease. In two of these patients, two glands were identified and one enlarged gland was removed and histopathology showed a

Table 1 Results of preoperative localization procedures results

	n	Positive	Negative	Not performed	Concordant positive localization studies	Concordant negative localization studies	No localization studies performed	Correctly predicted side	Sensitivity (%)
Scintigrafi	253	219	34	39	36	1	27	191	87.2
Ultrasound	71	61	10	221				47	77.0

Frequencies are displayed as n if not stated otherwise

Table 2 Pre -and postoperative follow-up data in patients operated with unilateral neck procedures for primary hyperparathyroidism

	Preoperatively	Follow-up 4 weeks	Follow-up 1 year	Follow-up 5 years	Follow-up 10 years	Follow-up 15 years
Patients at risk (*n*)	292	292	287	215	90	61
Patients followed-up (*n*)	292	279	275	164	70	51
Deceased (*n*)	–	0	5	31	57	69
Missing (*n*)	–	13 (4.5)	12 (4.2)	51 (23.7)	20 (22.0)	10 (16.4)
(% of pat. at risk)						
Cured *n* (% of pat. at risk)	–	277 (99.3)	271 (98.5)	163 (99.4)	70 (100)	51 (100)
Persistent disease (*n*)	–	3	3	–	–	–
Recurrence (*n*)	–	–	–	1	0	0
P-calcium (mmol/L)	2.74	2.34	2.31	2.33	2.36	2.35
(median and interquartile range)	2.63–2.85	2.27–2.41	2.25–2.39	2.28–2.39	2.28–2.42	2.27–2.44
S-ionized calcium (mmol/L)	1.46	1.24	1.22	1.22	1.22	1.23
(median and interquartile range)	1.41–1.52	1.21–1.27	1.2–1.26	1.20–1.25	1.2–1.25	1.20–1.25
P-PTH (pmol/L)	10	5.2	4.65	4.55	4.25	4.7
(median and interquartile range)	7.4–14	3.85–7.3	3.5–6.35	3.55–6.05	3.2–6.2	3.6–5.4
Creatinine	71	–	72	74	70	73
(median and interquartile range)	60–85		61–83	66–91	62–82	64–87
S-25OHD (nmol/L)	50	45	56	64	a	a
(median and interquartile range)	37–64	38–62	36–69	45–80		

[a] Not measured routinely 10 and 15 years after surgery

– Not applicable

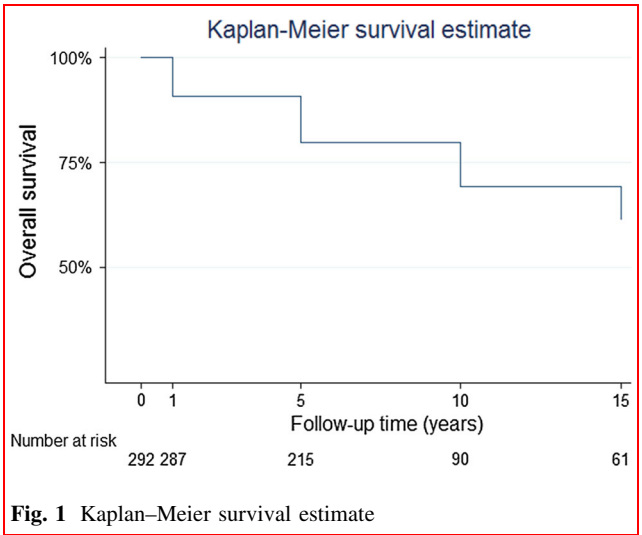

Fig. 1 Kaplan–Meier survival estimate

parathyroid adenoma. In the third patient, only one gland was identified and excised with iOPTH decreasing >50 %. Histopathology, however, showed normal parathyroid tissue. This patient had a preoperatively elevated level of Creatinine and developed renal insufficiency at 5 years of follow-up. Intraoperative PTH was false positive in all three patients according to the Miami criteria (21). None of the patients have been re-operated.

Recurrent disease

During 15 years of follow-up one patient was diagnosed with recurrent disease 5 years after primary surgery. This patient had a positive preoperative localization with sestamibi for the upper left parathyroid gland, ultrasound showed an enlarged thyroid gland but no parathyroid adenoma. After removal of the upper left gland, iOPTH decreased by 61 %. In this patient, PTH was in the normal range at 10 min after gland excision, although this was not used for decision-making at the time for the operation. The lower right gland was identified and macroscopically normal. Histopathology showed a parathyroid adenoma with a rim of suppressed normal parathyroid tissue. Postoperatively ionized calcium levels were in the upper normal range with PTH elevated and 25 OHD at 25 nmol/L 1 year after surgery. Supplementation with Vitamin D was initiated, but had to be terminated due to increasing calcium levels. At follow-up 5 years after surgery the patient had clear biochemical signs of recurrent disease with levels of ionized calcium, total calcium and PTH above the normal range. Sestamibi scan and ultrasound were negative and the patient was referred to the department of endocrinology for further follow-up. The patients' calcium levels have been stable until April 14th 2013 without further treatment.

Discussion

The aim of this study was to investigate the risk for long-term recurrence in patients with pHPT operated with a unilateral approach with the use of iOPTH.

In contrast to other authors [6], the results showed that the risk for recurrence during a 15-year follow-up was very low. Due to the unilateral nature of the surgical procedure, there was no patient treated for long-term hypocalcaemia. The long-term success rate of a unilateral approach to pHPT in the present investigation is in agreement with previous retrospective studies, some of them reporting on patients operated without the use of ioPTH [5, 22, 29].

In the present study, cure of pHPT was defined strictly as normocalcemia (ionized calcium <1.35 mmol/L and or total calcium levels <2.50 mmol/L. It may be argued that patients with a normal calcium levels but with an increase in PTH, may suffer from persistent sub-clinical pHPT. However, postoperatively elevated PTH levels after pHPT surgery are not uncommon [30–36], and have been shown to be caused by multiple factors, such as vitamin D insufficiency [32, 34], impaired renal function [33, 35], and decreased peripheral sensitivity for PTH [37]. Patients displaying constantly elevated PTH levels after surgery should probably become subject to an individualized, prolonged follow-up program [33, 34]. In the present study, no patient had persistently elevated PTH levels up to 15 years after surgery.

Two of the three patients with persistent disease, were initially diagnosed with solitary parathyroid adenoma, as was the patient with recurrent disease. The patient with recurrent disease may have a true recurrence or sub-clinical disease. All patients with persistent or recurrent disease had a false positive result of iOPTH, which shows, in agreement with other studies that within the subgroup of multi glandular disease, double adenomas are poorly predicted [38, 39].

In four cases, histopathology report suggested parathyroid hyperplasia due to absence of suppressed, normal parathyroid tissue. All four patients were biochemically cured, without signs of long-term recurrence after removal of 1 parathyroid gland. This clearly illustrates the difficulty in distinguishing between parathyroid adenoma and hyperplasia by histology alone.

For reliable selection and time-effective operation scheduling, ultrasound, and sestamibi scintigraphy was utilized for preoperative localization procedures. Patients with negative preoperative localization procedures seem to have a higher incidence of multiglandular parathyroid disease, smaller adenomas with higher count of chief cells, atypic adenoma localization, and/or concomitant thyroid disease which implicates more extensive surgery and frequent use of bilateral neck exploration [40–42]. In a previous study [27], it has been shown that some of these patients may be operated with a unilateral procedure with the use of iOPTH, which is substantiated with the results from the present investigation; none of the patients with negative preoperative localization procedures recurred.

There are some limitations to the present investigation. There was an inevitable loss of follow-up due to mortality and co-morbidity in this aging patient population with predominantly mild disease. Data on all patients with non-hereditary pHPT undergoing first time surgery with the intention of unilateral or focused exploration was collected prospectively. Patients that did not decrease >50 % in iOPTH, however, had to be excluded peroperatively. Therefore, the results of this study cannot be applied to other patients groups than those who underwent successful unilateral or focused parathyroid exploration.

However, this was a prospective single center observational study with up to 15-year follow-up. All patients were followed by the attending surgeons. Further, the patient cohort consisted of predominantly localized parathyroid disease but patients with negative localization studies were also included. With increasing numbers of patients with asymptomatic pHPT and some research pointing towards decreasing benefits of surgical intervention [43, 44], future treatment recommendations should be individualized for treatment benefits and to minimize adverse effects and cost of treatment and surveillance.

Conclusions

This study confirms a high success rate with a very low risk for recurrent disease in patients with sporadic pHPT operated with a unilateral procedure with the use of iOPTH. Long-term follow-up of this patient category seems not to add any safety benefits.

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