Langenbecks Arch Surg (2009) 394:851–860
DOI 10.1007/s00423-009-0540-6

ORIGINAL ARTICLE

Impact of modern techniques on short-term outcome after surgery for primary hyperparathyroidism: a multicenter study comprising 2,708 patients

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Received: 16 June 2009 / Accepted: 1 July 2009 / Published online: 18 July 2009

Abstract
Purpose Preoperative localization procedures and the use of intraoperative parathyroidism (iOPTH) have led to a shift of paradigm from bilateral neck exploration to focused parathyroidectomy in primary hyperparathyroidism (pHPT). However, only a small number of randomized trials from specialized centers have been published. The main purpose of the study was to analyze the impact of localization procedures and iOPTH on short-term outcome after pHPT surgery in a multi-institutional setting.
Methods An audit for quality assurance in pHPT surgery was performed in 23 Scandinavian departments in 2004–2008. Data were gathered prospectively in a database. Two thousand seven hundred and eight patients were registered and 78% were females. The median serum calcium level was 2.79 mmol/l.
Results Localization procedures were performed in 1,831 patients (68%), (sestamibi in 54% and ultrasound in 41%) and iOPTH in 792 operations (29%). Bilateral exploration was performed in 61%, focused parathyroidectomy in 17%, and unilateral exploration in 22%. Histology showed parathyroid adenoma in 82%, with the median weight of 0.6 g. The alleviation of hypercalcemia at the first follow-up was 93% (94% for primary operation). In the multivariate logistic regression analysis, iOPTH increased cure rate (OR 1.70, 95% CI 1.14–2.53, p=0.0092). The risk for postoperative medically treated hypocalcemia decreased with the use of localization procedures (OR 0.56, 95% CI 0.43–0.78, p=0.0004) and iOPTH (OR 0.56, 95% CI 0.39–0.90, p=0.0015).
Conclusions Localization procedures and iOPTH decreased the risk for hypocalcemia after pHPT surgery. Additionally, iOPTH influenced short-term cure rate favorably.

Keywords Primary hyperparathyroidism · Localization procedures · Intraoperative PTH · Surgical strategy · Outcome

Presented at the XVI meeting of the European Surgical Association Vienna, April 17–18th, 2009

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Introduction

Surgery for primary hyperparathyroidism (pHPT) has undergone a remarkable change during the last 15 years, from bilateral neck exploration to focused parathyroidectomy.

In 1971, the concept of limited parathyroid exploration was suggested by CA Wang [1]. However, it was Sten Tibblin who, with his landmark paper "Unilateral parathyroidectomy in hyperparathyroidism due to single adenoma" published in the Annals of Surgery in 1982 [2], started the new era of parathyroid surgery.

The concept of limited parathyroidectomy remained controversial until further refined localization procedures, most notably sestamibi scintigraphy and high-resolution ultrasound as well as intraoperative measurement of PTH (iOPTH), were introduced.

However, the cost effectiveness and sensitivity of preoperative localization examinations are debated [3, 4], and the use of iOPTH is highly controversial [5–16]. Furthermore, a risk for recurrence due to intraoperatively missed parathyroid gland pathology during limited neck exploration has been reported [17–19].

Until this date, only a few *single-center* randomized trials comprising a comparatively modest number of patients have been published evaluating the new techniques [3, 20–30]. The trials suggest a small benefit for unilateral or focused parathyroidectomy, including a lower risk for biochemical and symptomatic postoperative hypocalcemia, reduced operating time, and improved cosmesis compared to the classical bilateral approach.

However, only in two of these trials (comprising n=139), included patients that were *not selected* on the basis of the results of the preoperative localization procedures [23, 29].

Taking into account the number of parathyroidectomies being performed annually worldwide and the costs for localization procedures and iOPTH, studies regarding the impact of the new techniques on a multi-institutional level are therefore of great importance.

The Scandinavian Quality Register for Thyroid and Parathyroid Surgery is an on-line database for the quality assurance of diagnostics, surgical treatment, and follow-up for patients with surgical disease in the thyroid and parathyroid glands. Thus, the register can gather results from specialized as well as non-specialized departments, and obtain a large cohort of patients, within a comparatively short time. Data quality is checked by open audit.

We report the results of surgery for pHPT, with the emphasis on the impact of localization procedures and iOPTH on short-term outcome.

Methods

The database

The Scandinavian Quality Register for Thyroid and Parathyroid Surgery (www.thyroid-parathyroidsurgery.com) was launched in 2004 as part of a regional, EU-funded, health-care cooperation project between Lund University Hospital and the University Hospital of Copenhagen, Rigshospitalet.

The database is recognized by the Swedish National Board for Health and Social Welfare as the national registry for thyroid and parathyroid surgery. However, the register is open to participation by all departments within Scandinavia that carry out surgical treatment in this field. 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 the respective country. Participating departments are responsible for compliance with national legislation regulating register participation, including information and acceptance of patients where applicable.

Patients

The register is an on-line database, and the present report is based on 2,708 consecutively registered operations for pHPT by 23 participating departments until August 3, 2008. Follow-up was performed 1–6 weeks after surgery and is further scheduled for 6–12 months postoperatively.

Registered variables

Preoperatively

Department, surgeon (consultant vs. assisted), gender, age, symptoms (yes/no), serum calcium level, previous thyroid operation, type of operation (primary vs. re-operation), localization procedure (performed vs. not performed and type of procedure), and hereditary or sporadic disease.

Perioperatively

Date of operation, type of exploration (bilateral neck exploration, unilateral neck exploration, focused operation), video-assisted operation (yes/no), conversion rate by minimal-invasive surgery, type of anesthesia, number of identified and excised parathyroid glands, autotransplantation of parathyroid glands (yes/no), other operations performed, identification of recurrent laryngeal nerves and 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.

Postoperatively

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 patient was 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.

Results of localization procedures

The results of localization procedures were compared to the results of neck exploration, definitive histology, and postoperative calcium status at the first follow-up after discharge and were graded as follows: true preoperative localization of solitary adenoma (TP); false preoperative localization of solitary adenoma (FP); correct position of one pathologic gland, but multiglandular disease not predicted; false prediction of multiglandular disease in solitary adenoma; correct prediction of multiglandular disease; and lastly, negative/inconclusive preoperative examination.

Intraoperative PTH (iOPTH)

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 [31] used the so-called Miami criteria [20] for biochemical cure. The results from iOPTH was 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 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. Factors associated with outcome were evaluated by simple and multiple logistic regression analysis. A p value of <0.05 was considered significant. The impact of localization procedures and iOPTH on outcome data was analyzed as intention to treat, i.e., regardless of outcome, and categorized as used vs. not used.

Results

Demographics

Two thousand seven hundred and eight patients were registered. The preoperative median serum calcium level was 2.79 mmol/l (10% percentile 2.60 mmol/l; 90% percentile 3.08 mmol/l). Clinical data on the patients are shown in Table 1.

Localization procedures

Preoperative localization procedures were performed in 1,831 patients (68%), sestamibi scintigraphy in 1,473 patients (54%), ultrasound in 1,120 patients (41%), CT in 62 patients (2%), MRI in eight patients (0.3%), venous sampling in 32 patients (1%), and PET in 34 patients (1%).

Table 1 Clinical data on the 2,708 patients with primary HPT registered in the web-based database

Variable	
Age (years), median (range)	62 (range 1–94)
Female gender, *n* (%)	2,113 (78%)
Symptomatic disease, *n* (%)	1,954 (72%)
Sporadic disease, *n* (%)	2,612 (96%)
Primary operation, *n* (%)	2,557 (94%)
Previous thyroid surgery, *n* (%)	112 (4%)

Surgery

Bilateral neck exploration was performed in 1,658 (61%) of the operations, focused parathyroidectomy in 465 operations (17%), and unilateral exploration in 585 operations (22%) (for definitions, see Methods section).

Of the patients planned for focused surgery, 67 patients (13%) were converted to bilateral neck exploration; and of the patients planned for unilateral exploration, 75 patients (11%) were converted to bilateral exploration. Thus, for those patients that underwent bilateral neck exploration, this was also the preoperatively planned approach in 91% of the operations.

At surgery, a solitary parathyroid adenoma was found in 81.5%, hyperplasia in 14.1%, parathyroid cancer in 0.2% of the patients, and in 4.2% of the operations the exploration was negative.

The median weight of a solitary parathyroid adenoma was 600 mg (25% quartile 310 mg; 75% quartile 1,200 mg).

iOPTH was used during 792 operations (29.2%) and was correct compared to definitive histology and postoperative calcium levels in 93.4%; the investigation was false positive (FP) with postoperative persistent hypercalcemia in 16 patients (2%) and false negative (FN) leading to unnecessary bilateral exploration in 35 patients (4.4%).

The results of sestamibi scintigraphy and ultrasound compared to the findings at exploration, the definitive histology, and postoperative calcium levels are shown in Table 2.

A solitary focus on sestamibi scintigraphy was found in 1,106 patients (75.1%), but was TP for a single adenoma only in 64.1%. At ultrasonography, a solitary focus was found in 755 patients (67.4%) but was TP for a single adenoma only in 58.5%.

Both investigations were used in 771 patients (28.5% of all patients). In 395 of these patients (51.2%), the investigations were concordant for a solitary focus but were TP for a single adenoma only in 358 patients (46.4%); in ten patients (1.3%), the enlarged gland found was part of a not predicted multiglandular disease, and in 27 patients (3.5%) the investigation was concordant false positive.

Thus, the positive predicted value of a concordant single focus shown by sestamibi scintigraphy and ultrasonography to predict for a solitary parathyroid adenoma was 90.6%.

Complications

Postoperative re-bleeding occurred in 22 patients (0.8%), and 32 patients (1.2%) were treated due to postoperative wound infection. Thirty-eight patients (1.4%) were treated with i.v. calcium postoperatively due hypocalcemia.

At discharge, 601 patients were medicated with oral calcium at a fixed dose (22.2%) and 216 patients (8.0%) were treated with vitamin D analog therapy. Both drugs were used in 202 patients (7.5%). The patients on oral calcium therapy had lower serum calcium levels the first postoperative day compared with patients without treatment ($p<0.0001$).

Follow-up

At the first follow-up, which was performed within 6 weeks, 39 patients (1.4%) had a unilateral paresis of the recurrent laryngeal nerve, and bilateral paresis was registered in one patient. However, of note, postoperative laryngoscopy was performed only in 1,200 patients (44.3% of the whole group of patients).

Thirty-five patients (1.3%) were re-operated on within 6 weeks due to persistent hypercalcemia, and of those, ten (28.6%) were cured. The calcemic status at the first follow-up is seen in Table 3. Taking into account also the patients that were re-operated before the first scheduled follow-up, 190 patients (7%) showed persistent disease after operation: 6% for patients with primary operation and 15% for patients undergoing re-operation. For the patients followed after re-do surgery, only 49% were normocalcemic without treatment and 24% were on oral calcium and/or vitamin D analog therapy. In comparison after primary operation, 73% of the patients were normocalcemic without treatment and 15% were treated with oral calcium/and or vitamin D analog therapy.

Uni- and multivariate analysis of the risk for medically treated hypocalcemia at the first postoperative follow-up was performed for age and gender as well as clinically well-established risk factors (Tables 4 and 5).

In the univariate analysis, the risk for medically treated hypocalcemia was associated with the number of identified and resected parathyroid glands, autotransplantation of a parathyroid gland, the preoperative levels of total calcium, hyperplasia, hereditary pHPT, re-operation for pHPT, and thymectomy.

In the multivariate analysis, the risk increased with the number of identified parathyroid glands, the weight of excised parathyroid tissue, autotransplantation of parathyroid tissue, operation for hyperplasia, and patients undergoing re-operation. However, hypocalcemia decreased with the use of preoperative localization procedures (analyzed as intention to treat): for all patients 10.7% vs. 22.9% and for primary operation 9.7% vs. 22.6%. Furthermore, the risk decreased with the use of iOPTH: for all patients 9.7% vs. 16.6% and for primary operation 7.5% vs. 16.5%.

A uni- and multivariate analysis of variables associated with the alleviation of hypercalcemia at the first follow-up was performed (Tables 6 and 7).

Table 2 Results from the preoperative investigations with sestamibi scintigraphy and ultrasound

Procedure	True localization of solitary adenoma (TP) *n* (%)	False localization of solitary adenoma (FP) *n* (%)	Correct position of one pathologic gland, but multiglandular disease not predicted *n* (%)	False prediction of multiglandular disease in solitary adenoma *n* (%)	Correct prediction of multiglandular disease *n* (%)	Negative examination *n* (%)
Sestamibi scintigraphy *n*=1,473	944 (64.1%)	107 (7.3%)	55 (3.7%)	6 (0.4%)	10 (0.7%)	351 (23.8%)
Ultrasound *n*=1,120	655 (58.5%)	73 (6.5%)	27 (2.4%)	7 (0.6%)	10 (0.9%)	348 (31.1%)

In the univariate analysis, the alleviation of hypercalcemia was associated the preoperative levels of calcium and with the number of excised parathyroid glands. Furthermore, the chance was lower for patients undergoing reoperation for pHPT and for patients with thyroid resection during the procedure. However, the possibility increased for patients undergoing operation with iOPTH.

In the multivariate analysis, the chance for alleviation of hypercalcemia increased with the number of excised parathyroid glands and was higher for patients undergoing unilateral or focused surgery compared to bilateral surgery. However, the chance was lower in patients subjected to redo surgery. Furthermore, the use of iOPTH, analyzed as intention to treat (used vs. not used), increased early cure rate: for all patients from 92.3% to 95.0% and for primary operation from 92.8% to 95.8%.

Notably, patients with negative or inconclusive examination on sestamibi scintigraphy or on ultrasound more often had persistent hypercalcemia compared to those patients with a focus seen on the examinations (Figs. 1 and 2).

Discussion

With the event of more accurate localization procedures, as well as the development of rapid assays for the measurement of iOPTH, and with the notion that the vast majority of pHPT patients suffer from a solitary parathyroid adenoma, a clear trend towards more limited parathyroid surgery has been evident [32].

It has been claimed that a focused approach could decrease operation time as well as complication rate, improve cosmesis, and decrease costs. However, only two published trials addressed this issue by including patients not selected on the basis of preoperative localization procedures [23, 29]. This is of importance since it has been shown that patients with a positive localization examination have a better outcome than patients with a negative examination [33, 34], and this was also substantiated by the results of the present investigation.

The cost effectiveness of localization procedures is controversial [3, 35]. In the present study, sestamibi scintigraphy was TP for a solitary adenoma in 64% of the patients and in 58% of the patients for ultrasound. The reason for this low sensitivity is not clear, although ultrasonography is known to be highly operator dependent, and a wide range of accuracy for sestamibi scintigraphy has been reported in a recent meta-analysis [4]. Thus, the sensitivity of sestamibi scintigraphy has been associated with the size of the parathyroid adenoma, the level of calcium and PTH, as well as the oxyfil content of the parathyroid adenoma, and concomitant thyroid disease [16, 33, 36–39]. In the present study, the median adenoma weight was comparatively low, and the majority of patients only had mild hypercalcemia. Thus, a decreased sensitivity could be expected. However, technical [40] and analytical aspects [34, 41, 42] could also be of importance, and therefore, a Scandinavian investigation is ongoing to clarify this issue.

In the present study, there was a clear discrepancy between the number of localization procedures and the

Table 3 Calcemic status at the first postoperative follow-up 1–6 weeks postoperatively

Variable	Number	Percent
Calcium below the reference range, regarded as asymptomatic (not treated)	47	1.7
Hypercalcemia (spontaneous)	180	6.7
Normocalcemia	1,962	72.5
Treatment with calcium and/or vitamin D analog therapy	396	14.6
No data available	123	4.5

Table 4 Univariate analysis of variables associated with medically treated hypocalcemia at the first postoperative follow-up

Effect	Odds ratio estimate	Lower 95% confidence limit for odds ratio	Upper 95% confidence limit for odds ratio	*p* value
Age (years)	0.998	0.990	1.006	0.6121
Number of identified parathyroid glands	1.344	1.224	1.476	<0.0001
Number of excised parathyroid glands	1.693	1.458	1.967	<0.0001
Serum total calcium (mmol/l) preoperatively	0.568	0.352	0.915	0.0200
Weight of excised parathyroid tissue	1.028	0.994	1.062	0.1040
Autotransplantation of a parathyroid gland yes vs. no	6.633	3.204	13.732	<0.0001
iOPTH used vs. not used	0.956	0.560	1.630	0.8675
Histology hyperplasia vs. adenoma	2.929	1.768	4.851	<0.0001
Gender male vs. female	1.054	0.618	1.799	0.8467
Sporadic disease vs. hereditary disease	0.207	0.0112	0.0382	<0.0001
Localization procedure used vs. not used	1.111	0.6970	1.772	0.6575
Previous thyroid surgery yes vs. no	4.011	1.843	8.729	0.0005
Symptomatic patient yes vs. no	0.960	0.586	1.570	0.8694
Thymectomy during surgery yes vs. no	2.269	1.174	4.387	0.0148
Thyroid resection during surgery yes vs. no	2.044	1.146	3.645	0.3236
Type of exploration I. Unilateral neck exploration vs. bilateral neck exploration	0.889	0.502	1.573	0.6859
Type of exploration II. Focused operation vs. bilateral neck exploration	0.804	0.433	1.492	0.4897
Re-operation vs. primary operation	2.506	1.363	4.610	0.0031

Table 5 Multivariate analysis of variables associated with medically treated hypocalcemia at the first postoperative follow-up

Effect	Odds ratio estimate	Lower 95% confidence limit for odds ratio	Upper 95% confidence limit for odds ratio	*p* value
Age (years)	1.001	0.991	1.010	0.8980
Number of identified parathyroid glands	1.234	1.032	1.476	0.0214
Number of excised parathyroid glands	1.250	0.976	1.600	0.0772
Serum total calcium (mmol/l) preoperatively	0.726	0.419	1.259	0.2547
Weight of excised parathyroid tissue	1.047	1.010	1.085	0.0126
Autotransplantation of a parathyroid gland yes vs. no	3.463	1.870	6.412	<0.0001
iOPTH used vs. not used	0.561	0.393	0.801	0.0015
Histology hyperplasia vs. adenoma	1.593	1.095	2.319	0.0150
Gender male vs. female	0.986	0.717	1.355	0.9284
Sporadic disease vs. hereditary disease	1.037	0.531	2.027	0.9144
Localization procedure used vs. not used	0.577	0.425	0.783	0.0004
Previous thyroid surgery yes vs. no	1.045	0.494	2.208	0.3236
Symptomatic patient yes vs. no	1.067	0.799	1.424	0.6610
Thymectomy during surgery yes vs. no	1.323	0.827	2.117	0.2432
Thyroid resection during surgery yes vs. no	1.240	0.809	1.901	0.3236
Type of exploration I. Unilateral neck exploration vs. bilateral neck exploration	0.731	0.462	1.157	0.1815
Type of exploration II. Focused operation vs. bilateral neck exploration	0.859	0.507	1.456	0.5721
Re-operation vs. primary operation	4.052	2.183	7.524	<0.0001

Table 6 Univariate analysis of cure rate at the first follow-up in 2,708 patients operated due to primary hyperparathyroidism

Effect	Odds ratio estimate	Lower 95% confidence limit for odds ratio	Upper 95% confidence limit for odds ratio	*p* value
Age (years)	0.999	0.989	1.009	0.8831
Number of identified parathyroid glands	1.120	0.993	1.264	0.0654
Number of excised parathyroid glands	1.696	1.237	2.324	0.0010
Serum total calcium (mmol/l) preoperatively	0.577	0.334	0.996	0.0484
iOPTH used vs. not used	1.698	1.140	2.529	0.0092
Gender male vs. female	0.839	0.593	1.185	0.3186
Sporadic disease vs. hereditary disease	1.778	0.930	3.401	0.0818
Localization procedure used vs. not used	1.044	0.763	1.427	0.7885
Previous thyroid surgery yes vs. no	0.606	0.326	1.126	0.1132
Symptomatic patient yes vs. no	1.060	0.765	1.468	0.7267
Thyroid resection during surgery yes vs. no	0.617	0.411	0.925	0.0196
Type of exploration I. Unilateral neck exploration vs. bilateral neck exploration	1.136	0.795	1.623	0.4852
Type of exploration II. Focused operation vs. bilateral neck exploration	1.481	0.0968	2.267	0.0702
Re-operation vs. primary operation	0.307	0.194	0.483	<0.0001

surgical strategy being employed during operation. Thus, localization procedures were performed in 68% of the patients, but focused or unilateral surgery was performed only in 17% and 22% of the patients, respectively. Since the conversion rate from these procedures to bilateral surgery was only slightly above 10%, this logically means that, for the majority of patients operated with a bilateral procedure, this was also the preoperatively planned approach. Thus, either the preoperative localization examination was performed by the referring physician regardless of the surgical strategy being employed by the specific surgical center or the surgeon did not trust or failed to act on the result of the investigations.

In this particular setting, it is therefore of great interest that, in spite of the above discussed shortcomings, the present study shows a clear reduction of medically treated hypocalcemia in the early (<6 weeks) follow-up phase for patients subjected to preoperative localization examinations and analyzed as intention to treat. The figures were almost identical even if the patients undergoing re-operation were excluded. The results therefore substantiate previous observation from randomized controlled trials [22, 23].

Table 7 Multivariate analysis of cure rate at the first follow-up in 2,708 patients operated due to primary hyperparathyroidism

Effect	Odds ratio estimate	Lower 95% confidence limit for odds ratio	Upper 95% confidence limit for odds ratio	*p* value
Age (years)	0.997	0.986	1.008	0.5528
Number of identified parathyroid glands	1.215	0.996	1.480	0.0542
Number of excised parathyroid glands	1.540	1.115	2.127	0.0088
Serum total calcium (mmol/l) preoperatively	0.624	0.355	1.098	0.1021
iOPTH used vs. not used	1.698	1.140	2.529	0.0092
Gender male vs. female	0.855	0.598	1.222	0.3897
Sporadic disease vs. hereditary disease	1.882	0.907	3.904	0.0893
Localization procedure used vs. not used	0.886	0.609	1.288	0.5257
Previous thyroid surgery yes vs. no	0.857	0.434	1.693	0.6570
Symptomatic patient yes vs. no	1.033	0.740	1.443	0.8470
Thyroid resection during surgery yes vs. no	0.735	0.478	1.129	0.1599
Type of exploration I. Unilateral neck exploration vs. bilateral neck exploration	2.071	1.257	3.413	0.0043
Type of exploration II Focused operation vs. bilateral neck exploration	2.488	1.370	4.520	0.0028
Re-operation vs. primary operation	0.328	0.187	0.574	<0.0001

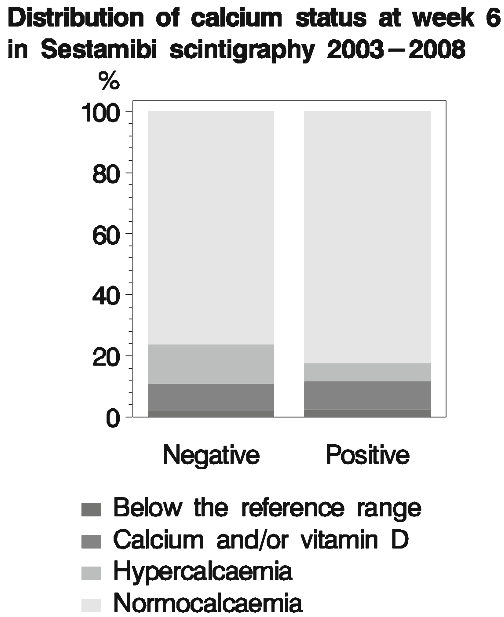

Fig. 1 Calcemic status at the first follow-up in patients with negative and positive sestamibi scintigraphy, respectively

The importance of iOPTH during surgery for pHPT has been under debate. Some authors claim that the use is not cost effective [11, 15], whereas others find the method very useful [5, 6, 16]. The reasons for these different views are not quite clear, but a difference in patient cohorts could be suggested. Thus, small adenomas give rise to a significant number of FP investigations, in this study around 7%. Moreover, the investigations showed a solitary focus in spite of multiglandular disease in further 3–4% of the patients. Concordant TP investigations for solitary parathyroid adenoma on sestamibi scintigraphy and on ultrasound were found only in 46% of the patients.

In the present study, the use of iOPTH was highly accurate, but FP and FN investigations do occur (2% and 4%, respectively). Nevertheless, analyzed as intention to treat, the use of iOPTH decreased the risk for medically treated hypocalcemia at the first follow-up.

At the first follow-up, an analysis of the risk for persistent disease was performed including also patients that had been re-operated on before the first follow-up due to failed primary exploration. This multivariate analysis showed that the use of iOPTH increased the chance for alleviation of hypercalcemia. It may be argued that the results obtained (early cure rate of 95.8% after primary surgery) are not better than those that can be achieved with the classical bilateral exploration. However, this argument is doubtful, since there is a trend to surgically treat more patients with mild disease and small adenomas, and these patients tend to be more difficult to operate on. Furthermore, bilateral exploration does come at a prize, i.e., an increased risk for early biochemical and medically treated hypocalcemia [23, 43].

The argument regarding cost effectiveness is important but difficult to analyze given the variety in health care systems worldwide: waiting lists, costs for re-operation, sick leave, localization examinations, iOPTH, etc. It can be argued that, providing that the patient is well informed and has accepted the risk, a difference of 3% in cure rate could for some be justifiable. However, in this balance, it must also be taken into account that the use of iOPTH was associated with a lowered risk for postoperative hypocalcemia.

There are some shortcomings in the present investigation; since departments joined the database at different time points during the study, the impact of surgical volume can as yet not be evaluated. Such analysis, which will be performed in the future, will provide useful information on the impact of the new techniques in relation to high- and low-volume centers. Furthermore, the present study does not provide long-term follow-up data. Such data will be gathered during the coming years. Nevertheless, short-term data provided in the present investigation shows that the new surgical techniques do benefit patients with pHPT also in a multi-institutional setting.

Conclusion

In this cohort of patients with pHPT, representing large and specialized as well as smaller Scandinavian departments, it was found, in spite of shortcomings in sensitivity and accuracy of preoperative localization examinations as well as a large number of patients undergoing bilateral neck exploration, that the use of localization procedures was

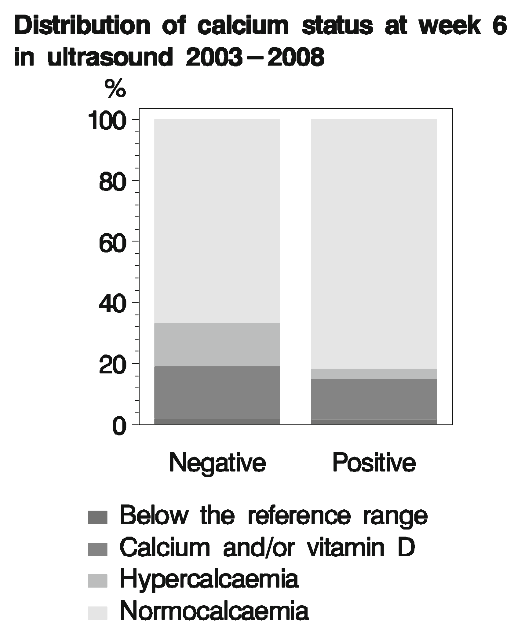

Fig. 2 Calcemic status at the first follow-up in patients with negative and positive ultrasound examination, respectively

associated with a risk reduction for postoperative treated hypocalcemia. Furthermore, the use of iOPTH decreased both medically treated hypocalcemia and increased early cure rate after surgery for pHPT.

Acknowledgement This study was supported by grants from:
The European Union (Interreg. IIIA)
The Swedish Board of Health and Social Welfare
The Swedish Association of Local Authorities and Regions
The following departments participated in this study:
Department of Surgery, Lund University Hospital
Department of Breast and Endocrine Surgery, Copenhagen University Hospital Rigshospitalet
Department of Surgery, Central Hospital, Kristianstad
Department of Surgery, Helsingborg Hospital
Department of Surgery, University Hospital of Uppsala
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Department of Surgery, Växjö Central Hospital
Department of Surgery, Västerås Central Hospital
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