



Minimally Invasive Parathyroidectomy without Intraoperative PTH Performed after Positive Ultrasonography as the only Diagnostic Method in Patients with Primary Hyperparathyroidism

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Abstract

Background A positive and concordant result of at least two diagnostic modalities is generally recommended prior to focused parathyroidectomy. The aim of this study was to analyze the results of surgery and the accurateness of preoperative ultrasonography (US) as single localization modality in patients who underwent parathyroidectomy without the adjunct of intraoperative Parathormone (PTH) measurement.

Methods The cases with a preoperative US as the only localization technique, who underwent parathyroidectomy between 10/1999 and 12/2017, were selected from a prospectively maintained database. Therefore, a total number of 242 patients with a mean age of 58.6 ± 13.7 years were included in the present study. US was performed by referral endocrinologist or by the surgeon during office visits.

Results The overall “cure rate” was 99.2% (240 out of 242 patients). In 228/242 patients (94.2%), a drop of perioperative PTH levels consistent with the definition of cure was observed on the day of surgery. In four of the remaining 14 patients, healing was confirmed by PTH level dropping into the normal range on the first postoperative day. Eight patients were cured after a reoperation was performed at our department. Postoperative complications included one case of permanent recurrent laryngeal nerve palsy (0.4%).

Conclusions If performed by an experienced endocrinologist and/or endocrine surgeon, a positive US could be the only preoperative localization study in patients with pHPT. Moreover, the add-value of intraoperative PTH is limited. Major advantages of US are a very high accuracy, the ease of performance (accessibility) and its cost-effectiveness compared with Sesta-MIBI scintigraphy.

Introduction

Primary hyperparathyroidism (pHPT) with its characteristic clinical and biochemical manifestations [1, 2] occurs in approximately 1% of the population and has a rising incidence from 10/100.000 individuals under 40 years to 60/100.000 individuals in those over 60 years [3, 4]. A

solitary parathyroid adenoma is responsible for 80–90% of cases affected by pHPT [3, 5]. The remaining patients suffer from multiglandular disease (2–5%) and chief cell hyperplasia (15–20%). Parathyroid carcinoma is an extremely rare disease (< 1%) [5, 6]. Surgical therapy still represents the best treatment including resection of all enlarged parathyroid gland(s) [5].

Preoperative localization of the enlarged parathyroid gland(s) is the essential precondition to successfully perform any technique of focused surgery. The minimally invasive video-assisted parathyroidectomy (MIVAP) is the preferred surgical approach in our department. Since its first description in 1998 by Miccoli [7], this technique has

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become a standard operative approach in the treatment of sporadic pHPT with worldwide acceptance [8]. Moreover, our group has demonstrated feasibility of the bilateral exploration by video-assisted approach also in case of unclear localization [9, 10].

Technetium-99-sestamibi scintigraphy (Sesta-MIBI) and ultrasonography (US) of the neck are variably used as first-line diagnostic tools. The US is less expensive, noninvasive and does not use ionizing radiation [3, 4]. However, US is a highly operator-dependent technique with a sensitivity ranging from 33 to 92% [11–14]. There is evidence that, if an experienced endocrine surgeon, who is familiar with the cervical anatomy, performs the US, the sensitivity goes up to 60–89% and thus it is equivalent or superior to radiology-based US. The sensitivity of Sesta-MIBI-scintigraphy is reported to be between 44 and 98% [11, 15–22]. The question about the optimal sequence between US and Sesta-MIBI is still under debate with some advocate initial US followed by Sesta-MIBI in doubtful cases and other advocate initial Sesta-MIBI followed by US in equivocal cases [15]. Despite the good results of US, many endocrine centers still employ the preoperative combination of multi-imaging modalities [3]. Computed tomography (CT), magnetic resonance imaging (MRI) and ^{11}C -methionine scintigraphy have been added in recent years in cases of failed localization [23]. The conventional or video-assisted bilateral neck exploration is recommended in case of negative or discordant localization studies [24, 25].

The addition of the intraoperative parathyroid hormone monitoring (io-PTH) is helpful to provide confirmation that hyperfunctioning parathyroid tissue is removed [26, 27] and has been advocated (actually) as an unavoidable tool during focused parathyroidectomy [28, 29].

The aim of this study was to analyze the results of parathyroidectomy after positive preoperative US as the single localization modality and without io-PTH determination in patients with pHPT.

Methods

All patients with a pHPT, who underwent parathyroidectomy at our department between November 1999 and December 2017 and had a preoperative ultrasonography as the only localization technique, were included in this retrospective observational study. The patients were identified from a prospectively maintained database containing all patients who underwent surgery for primary and secondary hyperparathyroidism at the Kliniken Essen-Mitte. During the study period, a total number of 1348 patients with pHPT underwent surgical therapy. Among them, 242 patients (187 females and 55 males) with a mean age of 58.6 ± 13.7 years met the inclusion criteria. The

preoperative characteristics of the patients are summarized in Table 1.

Ultrasonography

The patients included underwent outpatient ultrasonography by the referral endocrinologist, if the localization was clear. The operating surgeon performed an additional ultrasonography at the time of presentation or on the day of surgery.

If the position of the abnormal gland was predicted and confirmed at surgery, the US result was considered true positive. The side and not the exact location (upper vs. lower) of the glands were evaluated. Based on possible gland locations (242 patients, total 968 possible positions), sensitivity, specificity, positive and negative predictive values were calculated.

Perioperative PTH

Intraoperative blood samples from a peripheral vein measuring intact parathyroid hormone (PTH) were collected before skin incision (after induction of the anesthesia) and 15 min after resection of the parathyroid gland(s). However, if the enlarged parathyroid gland was found and resected, the procedure was stopped without waiting for the results of io-PTH. The operation was considered successfully, if PTH dropped postoperatively more than 50% from the preoperative level or in the normal range. If the postoperative PTH was still above the normal range on the day of surgery, a second sample was obtained on the first postoperative day. This strategy was consequently followed prior to considering a surgical re-exploration. If PTH levels were still elevated, a reoperation was performed eventually after additional localization studies in accordance with the intraoperative finding of the first surgery. Intact PTH was measured with a commercially available

Table 1 Preoperative characteristics of the patients

Female/male (ratio)	3.4:1
Mean age	58.6 ± 13.7 years
Symptoms	
Asymptomatic	178 patients
Nephrolithiasis/urolithiasis	29 patients
Osteoporosis	25 patients
Gastritis/ulcera	4 patients
Pancreatitis	1 patient
Neurological symptoms	5 patients
Concomitant goiter	43 patients
Preoperative PTH levels	237.2 ± 239 pg/ml

immunoluminescence assay with a normal range of 10–65 pg/ml. An intraoperative frozen section analysis was not used in any of our cases.

Surgery

The slightly modified surgical technique was based on the previously described procedure for minimally invasive video-assisted PTX [30].

The patient's head was not hyperextended. A 1.5–2-cm central suprasternal neck incision was performed in a skin fold. Now, external retractors maintaining the space between the thyroid gland and the strap muscles were applied. A 5 mm 30° videoscope (Karl STORZ Endoskope, Tuttlingen, Germany®) was used for visualization. The recurrent laryngeal nerve was identified, if deemed necessary according to the location of the parathyroid gland. The routine use of intraoperative neuromonitoring was introduced in 2015. After identification of the abnormal parathyroid gland, a gentle dissection—avoiding lesion of the capsule—was performed. The vessel pedicle was cut through bipolar diathermy, and no clips were used. Finally, reabsorbable sutures closed the platysma and the skin. Drains were not used in any patients. All patients underwent a pre- and postoperative direct laryngoscopy to assess the vocal cord function.

Follow-up was obtained contacting the general physician or the referral endocrinologist.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation (SD). Statistical analysis was performed using a commercially available program (Prism 5; GraphPad Software Inc., La Jolla, USA).

Results

In 206 patients, the position of the parathyroid adenoma was correctly predicted by the US. Moreover, in 19 cases the side of the adenoma even if not the exact position of the gland (upper vs. lower) was revealed by the US. According to our definition of a true positive examination, these 19 cases were considered as correctly localized. In seven cases instead of an incorrect prediction ($n = 5$) or no localization ($n = 2$) by US, patients were cured at primary exploration. These seven patients did not undergo any other diagnostic because a thyroidectomy for multinodular goiter was planned. The cure rate after initial surgery was 96% (232/242 patients, Table 2).

A significant drop of perioperative PTH levels in the normal range was observed in 228/242 patients (94.2%).

The mean postoperative PTH level (15 min after resection) in these patients was 40.4 ± 40 pg/ml. In four of the remaining 14 patients, the PTH dropped to normal level on the first postoperative day and was therefore consistent with the definition of cure adopted in the study.

Ten patients had a persistent disease. Among them, eight patients underwent a reoperation in our department (Table 3). The postoperative PTH dropped to normal values in all reoperated cases.

In two cases, a thyroid nodule was resected instead of parathyroid tissue as confirmed by the final histology. Both patients underwent re-exploration on the first postoperative day without performing any other localization technique. In one patient, the revision started at the same side where the caudal (thyroid) nodule was resected and finally a parathyroid adenoma was found cranially. The other patient required a bilateral exploration and resection of two parathyroid adenomas on the opposite side. PTH levels decreased perioperatively from 168 pg/ml to 16 pg/ml and from 632 pg/ml to 71 pg/ml, respectively.

In five cases, a second parathyroid adenoma was found during the reoperation with a consecutive drop of PTH to normal values in all patients. In three out of five patients, the second adenoma was on the contralateral side. Prior to reoperation, a sesta-MIBI-scintigraphy was performed in three patients and a computed tomography (CT) in one. One patient underwent reoperation after additional ultrasound showing the second enlarged parathyroid gland.

In one case, a parathyroid adenoma, confirmed by final histology, was resected at the initial operation. Because of the missing adequate PTH decrease postoperatively (229 pg/ml to 155 pg/ml), a reoperation with a bilateral exploration was performed 1 day later and thymic tissue was resected, but no other parathyroid adenoma was found. PTH was still elevated (125 pg/ml), postoperatively. Nevertheless, calcium levels decreased perioperatively from 2.67 to 2.25 mmol/l. No further exploration was planned. Two years after surgery, the current calcium and PTH

Table 2 Summary of the correctness of preoperative localization and cure rate

Localization	N
<i>Correct</i>	225
<i>Wrong</i>	7
Cure at primary surgery	N
<i>Yes</i>	232
<i>No</i>	10
Reoperation	8
Persistent disease	2

levels are 2.2 mmol/l and 53 pg/ml, respectively, demonstrating healing.

Two patients were discharged after the first surgery, and a second exploration was rejected by the patients. In the first patient, a multinodular goiter and a parathyroid adenoma were diagnosed by ultrasonography preoperatively. A subtotal thyroidectomy was performed and the preoperative as parathyroid gland described nodule was found to be a cystic thyroid nodule. Consecutively, a bilateral neck exploration was performed. However, no enlarged parathyroid gland was found. The histological examination also found not intrathyroidal parathyroid tissue. The preoperative values of calcium (3.25 mmol/l) and PTH (141 pg/ml) did not decrease postoperatively. We contacted this patient recently 15 years after the operation. No further surgery was performed, and current calcium and PTH levels were 2.63 mmol/l and 77 pg/ml, respectively. In the second case, a parathyroid adenoma was described by ultrasonography at the level of the left lower pole of the thyroid. Intraoperatively, the left inferior parathyroid gland was found to be slightly enlarged and the left upper parathyroid gland was normal. The left inferior parathyroid was removed. Histological examination described a microfollicular adenoma of the thyroid with hyperplastic parathyroid tissue. Calcium and PTH levels did not decrease postoperatively. No further surgeries were performed, and current calcium and PTH levels were 2.83 mmol/l and 112 pg/ml, respectively, showing persistent disease 16 years after primary exploration.

The overall cure rate, including reoperations, was 99.2% (240/242 patients). The incidence of multiglandular disease was 2.5% (6/242 patients), and it was misdiagnosed in all cases due to the missing io-PTH. Considering these results,

the sensitivity and specificity of the US in our study are 85.5% and 96.2%, respectively. The positive and negative predictive values are 88.8% and 95.1%, respectively. No recurrent disease was reported in any of the patients.

Postoperative complications included six cases of recurrent laryngeal nerve palsy (6/242 patients; 2.5%). During follow-up, a normalization of the voice was registered in five patients. In one case, this was confirmed by laryngoscopy. Three patients were contacted by phone and refused an additional laryngoscopy due to their symptom freedom. One patient died 6 years after the operation, and therefore the follow-up information was obtained contacting the general physician, who confirmed a normal voice 3 months after the operation. Persistent recurrent laryngeal nerve palsy was confirmed in one patient 1 year after the operation. In summary, the rate of permanent recurrent laryngeal nerve palsies was 0.4%.

Discussion

The minimally invasive approaches to pHPT and therefore firstly the MIVAP-approach have focused attention on the accuracy of preoperative localization diagnostics. The combination of US and Sesta-MIBI has been considered the standard. In studies using Sesta-MIBI-scintigraphy and US as preoperative localization tests, a 95% accuracy is reported [31, 32].

In the context of radiation protections and from the economic point of view, US is superior to all other localization tools. In the present study, the “cure rate” with US alone after initial surgery was 96% (232/242 patients). This result is in concordance with the study by Butt et al. [3],

Table 3 Results of surgery in eight out of 10 patients with persistent disease

Patient	Primary surgery	Intraoperative finding at re-exploration	Disease status
1	Thyroid tissue removed	Parathyroid adenoma found on the correct side	Cured
2	Thyroid tissue removed	Double adenoma on the contralateral side	Cured
3	Pathological parathyroid tissue removed	Second enlarged parathyroid gland on the same side	Cured
4	Pathological parathyroid tissue removed	Second enlarged parathyroid gland on the same side	Cured
5	Pathological parathyroid tissue removed	Second enlarged parathyroid gland on the contralateral side	Cured
6	Pathological parathyroid tissue removed	Second enlarged parathyroid gland on the contralateral side	Cured
7	Pathological parathyroid tissue removed	Second enlarged parathyroid gland on the contralateral side	Cured
8	Parathyroid adenoma removed	Bilateral exploration, thymic resection, no pathological parathyroid tissue at final histology	Cured

who reported a correct localization of 98%. In this study, 100 patients underwent PTX by a single surgeon between 2004 and 2012. Besides an US including preoperative marking of the lesion, no other localization test was performed [3].

The second point to be highlighted in this study is that the completion of the operation and anesthesia has not been conditional of the results of the io-PTH measurement. A study by Najafian found that intraoperative PTH measurement changed intraoperative management in only 3% (16/482 patients). However, in four of these 16 patients (25%) no additional parathyroid adenomas were found [33]. Nevertheless, two of these four patients were cured. Thus, intraoperative PTH measurement causes longer operative time and additional costs. Similar results were found by Zawawi et al. who showed that intraoperative PTH measurement had no additional benefit in 99% of patients with two preoperative localization studies. However, due to intraoperative PTH measurement operation time was 31 min longer [34].

Intraoperative PTH measurement is also of particular importance from the economic point of view. This topic was analyzed by Morris et al. with a sensitivity analysis. They found that the cure rate was increased by io-PTH only marginally while incurring approximately 4% additional costs [35]. Consecutively, it has to be discussed, if it is more cost-effective to perform an io-PTH in all patients or doing a reoperation in only few cases. In our patients, an io-PTH was not necessary in 232/242 patients. On the other hand, the waiver of io-PTH was responsible for reoperations in eight cases and overseeing of multiglandular disease in six of that. In general, the incidence of multiglandular disease was very low, so the benefit of io-PTH seems to be limited when compared to the costs.

In a study by Jabiev et al. analyzing 442 patients with pHPT, a multiglandular disease was observed in 6% of all patients analyzed. Of these, in only 26% all of their abnormal glands were localized correctly [5]. These findings are concordant to a study by Kairys et al., who evaluated 48 patients with pHPT. The sensitivity and specificity of the preoperative surgeon who performed US were higher in single gland disease [18]. In our study, a second parathyroid adenoma was found in 6/242 patients (2.5%). In comparison with Jabiev, the prevalence of these multiglandular diseases is lower. However, in none of these patients the second enlarged parathyroid gland was detected preoperatively. In three of our patients, a scintigraphy and in one patient a computed tomography were necessary to cure these patients. All additional localization tests correctly detected the second enlarged gland. Two patients had no additional localization test before reoperation.

A large study by Berber et al. evaluated 1000 patients with pHPT, secondary and tertiary hyperparathyroidism as well as familial hyperparathyroidism. In these patients, 1845 abnormal glands were identified. US was superior to sesta-MIBI-scintigraphy at localizing enlarged parathyroid glands in all patient subgroups. In univariate analysis, factors that impaired accurate gland localization by US included increased body mass index, lower serum calcium and PTH levels, female sex, increasing age, presence of a goiter, smaller gland size and parathyroid volume. Body mass index, gland size and volume were the most important variables in multivariate analysis. The accuracy of US was as lower the body mass index was and as larger the parathyroid gland. The speciality in this study is that all (!) patients had a bilateral neck exploration with visualization of all parathyroid glands. Consecutively, all visually enlarged parathyroid glands were removed [36].

The limitations of the present study are its retrospective and single-center design. Another point to be addressed as a limitation is the high variety of sonographers who performed an US. Nevertheless, the cure rate was extremely high, demonstrating that the expertise of sonographers is an important factor. Another limitation of this study is the follow-up that was performed not by the surgical department. The patients were sent back to the referral endocrinologist, which is usual to inform the surgeon by letter in case of recurrence and to refer them for redo-surgery if required. However, as no patient was sent for a reoperation by the referral endocrinologist, we assumed that no recurrent disease occurred in our patients.

In summary, the present study demonstrates that the results of parathyroidectomy following US are good, comparable to those of combination studies. Therefore, US performed by an experience endocrine surgeon or endocrinologist should be the first preoperative localization study in patients with pHPT. Major reasons therefore are over the equal accuracy, the ease of performance and its cost-effectiveness compared with Sesta-MIBI-scintigraphy.

Although most guidelines, endocrinologists and endocrine surgeons consider io-PTH as a routine part of parathyroidectomy and recommend two preoperative diagnostic tests as a gold standard, we could demonstrate that parathyroidectomy with only US as preoperative localization study is feasible and safe. Moreover, io-PTH is a valuable tool to prove the cure of patients with pHPT and to prevent a reoperation, if the patient suffers from a multiglandular disease. However, the ascertainment of the values should not prolong the operation. Therefore, this is the first study demonstrating the parathyroidectomy with comparable cure rates is also possible with only one preoperative localization test and without any intraoperative additional test.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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