Effectiveness of Intraoperative Parathyroid Monitoring (ioPTH) in predicting a multiglandular or malignant parathyroid disease

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HIGHLIGHTS

- The best surgical approach for parathyroidectomy and the use of routine intraoperative parathyroid hormone (ioPTH) monitoring is still debated.
- ioPTH monitoring could be a reliable marker to predict a malignant disease during parathyroidectomy.
- In case of malignant parathyroid disease, ioPTH monitoring show higher ioPTH baseline value and superior drop compared to benign disease.
- There are no significant differences in ioPTH in atypical adenomas and in multiglandularular disease.
- ioPTH monitoring is able to reinforce indication for a minimal-invasive approach
- Accurate patient selection is important to achieve the best results.

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ABSTRACT

Aim: The main goal of our study was to confirm the usefulness of intra-operative parathyroid hormone (PTH) monitoring (ioPTH) when using minimally invasive techniques for treatment of sporadic Primary hyperparathyroidism (pHTP). Furthermore, we aimed to evaluate if ioPTH monitoring may help to predict the etiology of primary hyperparathyroidism, especially in malignant or multiglandular parathyroid disease.

Methods: A retrospective review of 125 consecutive patients with pHPT who underwent parathyroidectomy between 2001 and 2016 at the Department of General Surgery was performed.
For each patient, the specific preoperative work-up consisted of: high-resolution US of the neck by a skilled sonographer, sestamibi parathyroid scan, laryngoscopy, and serum measurement of PTH, serum calcium levels, and serum 25(OH)D levels.

Results: The study included 125 consecutive patients who underwent surgery for pHPT. At the histological examination, we registered 113 patients with simple adenomatous pathology (90,4%), 5 atypical adenomas (4%), 3 cases of parathyroid carcinoma (2,4%),, , and 4 histological exams of different nature (3,2%). Overall, 6 cases (4,8%) of multiglandular disease were found. We reported 10 cases (8%) of recurrent/persistent hyperparathyroidism: 1/10 in a patient affected by atypical adenoma, 9/10 in patients with benign pathology. Regarding these 10 cases, in three (30%) patients, ioPTH wasn't dosed (only frozen section (FS) exam was taken), in 5 cases (50%) ioPTH dropped more than 50% compared to basal value (false negative results), and in 2 (20%) cases, ioPTH did not drop >50% from the first samples taken, the extemporary exam had confirmed the presence of adenoma and the probable second hyperfunctioning adenoma was not found.

Conclusions: IoPTH determinations ensure operative success of surgical resection in almost all hyperfunctioning tissue; in particular it is very important during minimally invasive parathyroidectomy, as it allows avoiding bilateral neck exploration. The use of ioPTH monitoring offer increased sensitivity in

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detecting multiglandular disease and can minimize the need and risk associated with recurrent operations, and may facilitate cost-effective minimally invasive surgery. Moreover, intraoperative PTH monitoring could be a reliable marker to predict a malignant disease during parathyroidectomy, showing higher ioPTH baseline value and superior drop compared to benign disease.

1. Introduction

Primary hyperparathyroidism (pHPT) is a clinical condition characterized by an autonomous production of parathyroid hormone (PTH), which causes hypercalcemia and hypophosphatemia. pHPT can have serious clinical manifestations. Nearly all patients with parathyroid problems have symptoms. Sometimes the symptoms are really obvious, like kidney stones, frequent headaches, fatigue, and depression. Sometimes the symptoms are not so obvious, like high blood pressure and the inability to concentrate [1,2]. pHPT is due to single gland disease in approximately 70–95% of cases, gland hyperplasia responsible for 15%, double adenoma 4% or rarely caused by parathyroid carcinoma https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4556812/ [3,4]. Associations include familial syndromes such as Type 1 and 2 Multiple Endocrine Neoplasia (MEN). Curative treatment is the surgical removal of pathological parathyroid glands. The only curative treatment for pHPT is surgical removal of the pathologic glands (one or more) [1,2,5–7].

The valid operative standard for the pHPT has been bilateral neck exploration (BNE) and the visualization of all parathyroid glands [2]. However, the increasing sensitivity of preoperative localization methods such as 99Tc-sestamibi scanning and ultrasound in combination with intra-operative parathyroid hormone monitoring (ioPTH) assay have led to the use of minimally invasive procedures in parathyroid surgery.

The two main minimally (oriented) operative approaches are minimally invasive parathyroidectomy (MIP) or minimally invasive video-assisted parathyroidectomy (MIVAP). These minimally invasive approaches replaced progressively the traditional bilateral neck exploration in the treatment of pHPT because of their significant advantages, especially in terms of cosmetic results, postoperative pain, and postoperative recovery [6–10].

According to literature, the minimally invasive targeted approach finds better indications for patients with well-localized single adenoma, not bigger than 3 cm, without simultaneous thyroid disease or malignancy and without previous irradiation of the neck [8,9,11]. Despite this, nowadays this kind of approach may be performed also in patients with uncertain pre-operatory localization, with bigger adenomas or with multiglandular disease. Moreover, the concomitant thyroid disease or previous radiation are not absolute contraindications for MIP/MIVAP.

Intra-operative PTH monitoring was used for the first time in 1988 by Nussbaum SR et al., using an immuno-radiometric assay to measure PTH blood-levels to evaluate the complete removal of hyperfunctioning parathyroid tissue [12]. This technique improved during the following years, and in 1996 George Irvin developed an immunochemiluminescence method, and the “quick” ioPTH assay became commercially available for intraoperative use [13,14].

Nowadays, ioPTH is widely used in the majority of centers practicing parathyroid surgery. The most important advantage of ioPTH is the possibility to confirm, intraoperatively, the complete removal of hyper-functioning parathyroid tissue or to guide the surgeonto perform bilateral neck exploration [15–20]. Success is defined as a fall in PTH levels of >50% at 10 min post-excision compared to baseline (Miami criteria) – with an accuracy of 97% [13,14,21,22]. The main reasons for an inappropriate ioPTH drop are multiglandular disease and microadenomas. The use of ioPTH is recommended especially for those patients undergoing minimally invasive operation with a single preoperative localization study or two discordant preoperative localization studies [23,24].

The main goal of our study was to confirm the usefulness of ioPTH when using minimally invasive techniques for treatment of sporadic pHTP. Furthermore, we aimed to evaluate if ioPTH monitoring may help to predict the etiology of primary hyperparathyroidism, especially in case of malignant or multiglandular parathyroid disease.

2. Materials and methods

A In this retrospective study based on a prospectively maintained database, 125 patients who underwent surgery for PHPT between January 2001 and December 2015, in the UCO of General Surgery Department were included. Procedures were performed by 3 different surgeons.

Exclusion criteria were patients undergoing reoperations and with MEN1 syndromes.

All patients were studied preoperatively with ultrasound and 99mTc-SestaMIBI scanning.

Preoperative informed consent was obtained from all patients.

MIP or MIVAP by anterior approach was proposed for patients with sporadic pHPT due to a single gland disease, with an adenoma smaller than 35 mm as demonstrated by preoperative imaging, with localization of one unequivocally enlarged parathyroid gland on preoperative ultrasonography and 99mTc-SestaMIBI scanning.

Intact PTH was assayed by a sandwich electrochemiluminescence immunoassay [25].

Quick parathyroid hormone immunochemiluminometric assay (Access Immunoassay System on Access2 Beckman Coulter, UniCel® DxI 800 Beckman Coulter - Fullerton, CA) was performed intraoperatively in the last 95 surgical procedures (76%). Blood samples were collected in an EDTA tube from a peripheral vein by the anaesthesiologist at the designated times. Intraoperative measurement of serum PTH was performed at baseline (pre-incision, T0) and then at 5 (T1) and 10 (T2) minutes post excision of the macroscopically abnormal parathyroid gland. If necessary another sample was taken at 15 min (T3).

Operative Success was defined using the Miami Criteria: a fall in PTH levels of >50% at 5 or10 min post-excision compared to baseline which was obtained for each patient [26]. All patients were followed up 6 months post-operatively or longer if there were any concerns regarding biochemistry.

Operative failure and recurrent hyperparathyroidism were defined with the same criteria described by Irvin et al. [13,14].

Preoperative calcemia and PTH levels were systematically evaluated. All patients underwent ORL assessment before and after surgery to check vocal cord mobility.

Based on definitive histological examination, we subdivided the patients in four groups. Particularly: Group A: benign adenomas, Group B: atypical adenomas, Group C: multiglandular disease, and

Table 1
Baseline characteristics of patients.

A. Age and gender			
	≤65	>65	TOT
M	10 (8%)	19 (15,2%)	29 (23,2%)
F	44 (35,2%)	52 (41,6%)	96 (76,8%)
TOT	54 (43,2%)	71 (56,8%)	125 (100%)

B. Type of surgery			
MIVAP	MIP	Conventional parathyroidectomy	Parathyroidectomy with bilateral neck exploration
48 (38%)	40 (32%)	37 (30%)	13 (1%)

C. Gender and etiology					
	Single adenoma	Carcinoma	Atypical adenoma	Different diagnosis	TOT
M	24 (19,2%)	2 (1,6%)	1 (0,8%)	2 (1,6%)	29 (23,2%)
F	89 (71,2%)	1 (0,8%)	4 (3,2%)	2 (1,6%)	96 (76,8%)
TOT	113 (90,4%)	3 (2,4%)*	5 (4%)	4 (3,2%)	125 (100%)

*p-value: (0.0016).

Group D: parathyroid carcinomas. We analyzed the ioPTH curve in the four groups. For every patient we considered: age, gender,, preoperative imaging results, preoperative serum calcium, and parathyroid hormone concentrations,, type and length of surgery, ioPTH monitoring descending curve, frozen FS results (if performed), definitive pathology, postoperative serum calcium levels, length of hospitalization, complications and the recurrence/persistence rate with eventual need of further surgery.

Calcium levels were measured postoperatively during the first 4,24 and 48 h and one week after surgery, and measurement was repeated whenever necessary. Supplementation of calcium and calcitriol was administered only in symptomatic patients and/or those with hypocalcemia confirmed by laboratory test results and defined by serum total calcium level of less than 8.0 mg/dL. Hypoparathyroidism was considered permanent when it lasted for more than six months, even if asymptomatic.

95 (76%) patients underwent ioPTH monitoring, and 26 (27%) of these didn't need FS exam.

2.1. Statistical analysis

Concerning statistical analysis of ioPTH time profile, we used a linear-mixed effects model [27], using the lme4 package [28] implemented in R software [29]. The ioPTH time trend graph has been created with the lattice package [30], implemented in R software [31]. A *p*-value less than 0.05 was considered statistically significant.

3. Results

The study included 125 consecutive patients, 29 (23,2%) men and 96 (76,8%) women *(p = 0.0016)*. Baseline characteristics of the study cohort are described in Table 1. (Table 1). Patients' mean age at surgery was 65 years (SD = 12,88).

Regarding the preoperative imaging, in 48 patients (38%) there was a localization of one unequivocally enlarged parathyroid gland on preoperative ultrasonography and 99mTc-SestaMIBI. These patients underwent MIVAP. In 40 patients (30%) there was a localization of one enlarged parathyroid gland on preoperative ultrasonography or on 99mTc-SestaMIBI (not both) therefore these patients underwent MIP. In 37 cases (30%) conventional parathyroidectomy was performed.

Preoperative median of calcium and PTH values was 11.00 mg/dL (range: 10.00–13.20) and 394 ng/L (range: 111–1079) respectively.

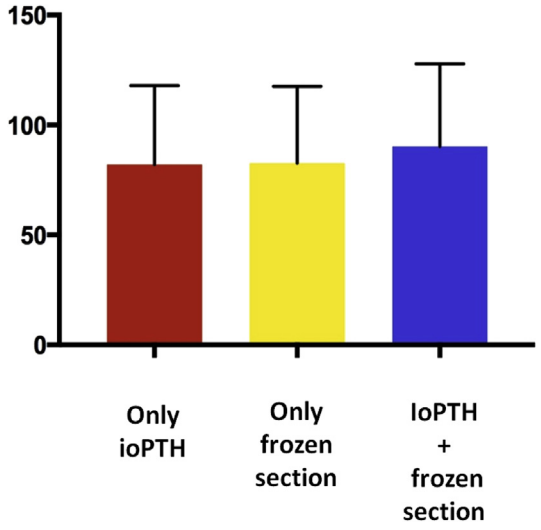

Fig. 1. Operative time with the different techniques (*p = 0.4857*). A p-value less than 0.05 was considered statistically significant.

122 (97.6%) patients were operated in elective surgery for hypercalcaemia complicated with decreased bone density or with renal disease. Three (2.4%) patients was operated in emergency due to extreme hypercalcaemia (adjusted serum calcium level, 12.5 mg/dL) with grossly elevated pHPT concentration of mean 1079 ng/L (reference range 15–65 ng/L).

Seven (5.6%) patients underwent planned BNE. In the remaining 118 patients, MIP or MIVAP surgery was performed under general anaesthesia through a single, respectively 3–4 cm or 1,5-2 cm skin incision in the central neck, 1–2 cm above the sternal notch.

Totally, 48 patients (38%) underwent MIVAP, 40 (32%) MIP, 37 (30%) conventional parathyroidectomy (for the surgeon choice and/or for the presence of associated neck diseases).

In 13 cases(1%) parathyroidectomy was performed after BNE.

In 40 (32%) patients another surgery (thyroid surgery, mastectomy, melanoma excision) was associated to parathyroidectomy.

Mean operating time was 87 ± 3 min (90 ± 5 in patients who underwent parathyroidectomy and ioPTH monitoring with FS exam, 82 ± 7 min in case of parathyroidectomy with ioPTH alone, 83 ± 6 in case of parathyroidectomy associated with FS exam without ioPTH monitoring *(p = 0.4857)* Fig. 1.

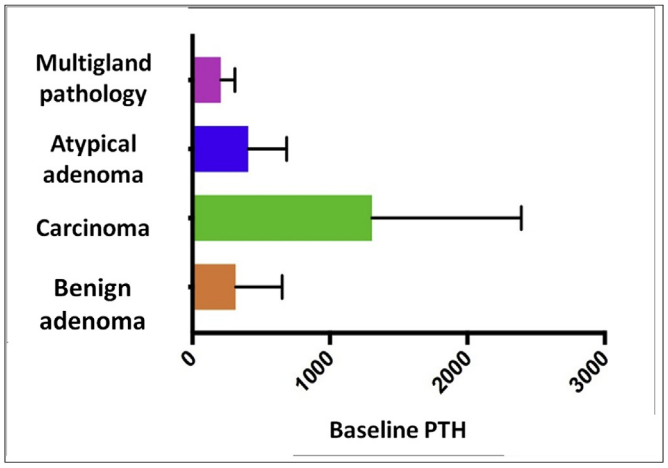

Fig. 2. Baseline PTH correlated to different pathologies.

Table 2
Trend of ioPTH during surgery.

	Baseline PTH(ng/L)	ioPTH at 10′ (ng/L)	ioPTH drop 10′ (ng/L)
Benign adenoma	314	45	86%
Multigland pathology	206	46	85%
Atypical adenoma	405	46.2	88.6%
Carcinoma	1306	91	99.3%

At the histological examination, 113 (90,4%) patients had simple, single adenomatous pathology (Group A). We registered 5 (4%) cases of atypical adenomas (Group B), 6 (4.8%) cases of parathyroid multiglandular disease, and 4 histological exams of different nature (3,2%). In 3 cases (2,4%),a parathyroid carcinoma (Group D) has been reported.

If we consider the relation with gender and final histology, we registered a greater involvement of female gender compared to males. In particular 29 (23,2%) men (24 adenomas, 2 carcinomas, 1 atypical adenoma, 2 different diagnosis) and 96 (76,8%) women (89 adenomas, 1 carcinoma, 3 atypical adenomas, 2 different diagnosis). The two groups showed similar distribution in etiologies *($p = 0.1670$)*.

The median hospital stay was 2 days (range 1–7 days), with a descending trend in the last six years, due to the increased use of a one-day-surgery approach. Analyzing the ioPTH curve in the four groups, we recorded an average basal PTH of 314 ng/L in benign adenomas, 405 ng/L in atypical adenomas, 206 ng/L in multiglandular disease, and 1306 ng/L in carcinomas (with a statistically significant value) *($p = 0.0016$)* Fig. 2.

Average ioPTH 10 min after excision was 57 ng/L, with a drop of 83%. In case of malignancy, 10 min-post-excision ioPTH was 91 ng/L, with a drop of 99.3% (as showed in Table 2). We registered 2 cases of false negative results in ioPTH 5-min drop in patients with multiglandular disease (33%). Mean ioPTH 10-min drop in these patients was 46 ng/L, with an average reduction of 85%.

To analyze the time trend of ioPTH, we primarily recorded dataset in "long" format [31]. In Table 2 we can see the decreasing and convex trend of PTH curves measured in patients with single benign adenoma, atypical adenoma, multiglandular disease, and

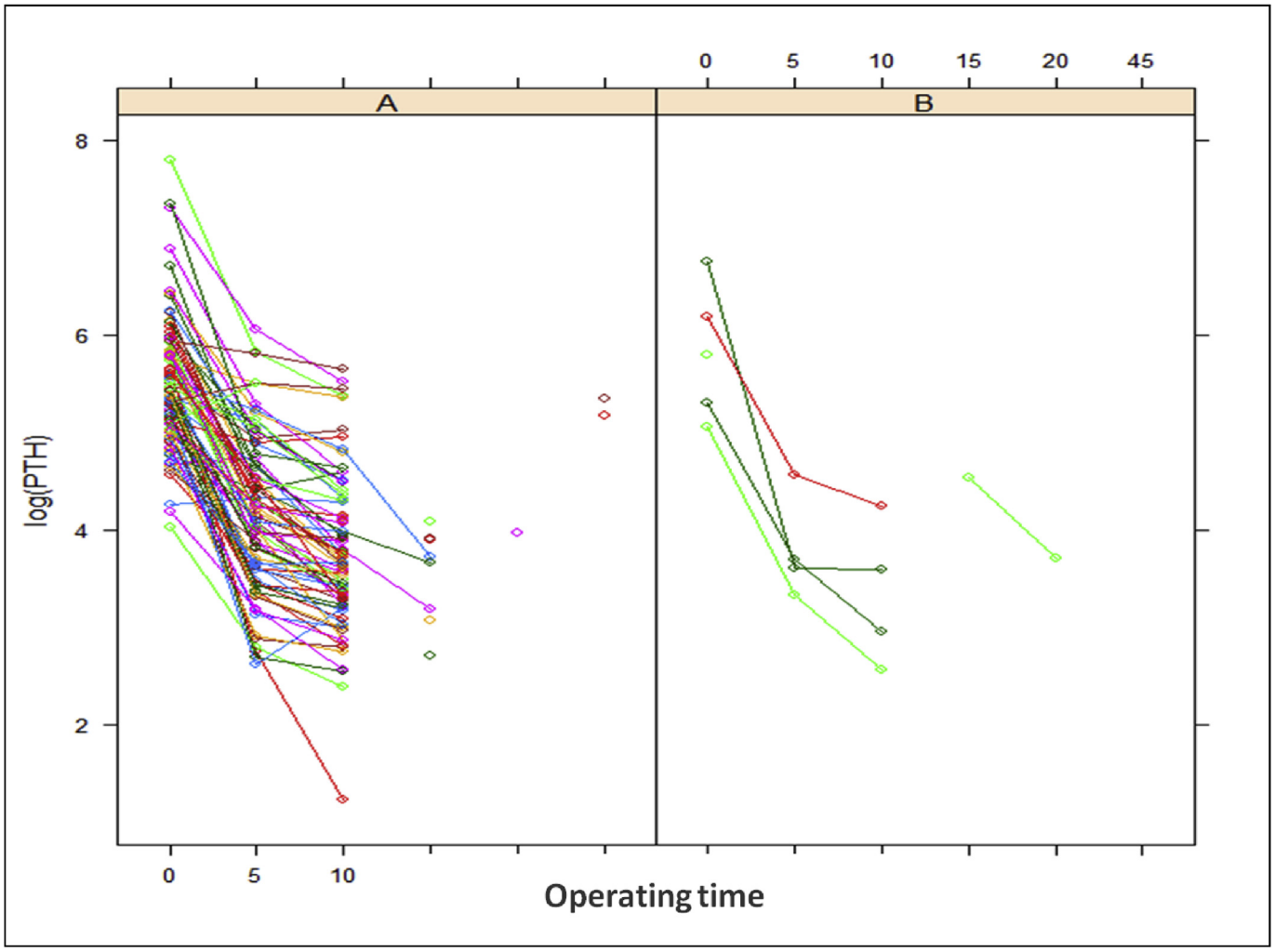

Fig. 3. Trend of ioPTH during surgery: parathyroid's adenomas vs atypical parathyroid's adenomas.

parathyroid carcinoma.

Using the “mixed effects model” [27], we analyzed differences between group A.

(113 patients with single benign adenoma) separately with the group including atypical adenomas (group B, 5 patients), with the group of patients with multiglandular disease (group C, 4 patients), and with the group of carcinomas (group D, 3 patients).

As showed in the graphs, we did not notice statistically significant differences comparing group A both with group B Fig. 3 and C Fig. 4, so that we can assume that there is no significant difference in ioPTH trend between patients suffering from benign disease and patients affected by borderline or multiglandular disease.

On the other hand, we found statistically significant differences comparing group A and group D, demonstrating that there is a significant difference in ioPTH trend between patients affected by single benign adenoma and patients diagnosed with parathyroid carcinoma Fig. 5.

The median of calcium values, 4 h after the operation was 9.38 mg/dL (range: 7.90–10.39) and the median hospitalization was 2 days (range: 2–5).

We reported 10 cases (8%) of recurrent/persistent hyperparathyroidism (9 of them between 2001 and 2011): 1/10 in a patient affected by atypical adenoma, 9/10 in patients with benign pathology. Regarding these 10 cases, in three (30%) patients ioPTH wasn't dosed (only FS fexam was taken), in 5 cases (50%%) ioPTH dropped more than 50% compared to basal value, and in 2 (20%), ioPTH didn't drop in a significant way, but extemporary exam had confirmed the presence of adenoma.

4. Discussion

pHPT is due to a single adenoma in 85%–95% of cases, and is often cured after adenoma removal. Multiple, minimally invasive surgical techniques have been developed over the last few decades for the management of sporadic pHTP. The use of ioPTH in combination with preoperative imaging has been useful to surgeons performing minimally invasive parathyroidectomy principally for adequacy of excision. However, in cases with multiglandular disease, bilateral cervical exploration remains the gold standard. Therefore, it is important to have an accurate estimation of the incidence of multiglandular disease in sporadic pHTP [32].

The first aim of our study was to confirm the usefulness of PTHIO when using minimally invasive techniques for treatment of sporadic pHTP. The current immunochemiluminescence method used to detect ioPTH was developed in 1996 by Irvin and his collaborators [8]. Since that year this technique has been widely used to

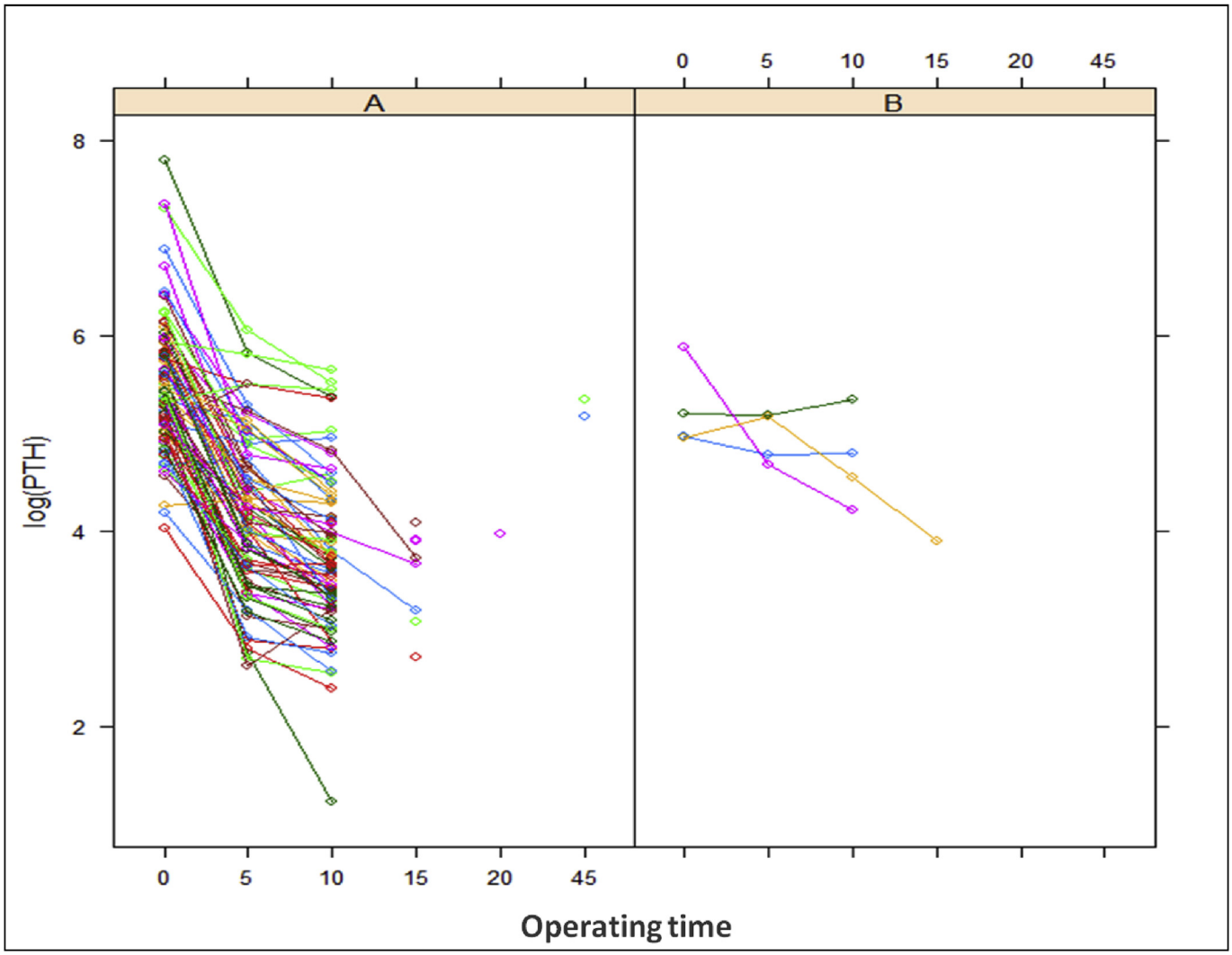

Fig. 4. Trend of ioPTH during surgery: parathyroid's adenomas vs parathyroid's multiglandular disease.

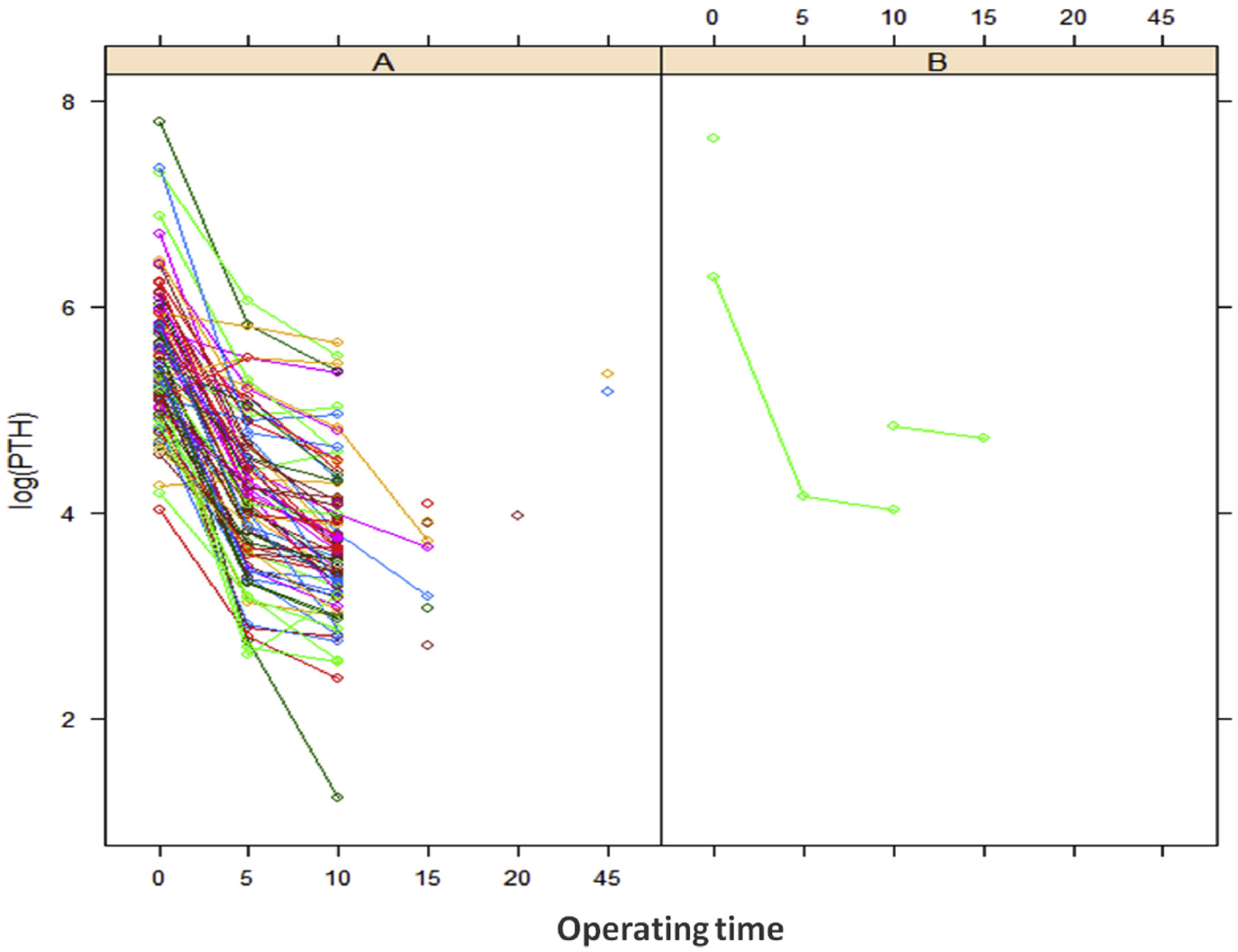

Fig. 5. Trend of ioPTH during surgery: parathyroid's adenomas vs parathyroid's carcinomas.

guide parathyroid surgery, helping - in association with the improvement in preoperatory imaging techniques to perform a less invasive surgery. Intraoperative PTH Assay during minimally invasive parathyroidectomy is considered helpful in the detection of double adenomas and may minimize the risk of recurrent surgery. In fact, it is demonstrated that when PTH did not drop >50% from the first samples taken, the presence of a second hyperfunctioning parathyroid adenoma should be suspected [3,10,11,13,14].

Our study confirms this trend, leading to a reduction of operative time (because it permits to avoid the FS examination of parathyroid gland, morbidity and post-operative pain, with a better aesthetic outcome [33]. From 2001 to 2016 ioPTH has been increasingly used associated to minimally invasive surgery (MIP/MIVAP), with a reduced use of conventional surgery technique and bilateral neck exploration. 70 patients (56%) had FS with or without ioPTH monitoring: the execution of extemporary exam was associated with a longer operative time compared with ioPTH monitoring alone. Moreover, some studies show a superiority of ioPTH in detection of residual hyperfunctioning parathyroid tissue: FS can confirm the presence of hyperplastic parathyroid tissue, but can't give information about residual hyperfunctioning tissue in the neck [14,19,25,34]. In 2015 Rajaei et al. [35] investigated the link between final ioPTH value (FioPTH) and hyperparathyroidism persistence/recurrence rate in patients who underwent parathyroidectomy. This study found that ioPTH drop of more than 50% can't make the surgeon sure of no risk of persistence or recurrence, unless FioPTH value is less than 40 ng/L. Authors demonstrated that FioPTH values $\geq$ 40 ng/L are associated with a major risk of persistence/recurrence after 2 years of follow-up, with an increased evidence of this risk after 5 years. Cases of recurrent or persistent pHPT in our study (10 cases, out of which 9 happened before 2011) suggest to be related to the intraoperative strategy used. Time intervals and cut-offs of ioPTH strictly depend on the criteria used in different centers. In our institute we performed a pre-incision sampling after anesthesia induction, a second sampling 5 min after parathyroid tissue removal, and another sampling after 10 or 15 min. If the drop did not meet the assumed criteria ($\geq$50%), additional samples were performed at 20 min and, if necessary, up to 45 min after parathyroidectomy. This monitoring strategy was used for every gland removed. Literature widely shows the utility of this kind of intraoperative monitoring, with greater benefits for those patients with an uncertain pre-operatory localization of the pathologic gland (only one imaging exam or two discordant exams). Khan et al., in 2015 [24], according to a previous study in 2008 [33], showed that ioPTH monitoring in patients with uncertain pre-operative imaging modified intraoperative management in 74% of cases, allowing the

surgeon to perform a less invasive surgery in 66% of patients. It has been demonstrated that patients with no localization imaging are more likely to undergo a less invasive surgery if ioPTH is used, allowing to reduce operating time with a higher rate of complete removal of pathological tissue. Anyway, association between ioPTH monitoring and mini-invasive parathyroidectomy guarantees a better accuracy of surgery and a rapid confirm of radical removal of pathologic glands also in patients with concordant ultrasound and scintigraphy. This is why ioPTH monitoring is routinely recommended in all the patients with primary hyperparathyroidism going through surgery [23].

Although it's widely accepted that intraoperative rapid determination of PTH represents a tool for monitoring the effectiveness of pHPT surgery, it isn't yet established that ioPTH makes sure that the patient doesn't have multiglandular disease or parathyroid carcinoma in fact, false-negative results using the rapid intraoperative parathyroid hormone (IOPTH) assay are reported in literature.

Multiglandular disease occurs in 9% of patients with sporadic pHTP [3,8,18] and cannot be excluded before surgery. Also, parathyroid cancer is not easily established before surgery.

The second objective of our study was to evaluate the possibility to use ioPTH to predict intraoperatively the most likely etiology of pHPT, analyzing basal PTH value and ioPTH drop. Particularly, we want to assess whether the baseline of PTHIO and how to PTHIO drop could be helpful in guiding us on the existence of a multiglandular parathyroid disease or carcinoma. For this purpose, we considered values of patients with carcinoma, atypical adenoma and multiglandular disease and compared them with the ones of patients with single benign adenoma. We registered no statistically significant difference in basal PTH values and in ioPTH descending trend comparing patients with carcinoma, atypical adenoma and multiglandular disease. On the other hand, we found differences comparing the single groups of patients with carcinoma and those with single benign adenoma. IoPTH in patients with carcinoma was considerably higher (1306 ng/L) compared with the adenoma group (314 ng/L); furthermore ioPTH curve in the carcinoma group was “steeper” than the one of the adenoma group, associated with a quicker PTH drop.

Surgical treatment of parathyroid malignancy is debated in literature. Few centers suggest parathyroidectomy as treatment, while most centers worldwide assume it to need a more radical procedure (parathyroidectomy with ipsilateral emithyroidectomy with or without central neck dissection). For this reason, it could be useful for the surgeon to predict pre and intraoperatively the most likely etiology, allowing a surely radical procedure and reducing operating time.

In our series, baseline high levels of ioPTH and very large volume of parathyroid gland at the surgical exploration, prompt us to perform the frozen section of the parathyroid lesion (suspicion of parathyroid cancer) and then to do an oriented surgical therapy.

Since parathyroid cancer incidence is around 1%, the first limit in this evaluation was the small number of patients with malignant disease. Sometimes ioPTH drop does not meet the criteria, and this behaviour is often associated with multiglandular disease, very small parathyroids or microadenomas. Concerning multiglandular disease, criteria are not met after one-gland-excision because of the remaining hyperfunctioning tissue. Our study supports the reason of a reduction not meeting criteria in patients with very small parathyroids and microadenomas being that they are often associated to a just slightly increased PTH, and for this reason ioPTH drop can be less than 50% of basal value [36]. In most cases failure of mini-invasive ioPTH-guided parathyroidectomy is due to surgeon decision to end the operation without proceeding with further gland exploration, notwithstanding with borderline drop in ioPTH; another reason may be false positive data in intraoperative PTH reduction, which are more common if drop is between 50 and 59% [37]. Anyway, the failure rate in parathyroid minimal-invasive surgery associated to ioPTH is very low, and ioPTH together with pre-operative localization imaging are very important instruments to guide intraoperative decisions and to confirm that radical surgery has been performed.

5. Conclusions

The use of ioPTH monitoring potentially offers increased sensitivity in detecting multiglandular disease, can minimize the need and risk associated with recurrent operations, and may facilitate cost-effective minimally invasive surgery. Intraoperative PTH monitoring could be a reliable marker to predict a malignant disease during parathyroidectomy, showing higher ioPTH baseline value and superior drop compared to benign disease. In our series, there were no significant differences in ioPTH trend in atypical adenomas and in multiglandular disease. However, ioPTH monitoring is reliable, when pre-operatory imaging is available, to reinforce indication for a minimal-invasive approach and to reduce length of surgery even without FS exam.

Ethical approval

Ethical approval was not requested.

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Author contribution

Chiara Dobrinja: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Giorgia Santandrea: Participated substantially in the execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Massimo Giacca: Participated substantially in the execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Elisabetta Stenner: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Maurizio Ruscio: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Nicolò de Manzini: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Conflicts of interest

All Authors have no conflict of interests.

Guarantor

Chiara Dobrinja.

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