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ORIGINAL ARTICLE

Results of surgery for sporadic primary hyperparathyroidism in patients with preoperatively negative sestamibi scintigraphy and ultrasound

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Abstract
Purpose The purpose of this study is to investigate the results of first-time surgery for sporadic primary hyperparathyroidism (pHPT) in patients with preoperatively negative sestamibi scintigraphy and ultrasound.

Methods Data were gathered prospectively in a multicenter database for quality control in parathyroid surgery. Between 2004 and 2008, 3,158 patients underwent first-time surgery for sporadic pHPT. A total of 984 patients were subjected to preoperative localization with ultrasound and sestamibi

All authors are members of the Steering Committee of the Scandinavian Quality Register for Thyroid and Parathyroid Surgery (www.thyroid-parathyroidsurgery.com).

Authors' contribution

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Analysis and interpretation of data were made by Anders O. J. Bergenfelz.

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scintigraphy, and in 173 patients, both investigations were negative. Intraoperative findings and early outcome are reported.

Results One hundred and fifty-five of 173 patients underwent bilateral neck exploration. The median weight of excised parathyroid tissue was 350 mg. In 23 patients (13.3%), the exploration was negative. A total of 112 patients (64.7%) had a histological diagnosis of parathyroid adenoma and 38 patients (22%) had multiglandular disease. Six weeks after operation, 164 patients were available for analysis, and 30 patients (18%) had persistent pHPT. The risk for persistent pHPT increased for patients with few intraoperatively identified (p=0.001) and excised (p=0.024) parathyroid glands. Patients operated with intraoperative parathyroid hormone (iOPTH) had lower risk for persistent pHPT 7/79 (9%) compared with 23/85 patients (27%) operated without iOPTH (p=0.003).

Conclusions Negative localization with sestamibi and ultrasound in pHPT infers a highly selected patient population with small parathyroid adenomas, an alarmingly high rate of negative exploration, and an increased risk for persistent disease. The use of iOPTH influences cure rate favorably.

Keywords Primary hyperparathyroidism · Intraoperative PTH · Sestamibi scintigraphy · Ultrasound

Introduction

Bilateral neck exploration for the treatment of primary hyperparathyroidism (pHPT) is one of the most successful procedures in surgery, with a success rate of >95% [1] However, with the introduction of preoperative localization procedures, most notably, sestamibi scintigraphy and high-resolution ultrasound, most recently performed by the parathyroid surgeon [2, 3], image-directed minimal invasive parathyroidectomy has been well established [4–6]. Image-guided minimal invasive parathyroid surgery has been shown to decrease postoperative hypocalcemia and is considered safe and effective [7, 8]. For patients with negative localization procedures, bilateral neck exploration is generally recommended [8] although limited exploration (focused operation or unilateral neck exploration) with the aid of intraoperative PTH (iOPTH) has been suggested to be an alternative approach [9].

It has been suggested that results are worse for pHPT patients with negative sestamibi scintigraphy [9–11]. Thus, it can be suspected that an inconclusive or negative result of a preoperative localization introduces a negative selection of patients. Therefore, if investigation with sestamibi scintigraphy and ultrasound are negative, surgery is probably more difficult than for patients with no localization investigation, or with a positive localization test. The use and accuracy of iOPTH have been challenged by several authors [12–14] and deemed not to be cost-effective for patients with two positive localizations tests. However, in a recent Positional Statement of the European Society of Endocrine Surgeons (ESES) on pHPT surgery, its use is recommended for patients with only one or no positive localization test [5, 15].

The hypothesis for the present study is that for patients with sporadic pHPT undergoing first-time operation with preoperatively negative sestamibi scintigraphy and ultrasound, the outcome of surgery is inferior to established standards. Analysis is performed specifically with regard to the impact of iOPTH on surgical strategy, intraoperative findings, histology, and early outcome. The association between clinical and biochemical variables and outcome is also reported.

Data for the cohort have been gathered prospectively in the database of the Scandinavian Quality Register for Thyroid and Parathyroid Surgery between 2004 and 2008, and thus provide a multicenter and supranational perspective.

Material and methods

The database

Scandinavian Quality Register for Thyroid and Parathyroid Surgery (www.thyroid-parathyroidsurgery.com) is an on-line database launched in 2004 as part of a regional, EU-funded, healthcare cooperation project between Lund University Hospital and the University Hospital of Copenhagen, Rigshospitalet. From January 2009, also results of adrenal surgery are included in the database. The register is endorsed by several professional organizations—the Swedish and Danish Associations of Endocrine Surgeons as well as the Swedish Association of Oto–Rhino–Laryngeology, Head and Neck surgery. The register operates within the medico-legal framework of respective country. Participating departments are responsible for compliance with national legislation regulating register participation, including information and acceptance of patients where applicable.

Patients

Between January 1, 2004 and December 31, 2008, 27 departments reported data on 3,158 patients with sporadic pHPT and no previous thyroid or parathyroid surgery. Of the patients, 2,174 (69%) had a preoperative localization procedure performed. A total of 1,733 patients were operated after preoperative localization investigation with sestamibi scintigraphy, which was true positive for a

solitary parathyroid adenoma in 1,113 patients (64.2%) and 1,417 patients after ultrasonography, with a true positive result for a solitary parathyroid adenoma in 849 patients (59.9%). Other localization modalities were rarely used (CT, n=23; eight negative, MRI, n=5; four negative, Venous sampling, n=5; all negative PET, n=6; four negative)

Combined preoperative localization with sestamibi scintigraphy and ultrasonography was performed in 984 patients (31.2%), with concordant positive results for a solitary parathyroid adenoma in 467 patients (47.5%). In 173 patients (17.6%), both investigations were negative and these patients form the cohort for the present study thus encompassing 5.5% of the total number of patients (Fig. 1).

Follow-up was performed 1–6 weeks postoperatively.

Registered variables

Preoperatively

The variables assessed preoperatively were the Department, surgeon (consultant vs. assisted), gender, age, symptoms (yes/no), and serum calcium level.

Perioperatively

Perioperatively, the variables were date of operation, type of exploration (bilateral neck exploration, unilateral neck exploration, or focused operation), number of identified and excised parathyroid glands, autotransplantation of parathyroid glands (yes/no), other operations performed, identification of recurrent laryngeal nerves, noted nerve damage (yes/no), and iOPTH (yes/no and result).

A focused approach is defined as parathyroidectomy performed by minimal incision (<25 mm) with excision of a solitary parathyroid tumor, but without dissection for the identification of an ipsilateral parathyroid gland; a unilateral approach is an operation performed with an incision >25 mm with unilateral dissection for the excision of a solitary parathyroid tumor and the identification or excision of a normal ipsilateral parathyroid gland; a limited operation is parathyroidectomy performed either as a focused or a unilateral approach.

For the purpose of the database, a consultant surgeon is defined as a neck surgeon with specialist diploma in general surgery or ENT.

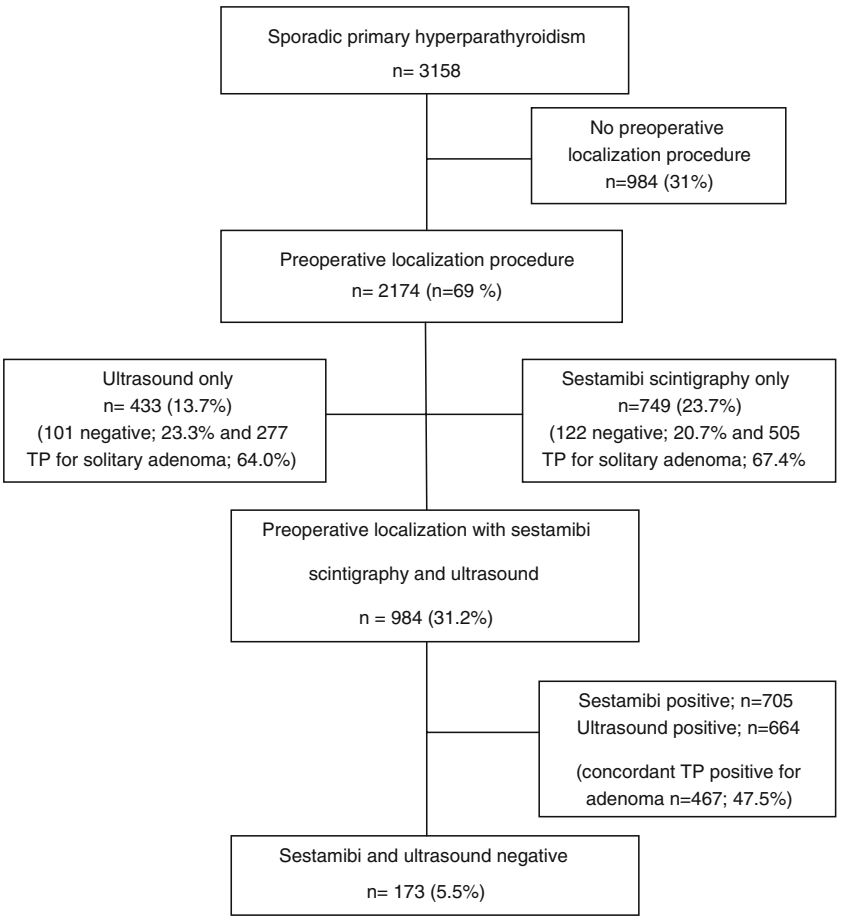

Fig. 1 Cohort of 3,158 patients with first-time surgery for sporadic pHPT. Numbers and percentage are shown

Postoperatively

Postoperatively, the following were assessed: complications, results of laryngoscopy and voice recording, histology and gland weight, calcium status at first follow-up (<6 weeks postoperatively); strictly normocalcemic, calcium below the reference range without treatment i.e., regarded as asymptomatic, hypocalcemia and in treatment with calcium and/or vitamin D analog therapy, spontaneous hypercalcemia and re-operated for pHPT (yes/no). Furthermore, the actual serum calcium level at this follow-up was recorded.

The patients were considered alleviated from hyperparathyroidism at the first follow-up if they were not hypercalcemic and had not been subjected to re-operation after the surgical procedure.

Medical treatment for hypocalcemia was only prescribed for hypocalcemic symptoms and/or when the serum level of total calcium was less than 2.00 mmol/l.

Intraoperative PTH

For departments that used iOPTH, the cut-off limit for the decrease of PTH levels to predict successful operation was reported. Of participating departments, all but one used the so-called Miami criteria [15] for biochemical cure. The results from iOPTH were graded as follows: correct iOPTH (TP), incorrect iOPTH/persistent pHPT in spite of "adequate" decline in PTH levels (FP), and misleading/insufficient decline in iOPTH in spite of adequate operation (FN).

Data validity

Data validity is controlled by yearly external audit of four participating departments chosen at random. Data quality is evaluated for two levels: the percentage of operated patients of a particular department that is registered in the database and the quality of data for the registered patients compared to the medical files. Thus far, the audit shows good data quality with an error of less than 5%.

Statistics

For continuous variables, the results are reported as median and percentiles if not stated otherwise. For nominal variables, numbers and percentage are given. For statistical evaluation of differences between groups, the Mann–Whitney *U* test was used for continuous variables, and for nominal variables, chi-square test was used, except when the frequency was expected to be less than five when statistical calculation was made with Fischer's exact test. A p value of <0.05 was considered significant. For nonsignificant outcome, results are given with three decimals. The impact of iOPTH for outcome data was analyzed as intention to treat, i.e., regardless of outcome, and categorized as used vs. not used.

Results

Surgery was performed by 11 departments which reported 173 patients with preoperatively negative sestamibi scintigraphy and ultrasound undergoing first-time operation for sporadic primary HPT. A total of 134 patients (77.5%) were females. The median age was 61 years (10% percentile, 47 years and 90% percentile, 78 years) and the median preoperative serum calcium level was 2.77 mmol/L (10% percentile, 2.61 mmol/L and 90% percentile, 2.99 mmol/L). PHPT-related symptoms were reported in 113 patients (65%). Bilateral neck exploration was performed in 155 patients (89.6%). The median weight of excised parathyroid tissue was 350 mg (10% percentile, 99 mg and 90% percentile, 1,712 mg).

At 6 weeks postoperatively, six patients (3.5%), had been re-operated due to persistent hypercalcemia, but only one of these patients became normocalcemic. At the first follow-up, 29 patients were hypercalcemic. Thus, including the successfully re-operated patient, 30 patients (17.3%) had persistent pHPT after the primary operation. A summary of surgical details and outcome at 6 weeks is shown in Table 1. Nine patients could, for a variety of reasons, not be followed, thus, 6 weeks' data are reported for 164 patients.

Data for patients with persistent pHPT at the 6 weeks follow-up, as well as the patients alleviated of hypercalcemia, is shown in Table 2. Patients with persistent HPT did not differ in age or preoperative symptoms (data not shown) compared with patients that were alleviated of hypercalcemia. However, the serum calcium levels in patients with persistent pHPT were slightly higher compared with patients without postoperative hypercalcemia.

Patients with persistent pHPT were more likely to have fewer parathyroid glands indentified and excised during surgery, and were to a lesser extent operated with the iOPTH. Excluding the 23 patients with negative exploration, seven of 36 patients (19.4%) with a histological diagnosis of hyperplasia were not alleviated of hypercalcemia at the first follow-up compared with eight of 106 patients (7.5%) with a parathyroid adenoma (p=0.060).

In the 164 patients that were available for follow-up at 6 weeks and with patients with persistent pHPT excluded from analysis (n=30), medically treated or asymptomatic hypocalcemia was found in three of seven patients with negative neck exploration vs. 18 of 127 patients with a positive intraoperative finding (p=0.077), and in nine of 29 patients with hyperplasia compared with nine of 98 patients with parathyroid adenoma (p=0.006). Furthermore, hypo-

Table 1 Surgical strategy, operation, histology, complications, and calcium status at 6 weeks in 173 patients undergoing surgery for sporadic primary HPT with negative preoperative localization with sestamibi scintigraphy and ultrasound

Variable	No.	Percent
Surgery		
Bilateral neck exploration	155	89.6
Total parathyroidectomy	3	1.7
Subtotal parathyroidectomy	21	12.1
Thymectomy	21	12.1
Thyroid surgery	31	17.9
Autotransplantation of parathyroid tissue	5	2.9
Complications		
Re-bleeding	1	0.6
Postoperative paresis of recurrent laryngeal nerve	1	0.6
Hypocalcemia which required iv calcium	1	0.6
Postoperative infection	2	1.2
Vitamin D analog therapy at discharge	12	6.9
Histology		
Adenoma	112	64.7
Hyperplasia	38	22.0
Negative exploration	23	13.3
Calcium status 6 weeks postoperatively		
Calcium below reference range without treatment (regarded as asymptomatic)	2	1.2
Treatment with oral calcium and/or Vitamin D analog	19	11.0
Hypercalcemia (spontaneous)	29	16.8
Normocalcemia	114	65.9
No data	9	5.2

calcemia at 6 weeks was more common in preoperatively asymptomatic patients (12/45) compared with symptomatic patients (9/89; $p=0.022$). IOPTH was used in 83 patients (48%) and was correct compared to intraoperative findings and outcome in 77 patients (92.8%), false positive (FP) in three patients with persistent pHPT in spite of adequate decline in PTH (3.6%), and false negative (FN) in three patients (3.6%) leading to unnecessary further neck exploration.

Preoperative variables for patients who were operated without iOPTH are shown in Table 3. Serum levels of calcium were slightly lower for patients who were operated with iOPTH. Otherwise, no significant differences in patients' demographics were found.

Table 2 Pre- and intraoperative data in patients with persistent pHPT at 6 weeks postoperatively compared with pHPT patients alleviated of hypercalcemia

Variable	Persistent pHPT $n=30$	Normo- or hypocalcemia $n=134$	P value
Age, years (mean±SD)	58±14	63±12	0.102
Gender, M/F	7/30	23/104	>0.999
Symptomatic, yes/no	17/13	89/45	0.313
Preoperative serum calcium, mmol/L (mean±SD)	2.82±0.13	2.77±0.19	0.054
Operation time min (mean±SD)	104±42	95±42	0.259
Distribution of number of indentified parathyroid glands (number 0/1/2/3/4)	2/4/3/10/11	0/9/23/31/71	0.001
Number of excised parathyroid glands (mean±SD)	1.1±1.0	1.4±0.8	0.024
Thyroid surgery (yes/no)	5/25	25/109	>0.999
Thymectomy (yes/no)	5/25	11/123	0.176
Autotransplantation of parathyroid tissue (yes/no)	0/30	5/129	0.586
iOPTH (used/not used)	7/23	72/62	0.003
Histology, $n=142$ (adenoma/hyperplasia)	8/7	98/29	0.060
Weight of excised parathyroid tissue, mg (mean±SD)	435±506	904±1,988	0.110

Table 3 Preoperative variables in pHPT patients operated without iOPTH

Variable	iOPTH used	iOPTH not used	*p* value
Age (years)	62±11	62±14	0.800
Gender F/M	64/19	70/20	>0.999
S-calcium (mmol/L)	2.75±0.14	2.82±0.26	0.001
Symptoms (yes/no)	54/29	59/31	>0.999

Mean±SD is shown for continuous variables and numbers for nominal variables

Thirteen of 83 patients (15.7%) operated with iOPTH underwent limited parathyroid exploration (focused or unilateral surgery; $p<0.032$ vs. patients operated without iOPTH. Intraoperative variables, histology, and outcome for the two groups of patients are shown in Table 4.

The distribution of numbers of identified parathyroid glands did not differ between the two groups of patients. Neither was there a difference in the number of excised parathyroid glands, thymectomy, and thyroid surgery or autotransplantation of parathyroid tissue between the two groups of patients (Table 4).

However, for patients operated with iOPTH, the median weight of excised parathyroid tissue was 400 mg (10% percentile, 177 mg and 90% percentile, 1,945 mg), which was slightly higher compared to patients operated without iOPTH, with a median weight of 330 mg (10% percentile, 87 mg and 90% percentile, 922 mg; $p=0.027$).

At discharge, more patients operated without iOPTH medicated with Vitamin D_3 analogs due to hypocalcemia compared to patients operated with iOPTH, 11% vs. 2%, respectively (Table 4). More patients were subjected to a negative exploration in patients who were operated without iOPTH compared to patients operated with iOPTH (19% vs. 7%, Table 4).

Before the 6 weeks follow-up, three patients of each group had been re-operated due to persistent pHPT. After re-operation, one patient in the group who had primary surgery without iOPTH became normocalcemic.

At the 6 weeks follow-up, there was a significant difference between the two groups in calcium status (Table 4). Excluding the nine patients that could not be followed, the rate of persistent pHPT for the non-iOPTH group was 23 of 85 patients (27%) vs. seven of 79 patients (9%) for the group operated with iOPTH ($p=0.003$), and the frequency of hypocalcemia was 14 of 85 patients (16%)

Table 4 Intraoperative variables, histology, medication for hypocalcemia at discharge and calcium status at 6 weeks in patients with negative sestamibi scintigraphy and ultrasound operated without iOPTH

Variable	iOPTH used	iOPTH not used	P value
Surgery			
Distribution of number of indentified parathyroid glands (number: 0/1/2/3/4)	0/5/16/16/46	0/8/11/27/42	0.175
Number of excised parathyroid glands	1.4±0.9	1.3±0.8	0.855
Thymectomy	8/83	13/90	0.334
Thyroid surgery	15/83	16/90	>0.999
Autotransplantation of parathyroid tissue	3/83	2/90	0.672
Medication for hypocalcemia at discharge			
Oral calcium (fixed dose)	21/83	16/90	0.228
Vitamin D analog therapy	2/83	10/90	0.024
Histology			
Adenoma	55/73	57/77	>0.999
Hyperplasia	18/73	20/77	
Negative exploration	6/83	17/90	0.024
Calcium status 6 weeks postoperatively			
Calcium below reference range without treatment (regarded as asymptomatic)	0/83	2/90	
Treatment with oral calcium and/or Vitamin D analog	7/83	12/90	0.011
Hypercalcemia (spontaneous)	7/83	22/90	
Normocalcemia	65/83	49/90	
No data	4/83	5/90	

Numbers and mean±SD are shown

in the non-iOPTH group vs. seven of 79 patients (9%) in the iOPTH group (p=0.145). Strict normocalcemia was achieved in 49 of 85 patients (58%) of patients operated without iOPTH and for 65 of 79 patients (82%) with iOPTH.

Discussion

To the best of our knowledge, the present study comprising 173 patients undergoing first-time surgery for sporadic pHPT with preoperatively negative sestamibi and ultrasonography comprises the largest cohort of this subgroup published thus far. The cohort comprised 17% of the patients subjected to preoperative localization with both modalities. The results of surgery are inferior compared to established standards for pHPT surgery.

The patients have an increased risk for hyperplasia compared with the total cohort of the Scandinavian database [16] and the adenomas are small. There is a high rate of negative neck explorations with an increased risk for persistent pHPT compared with the whole cohort of pHPT patients [16]. The risk for persistent pHPT increased with fewer identified and excised parathyroid gland and without the use of iOPTH and reached borderline significance for patients with hyperplasia. The risk for hypocalcemia increased in asymptomatic patients and in patients with hyperplasia, as well as operation performed without iOPTH. Although the number of patients was small, there was also a tendency that patients with negative findings at operation were at increased risk for hypocalcemia, most probably because of extensive exploration with risk for parathyroid damage.

The routine use of iOPTH remains controversial. However, its use in patients with negative or not concordant localization procedures was recommended in a recent positional statement of the ESES [5]. This recommendation is underscored by the results in the present study. The use of iOPTH decreased the risk for persistent pHPT from 26% to 8% and the risk for medically treated hypocalcemia from 16% to 8% at the 6 week follow-up. Even so, the risk for persistent pHPT and medically treated hypocalcemia is high.

There are some drawbacks in the present investigation. Although we have no indication that this is the case, it cannot be ruled out that there is a covariance between the use of iOPTH and surgical skill and/or volume. At present, the numbers preclude statistical analysis in this regard.

The present results are based on intraoperative findings and early outcome after surgery. The present cohort of patients will be followed for late results. However, clearly, if anything, the results could with time deteriorate, i.e., they will not change the cure rate for the better.

Conclusions

Patients with negative sestamibi scintigraphy and negative ultrasound localization before first-time surgery of sporadic pHPT are at an increased risk for negative neck exploration as well as persistent pHPT. The risk for persistent disease and for postoperative medical treatment of hypocalcemia should deliberated when advising the patients regarding operation, especially if the patients are asymptomatic. The results from the Scandinavian Quality Register for Thyroid and Parathyroid Surgery suggest that these patients be operated with iOPTH. It is an open discussion if centralization to high volume centers could further benefit this subgroup of patients.

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