

Modern Parathyroid Surgery and Intra-Operative Hormone Monitoring; Present Status, Future Concepts

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Abstract

New technologies look for practical applications and complex clinical problems search for innovations able to address them. This convergent course of clinical needs and technological innovation laid foundation for progress and success of modern health care. Our review looks at the present status and future concepts of parathyroid surgery in relation to important technological developments of the last few decades. We focus on describing how parathyroid operations have been transformed by the more accurate imaging and discuss impact of intra-operative PTH monitoring, a “disruptive technology” with a potential to change current clinical paradigm.

Keywords Hyperparathyroidism; Parathyroidectomy; Intraoperative parathyroid monitoring; Parathyroid hormone assay

Introduction

Primary Hyperparathyroidism (PHPT) is after diabetes and thyroid diseases the third commonest endocrine disorder and its incidence and prevalence is rising globally [1]. In the United Kingdom, the incidence of PHPT has been estimated to be 25/100,000 and prevalence has risen from 1.8 to 6.7 per 1000 between 1997-2006 [2,3]. These staggering figures imply that in the UK alone about half a million people suffer from this condition and 12,000 develop it each year. Similar trend is observed worldwide with incidence as high as 195/100,000 reported among females aged 70-79 in Southern California [4]. Uncontrolled over-secretion of parathyroid hormone (PTH) and high levels of calcium in blood and urine, pathognomonic features of PHPT cause significant morbidity and decrease quality of life. Some of the consequences of PHPT such as renal stones, osteoporotic fractures, and pancreatitis have been known for a century and became classical indications for parathyroidectomy. Association between PHPT and hypertension, cerebrovascular and cardiovascular events, diabetes, cancer and increased mortality have recently been recognized and widened criteria for surgery in patients previously classified as asymptomatic [5-7]. Not surprisingly, number of Parathyroidectomies performed in the NHS hospitals has doubled between 2000 and 2010 with similar trend is observed in other countries [8,9]. At the same time NHS in the UK and health systems in other countries are under severe financial pressure and reducing the cost of providing healthcare while maintaining excellent outcomes is their priority.

Introduction of intra-operative PTH monitoring concept based on defining biochemical cure by detecting 50% reduction of PTH concentration within minutes after removal of abnormal gland ushered in a new possibility of changing old paradigms by promise of improving overall cure rate reducing number of preoperative scans while increasing number of minimally invasive procedures. We performed a structured search of Medline and Embase Data base using Ovid interface with keywords extracted from the relevant MeSH

headings which were then combined giving the following search terms: (intraoperative and parathyroid), (quick assay and parathyroid) and (point-of-care and parathyroid). We included only human studies in English. Our review focuses on status of intra-operative PTH (IOPHT) monitoring in modern parathyroid surgery and discusses biological principle it is based on. It explores challenges of IOPHT monitoring and the need for future developments to enable its full potential as a ‘disruptive technology’ and facilitate its wide spread adoption.

Current Clinical Paradigm: The Dominant Role of Pre-operative Imaging

Historically, parathyroid surgery based on a principle of bilateral neck exploration (BNE), exposure of all four glands and removal of abnormal parathyroids as judged by their size has been performed for almost a century with remarkable success [10]. It relied on surgeon’s experience in interpreting intra-operative findings rather than on preoperative imaging and this led to popular view that “the only thing you need to localize before parathyroid surgery is a good surgeon”. However, majority of patients with sporadic PHPT have only one abnormal gland, while multiple glands involvement is less common (10%-15%) [1]. Therefore, surgical excision of the single overactive gland is curative in 85%-90% of cases and routine practice of full neck exploration with direct visualization of all glands was gradually replaced by Minimally Invasive Parathyroidectomy (MIP) as the new standard in most patients with sporadic PHPT [11-13]. MIP also known as focused parathyroidectomy is performed through small incisions and aims at removing just one gland. Successful implementation of MIP required accurate preoperative localization of the abnormal glands, and the current era of MIP is therefore heavily reliant on preoperative imaging modalities known as localization studies [14,15]. The two most popular tests used in current practice are neck ultrasound where criteria for defining abnormal gland is its size and nuclear scan MIBI where the strength of isotope signal corresponds to mitochondrial activity/density which enable identification of abnormal gland. Ultrasound is inexpensive widely available and has long been used to localize abnormal parathyroids

with a reported sensitivity ranging from 27%-89% [16,17]. However US is known to be operator dependent, not useful for retro-sternal mediastinal lesions and less sensitive for small sized and hyperplastic parathyroids especially when associated with thyroid nodules [18]. MIBI scan has been used to supplement sonographic localization with a reported sensitivity of 58%-90% [19,20] but its sensitivity is compromised with lower preoperative PTH level, multi-gland pathology and intake of Ca channel blockers [21,22]. Inability to confidently localize parathyroid adenoma with only one type of scan has led to the practice of performing both scans in an attempt to increase their accuracy. Concordant US and MIBI results signify precise co-localization by both imaging modalities and have been shown to localize solitary parathyroid adenoma with 95% sensitivity [23]. This level of certainty has generally been accepted as sufficient and patients with concordant findings are considered good candidates for MIP. The problem is that scans are concordant in only 65% of cases while discordant, negative or equivocal results which represent lack of co-localization have been frequently reported respectively in 38%, 17%, and 8% of cases [24,25]. Surgeons are hardwired for success but averse to failure and to maximize their chances of curing patients with single operation they pursue positive concordant localization allowing them to perform MIP.

Patients with discordant imaging often undergo further repetitive US and MIBI scans or have CT, MRI, choline or methionine nuclear scans, angiography or selective venous sampling (SVS) at a cost of increased radiation exposure, expense and patients inconvenience [26,27]. In cases when results of multiple scans remain inconclusive patients are scheduled for full neck exploration when "key hole" approach would be sufficient and bear negative implications such as unnecessary bigger scars, slower recovery and longer hospital stay, and sometimes are even advised against the operation.

Intra-Operative PTH Monitoring: Current Status

Evolution of PTH assay

Parathyroids play a central role in regulating calcium homeostasis by synthesis of new PTH, and its release from secretory granules. Changes in the concentration of calcium are sensed by calcium sensing receptors on chief cells and their adjusted activity results in rapid alterations in PTH secretion. PTH is an 84-amino acid peptide that binds to PTH receptor one and by activating adenylyl cyclase modulates bone metabolism, synthesis of 1,25-dihydroxyvitamin D in proximal tubules and reabsorption of calcium in the distal nephron. N terminal end of PTH is the domain involved in receptor activation and intact (1-34) region mimics the biological actions of the whole (1-84) peptide [28]. Assays recognizing N truncated PTH fragments are in fact measuring biologically inactive PTH fraction, an issue of concern in patients with renal impairment in whom C terminal fragments accumulate significantly [29]. The first generation PTH assay described by Berson in 1963 was a competitive immunoassay employing single radio-labeled antibodies directed either against N terminal, mid molecule or C terminal regions of the PTH peptide [30-33]. Its accuracy was limited because of their cross reaction with biologically inactive PTH fragments. In 1987, Nussbaum has introduced second generation of non-competitive immunoassays, which employed "sandwich technique" where two antibodies are directed against different regions of the PTH peptide [34]. A radio- or luminescence-labeled detector antibody is usually directed against the N terminal region of the PTH peptide (1-34) and a capture antibody is attached to

a solid phase and directed against the C terminal region of the PTH peptide [35]. Despite the improved accuracy of the latter assays they still cross react with non-bio active amino-truncated PTH fragment (7-84) mainly because the low specificity of the amino targeted antibodies. Third generation immune-assays have consequently been developed with a higher specificity of the N-terminal directed antibody i.e. recognizing only the first four to six N-terminal amino acids [36] thereby detecting at least theoretically only bioactive (1-84) PTH.

Principles behind Intra-Operative PTH Monitoring

These developments increased accuracy of PTH assays but they remained confined to the main hospital laboratory and used exclusively for routine diagnostics where long time to result (hours) was not a disadvantage. Timing of the assay became relevant when concept of observing dynamic changes of PTH concentration during parathyroid surgery and using this information to determine whether removal of abnormal parathyroid cured patient of hyperparathyroidism was introduced in 1988 by Nussbaum. He established that dropping PTH concentration to less than 40% of the baseline after 15 minutes of parathyroidectomy correlated with operative success (Figure 1) [37].

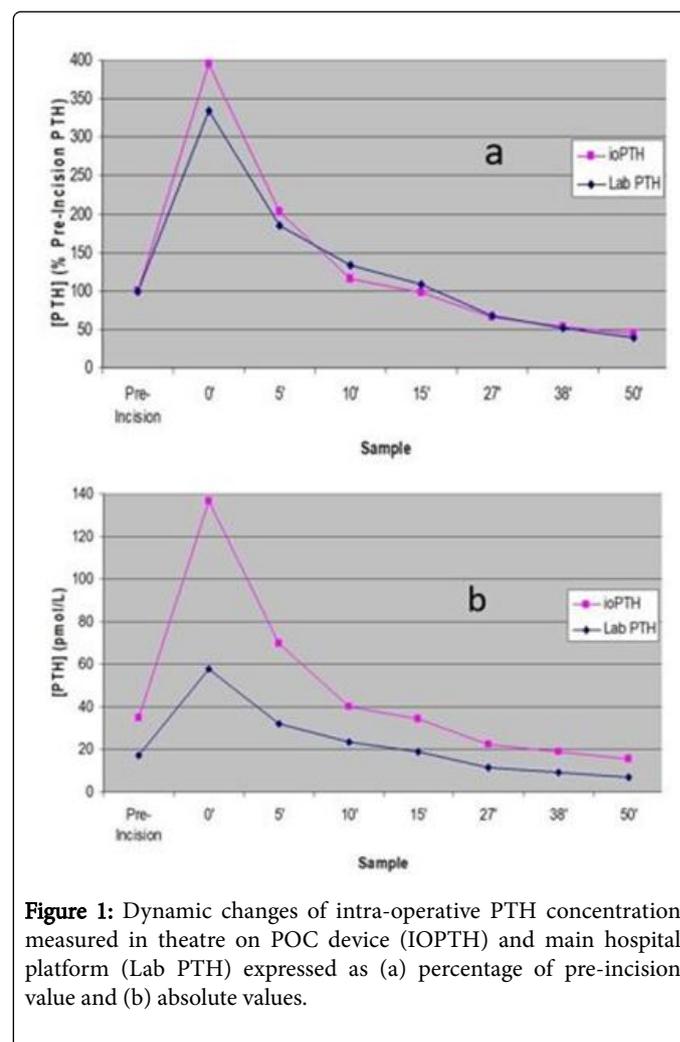


Figure 1: Dynamic changes of intra-operative PTH concentration measured in theatre on POC device (IOPTH) and main hospital platform (Lab PTH) expressed as (a) percentage of pre-incision value and (b) absolute values.

This strategy was based on three physiological facts: firstly PTH short half-life (mean 3 min, 28 sec); secondly being exclusively secreted

from the chief cells of the parathyroid gland; and thirdly suppression of the normally functioning glands by the excess of PTH [38,39]. Intra-operative PTH monitoring was further championed by Irvin who in 1993 proposed and evaluated a criterion for prediction of cure subsequently known as “Miami” criterion [40]. Other criteria for biochemical cure were subsequently developed taking into account

three factors; baseline PTH concentration measured either before incision or after gland dissection just before its removal, concentration of PTH 5, 10 or 15 minutes after resection, and either 50% reduction in PTH concentration or its return to normal values. Main differences between these criteria are the point of reference of initial and final PTH concentration and its timing (Table 1).

Drop	Baseline	Time		Sensitivity	Specificity	PPV	NPV	Accuracy	Ref
By percentage									
≥ 50%	Highest	5		88-91.7	97-100	99-100	64-80	90-93.8	[41,84]
≥ 50%	Highest	10	Miami	97-97.8	54.3-93.3	99-99.6	70-88	92.9-97.3	[41,45,49]
≥ 50%	Pre-incision	10	Vienna	82.1-92.2	88.6-99	96.8-99.6	56-60.9	80-92.3	[41,45,49,85]
≥ 50%	Pre-excision	10		78-85	97	100	58	78-87	[41,86]
≥ 50%	Pre-incision	15	Wisconsin	100	100	100	100	100	[78]
≥ 50%	Highest	20		96.5	93.3	99.4	70	96.3	[87]
To an absolute value									
≥ 50% AND normal	Highest	10	Mayo	75-96	86-98	99	42-68	79-95	[41,75]
≥ 50% AND normal	Pre-incision	10		91.8	66.7	98.7	22.2	90.9	[77]
≥ 50% AND below pre-incision value	Highest	10		94-100	93-97	97-99	77-100	95-98	[41,55]
Low normal ≤35 pg/ml	None	15	Halle	62.9-69.8	88.6-100	98-100	14.2-27.2	65-71.9	[45,49]
50% And/Or normal	Highest	20	Rome	82.9-83.2	90-100	99.4-100	21.4-26.3	83.6-83.8	[45,88]
Analysis of drop kinetics									
Formula for generation of PTH decay curve				100	80	96.7	100	97	[89]
Regression based nomogram				95	53.8	97.2	38.9	92.8	[90]

Table 1: Reliability (performance) of IOPTH monitoring using different criteria for cure.

Potential Errors and their Prevention

A false positive result is encountered when after the removal of enlarged parathyroid, PTH concentration drops to level indicating cure but the patient remains hypercalcaemic. This has been observed more frequently in patients with parathyroid cancer, double adenoma, concomitant thyroid surgery and renal impairment [41-44]. Technical errors resulting in underestimating PTH concentration could also lead to false positive results [41]. A false negative result on the other hand is defined as persistence of elevated PTH after the removal of suspicious gland and further exploration shows no additional parathyroid pathology and in due course the patient becomes normocalcaemic. False negative results are more likely if stringent criteria for cure i.e. those requiring drop to normal range (example: Halle and Rome) are used [45]. Excessive manipulation of the adenoma may induce a pre-excision spike resulting in post excision IOPTH not falling adequately despite eradication of the causative pathology [46,47]. Employing a pre-incision baseline based protocol (example: Vienna) in these cases would therefore increase the risk of false negative results [48].

Good understanding of physiology and dynamics of PTH curves in different diseases and willingness to apply this knowledge in interpreting PTH levels are the best way to avoid these pitfalls. Employing protocols using “strictly defined” rather than the “highest

attained” baseline and requiring drop to “normal” would avoid false positive results and work better in patients with multi-gland disease [41,49]. Patients with well localized adenomas would be best served by protocols requiring only 50% IOPTH drop since, they have the highest accuracy in this scenario [45]. Excessive manipulation of the adenoma results in a pre-excision spike and early devascularisation during the dissection leads to premature decrease of the PTH concentrations, recognizing these pre-excision peaks and troughs, their correct interpretation as well as avoiding undue manipulation of the gland prior to its excision, and collecting the pre-excision sample while the gland is still on an intact vascular pedicle should respectively avoid false negative and false positive results [47,50].

Another potential source of error could be due to the lack of understanding that different platforms use various antibodies and PTH concentrations will vary by about 10%-15%. This applies to measurements on different laboratory platforms as well as comparison between main laboratory and Point of Care (POC) devices used in the same hospital [35]. Proper calibration of the assay with strict adherence to manufacturer instructions preferably one day before the planned surgery to give time for technical support if needed, is essential to avoid technical errors.

Performance Consistency of IOPTH in Different Clinical Scenarios

Patients diagnosed with PHPT and undergoing parathyroidectomy could significantly differ in age, vitamin D status, and renal function and have several other co morbidities which potentially could affect accuracy of IOPTH testing. Their hyperparathyroidism could also

differ in severity be either sporadic or familial and caused by abnormality of single or multiple glands. Current evidence in the published literature summarised in Table 2 suggests that intraoperative PTH monitoring performs consistently and accurately in those different clinical scenarios and can be used in all patients with PHPT (Table 2).

Patient	N	Subgroups	performance	Ref
Age	833	<47, 47-73 or >73 years	Sensitivity, PPV and accuracy of IOPTH were not statistically different among patients aged <47, 47-73 and >73 years, and were consistently high. (Ranges: 93-97%, 96-99% and 90-96%)	[91]
Vitamin D status	351	sufficient or deficient	Sensitivity and accuracy of IOPTH were not statistically different between vitamin D sufficient and deficient patients.	[92, 93]
Renal function Disease	950	NRF or CRI	Percentage of true positive IOPTH results was not statistically different between NRF and CRI patients (95% and 97% at 15 minutes, is respectively)	[94]
Severity	707	Mild or conventional	accuracy of IOPTH was consistently high among patients with mild or conventional PHPT (95% and 98% respectively)	[95]
Number of diseased glands	222	SGD or MGD	Sensitivity and accuracy of IOPTH were 95% and 72% in SGD and MGD respectively, and were considerably higher than US and MIBI	[60]
Gland weight	59	Small (<1 g), large (1-3 g), giant (>3 g)	Sensitivity and accuracy of IOPTH were not statistically different among patients with small, large or giant tumours (Overall Sensitivity and accuracy 94.8% and 93.2% respectively)	[92]
Type of the disease	51	Sporadic	Sensitivity, specificity, PPV, NPV and accuracy of IOPTH was 98, 100, 100, 94, 98% respectively	[96]
	52	Familial (MEN)	Sensitivity, specificity, PPV, NPV and accuracy of IOPTH was 93.5, 0, 0, 87.8 respectively, with $\geq 75\%$ drop as the cure criterion.	[97]
	24	Familial isolated	Sensitivity, specificity, PPV, NPV and accuracy of IOPTH was 100, 71, 89, 100, 92% respectively- IOPTH performed considerably better than US and MIBI	[98]

Table 2: Performance of IOPTH in different patient and disease (PHPT) scenarios.

Advantages of Using IOPTH Monitoring

When IOPTH monitoring during parathyroid surgery was first introduced to clinical practice 30 years ago the greatest expected benefits were improvement of cure rates preventing surgical failures and avoidance of re-operations. It has been enthusiastically adopted by some surgeons advocating its use but scorned by others who claimed that cure rates were already high and introducing this technology was unnecessary. Recently, surgical approach to parathyroidectomy has shifted from full neck exploration to minimally invasive approach with the latter becoming a definite gold standard for majority of patients with PHPT [12]. This has added more weight to the argument in favor of using IOPTH to increase number of 'key hole' procedures without compromising high cure rate. Using IOPTH when MIP is planned has been recently recommended by American Association of Endocrine Surgeons [51]. Additionally, using IOPTH has a potential to reduce number of pre-operative scans with subsequent cost savings.

Improvement of surgical cure rates

The unique advantage of IOPTH monitoring is that it provides accurate and real-time information about concentration of PTH and guides surgical decision whether removal of a parathyroid gland was curative, and procedure can be stopped, or further exploration should be carried on. The ability to predict cure during the operation is an exclusive feature of this technology not shared with other

intraoperative adjuncts such as frozen section biopsy or methylene blue which are now made obsolete. Early reports compared results of BNE without and MIP with IOPTH and showed that MIP with IOPTH not only maintained high cure rate of BNE but also improved it by 1%-3%. Majority of more recent publications comparing MIP with and without IOPTH in patients with concordant or discordant imaging have shown improved cure rate by 3%-15% when IOPTH was performed. Studies including only patients with concordant US and MIBI demonstrated smaller gain from IOPTH improving cure rate by 1%-5.5% only two studies showed cure rate to be the same, or paradoxically worse possibly related to simultaneous use of radioactive guidance and small number of patients in the study [52,53]. Impact of IOPTH on re operative surgery is not well documented with one study showing no improvement and one demonstrating 18% improved cure rate with IOPTH use (Tables 3-5) [54,55].

BNE- No IOPTH		MIP-IOPTH		S?	R
N	CR%	N	CR%		
340	94	421	97	S	[99]
401	97	255	99	NS	[71]
55	89	49	90	NR	[100]
62	98	14	100	NS	[101]

184	97.3	33	100	NS	[102]
44	97.7	47	95.7	NR	[103]

Table 3: Cure rate in patients undergoing BNE without IOPTH and MIP with IOPTH.

No IOPTH		IOPTH		S?	R
N	CR%	N	CR%		
40	85	13	100	S	[104]
87	93.1	80	97.5	NR	[73]
15	100	5	100	ND	[52]
62	91.9	115	99.1	S	[79]
157	90	188	100	S	[78]
39	94.1	14	100	NS	[105]
44	97.7	47	95.7	NS	[53]

Table 4: Cure rates in patients undergoing MIP without IOPTH vs. MIP with IOPTH.

N	CR%	IOPTH added	S?	R
322	99	1%	NS	[57]
127	100	5.5%	NR	[106]
260	99.6	3.1%	S	[45]
338	97.9%	4.1%	S	[107]

S: significant, NS: not significant, NR: not reported, ND: not different, CR: cure rate

Table 5: Cure rate in patients with concordant imaging undergoing parathyroidectomy with IOPTH.

Increased Frequency of MIPs

Benefits of MIP are widely accepted by patients, surgeons and health providers and include less pain, quicker recovery, better cosmetic results and shorter hospital stay. There is a clear advantage in offering this approach to as many patients with PHPT as possible but current practice is based on performing it only in patients with concordant findings on US and MIBI.

MIP has been traditionally contraindicated in cases with discordant or equivocal imaging results because up to 14% of these patients have multiple gland involvement [56,57]. However, the ability of IOPTH monitoring to predict cure during surgery with high accuracy has encouraged many surgeons to perform MIP in patients who do not have perfect co-localization of abnormal parathyroid on imaging.

Published evidence in Table 6 shows that MIP was possible in 63% to 86% of patients with non-concordant imaging, with high cure rate of 93%-98%, which suggests that IOPTH monitoring has a potential to increase overall number of patients being selected and successfully treated with MIP and that using this technology should increase surgeons' confidence in achieving high cure rate (Table 6).

N	Cured		MIP			R
	N	%	Attempted	Completed	%	
50	49	98%	50	43	86	[87]
201	195	97%	201	NR	NR	[57]
85	79	93%	85	56	66	[24]
143	138	97%	143	114	80	[108]
106	NR	NR	NR	80	66.6	[25]
67	66	98.5	67	42	62.7	[109]

Table 6: Cure rate in patients with discordant or equivocal imaging undergoing parathyroidectomy with IOPTH.

Reduction in Number of Pre-Operative Imaging and Adoption of the "Single Scan" Paradigm

Perhaps the most exciting potential of intra-operative PTH monitoring in becoming "disruptive technology" could be its ability to change current paradigm which heavily relies on concordant multiple scans, and replacing it with a pragmatic step wise use of pre-operative imaging.

Currently used imaging modalities have similar ability to identify abnormal parathyroid and are more accurate when parathyroid are larger, heavier and inferiorly located but less so in patients with greater BMI, milder HPT, multiple glands pathology and nodular thyroid disease [58-60]. Comparison of US and MIBI in 120 patients showed no statistically significant difference in accuracy or positive predictive value (74% vs. 82% and 93% vs. 90%, respectively) [61].

Limited yield of second scan is demonstrated in two studies of 97 and 226 patients where US localized abnormal parathyroid in 84 (sensitivity 87%) and 173 (sensitivity 77%) cases while MIBI additionally localized only 6 and 30 cases [62,63].

These data suggest that multiple imaging aiming at concordant localization is not necessary and could be replaced by new paradigm which would rely on identification of abnormal parathyroid by single scan. The choice of the scan will depend on local radiological expertise but US should be considered as the first choice of investigation and additional scan such as CT or MIBI would be indicated only when initial imaging is negative.

Positive localization of a single abnormal gland cannot guarantee that its removal will achieve cure and surgeons would be reluctant to base their decision on this information alone. IOPTH monitoring however, has unique ability to predict cure and its superior performance in comparison to imaging both in initial and re-operative parathyroid surgery is demonstrated by studies summarized in Table 7. This shift of the burden of proof of predicting cure from pre-operative planning to intra-operative decision making is possible because biochemical monitoring is better than imaging at informing surgeons how many parathyroid glands need to be removed.

Other perioperative adjuncts commonly used in parathyroid surgery can't give such guidance. Frozen section and methylene blue can confirm that removed tissue is parathyroid but cannot reliably differentiate between adenoma and hyperplasia and says nothing about

function of remaining parathyroids and therefore don't improve cure rate [64-67].

IOPTH appears to perform better than gamma probe and one prospective study on 254 PHPT patients reported higher sensitivity, PPV and accuracy of IOPTH compared to radio-guided surgery (99%, 100% and 98% vs. 93%, 89% and 83%, respectively) [68].

IOPTH monitoring is therefore the only technology capable of real time functional confirmation of cure with high sensitivity, specificity and accuracy. It promises to re-establish the continuum of reasoning based on biochemical criteria by bridging the gap between diagnosis of PHPT and definition of cure both defined in biochemical terms (Table 7).

Patients	N	Investigation	Sensitivity	PPV	Accuracy	Ref
Patients who underwent initial surgery for benign PHPT	1361	US	61%	93%	56%	[110]
		MIBI	86%	87%	81%	
		IOPTH	98%	99%	98%	
Patients who underwent re-operative surgery for benign PHPT	228	US	68%	82%	61%	[111]
		MIBI	81%	90%	77%	
		IOPTH	99%	98%	97%	
Patients who were operated for PHPT	350	US	76.1%	75.0%	60.7%	[112]
		MIBI	71.6%	76.7%	59%	
		IOPTH	99.3	98.3	97.8	
Patients who were operated for sporadic PHPT	143	US	84.6	100	84.6	[113]
		MIBI	95	98.5	93.7	
		IOPTH	97.8	99.3	97.2	
Patients who were operated for sporadic PHPT	57	US	61.5	96.0	61.5	[114]
		MIBI	93.0	96.4	93.0	
		IOPTH	98.1	100	98.1	

Table 7: Results of studies comparing the performance of IOPTH, US and MIBI.

Intra-Operative PTH Monitoring: Future Concepts

IOPTH monitoring despite its significant advantages has not been universally adopted by surgeons performing parathyroid surgery. In the final paragraph of this review we identify and analyze possible barriers preventing this technology from wider adoption and discuss solutions able to get round them.

Main Laboratory vs. Point of Care PTH Testing

Logistics of current IOPTH monitoring is perhaps the most significant barrier to the adoption of this technology. Endocrine surgeons wishing to perform intra-operative PTH monitoring have a choice of either using their main laboratory or investing in Point-of-Care (POC) system which will allow PTH to be measured in the operating theatre. Routine diagnostic techniques used in main laboratories are not well suited for this particular testing need as they require not only complex infrastructure and skilled workforce but also willing cooperation of laboratory staff to accept inconvenience of dealing with samples arriving from operating theatre at unpredictable times. Main laboratories are stretched by providing routine diagnostic services and it is difficult for them to arrange for the ad hoc measurements of PTH on the main platform or release staff to attend operating sessions. This can interfere with their routine work and could be a critical barrier limiting its adoption.

The only currently available alternative solution is POC IOPTH system (example: Future Diagnostics) which is designed to be used in operating theatre as it is based on the large trolley equipped with multiple devices used during the assay, a valuable resource in operating theatre. Despite being superior to using main laboratory; it is bulky and occupies space; and importantly it still requires trained laboratory personnel and understaffed hospitals laboratories are reluctant to release them for off-site duties. This limits the ability of surgeons to schedule parathyroid operations when required and might have an impact on waiting times for parathyroid surgery.

Recent advances in engineering and bio-chemistry opened a possibility of constructing POC diagnostic devices which are simpler to operate and can be used by nurses or doctors already in theatre without a need for a dedicated laboratory technician. Innovation is needed in designing such a device for intraoperative PTH monitoring whose reliability of guiding the treatment in real time must reflect laboratory accuracy but at the same time allow measurements to be done anywhere and anytime without presence of the technician [69]. Such a device would have transformative effect on care of patients with PHPT [70].

Time to Result

Length of parathyroid surgery depends on multiple factors including not only the time needed to find abnormal single or multiple parathyroid which usually depends on the experience of the surgeon performing surgery but also choice of operating technique and perioperative adjuncts.

Published studies have demonstrated significantly shorter operative times in IOPTH-guided MIPs in comparison to BNEs without IOPTH [71,72] a finding almost certainly related to extent of dissection; being less in MIP. However, when MIP is performed addition of IOPTH can make operating time longer [52,73]. Such extra time is attributed to sample transportation which could be significantly longer if main laboratory is used but negligible if POC device is based in the operating theatre. Specimen preparation on all currently available platforms requires centrifugation of EDTA blood sample and takes minimum 3 minutes; this is followed by a sequel of time consuming steps such as pipetting, incubation and washout before readout could be obtained [35,74]. Speed of assay readout is very important as PTH is measured 4 to 5 times five minutes apart and currently each measurement takes 10-18 minutes or longer (example: STAT IO-I-PTH, FD and Elecsys 2010, RD). Clearly, new generation of POC microfluidic devices based in theatre and able to provide results in 3 to 5 minutes will be a great advantage. Relying on the drop of PTH concentration at 5 minutes will reduce number of measurements and time of surgery. Richards et al have shown that a 50% reduction has been observed in the five-minute measurement in 73% of cases making further testing in these patients unnecessary [75].

Cost

Use of the intra-operative PTH monitoring in its current format increases costs of parathyroidectomy incurred in the operating theatre and two cost analysis studies concluded that additional expense might not be justified because of only modest increase in cure rate and risk of false results [76,77]. However, both reports have restricted their case scenarios to patients with well localized abnormal parathyroid in which IOPTH is known to contribute least and neither of them considered the cost savings from increased number of MIPs, shorter hospital stay, and potential saving on preoperative imaging.

Cost savings associated with reduced hospitalization have been well documented in series where MIP with IOPTH was compared with BNE [71,72] and MIP without PTH monitoring [78,79]. IOPTH guided MIP performed as day-case with subsequent cost-effectiveness has been also shown to be safe and successful procedures in patients with well localized single gland parathyroid disease [80].

Pooling of more PHPT patients in a dedicated parathyroid surgery list would reduce the cost. Unpublished data from our institution showed IOPTH and FS come at a cost of £1845 and £1705, when five patients are operated on a single day as per our current practice (£369 and £341 per patient respectively). IOPTH cost comes from the use of two IOPTH test kits (48 tests each) £920, pay for laboratory staff £500, equipment £215, service contract £185, EQA £15, and incidentals £10. Further calculations showed the two IOPTH kits currently used for 5 patients can provide adequate measurements for seven patients reducing costs further and making IOPTH cheaper than FS (£264 per patient) [81]. Costs of calibration, price of assays and laboratory support could be potentially significantly reduced by new technical innovations leading to development of microfluidic POC devices [82].

Adoption of the aforementioned "single scan paradigm" would also significantly reduce the cost. Recent study on 208 PHPT patients operated at our institution showed that US correctly localized the disease in 193 out of 208 patients. In the remaining 15 patients MIBI was correct in 3, incorrect in 8, and negative in 4 patients. Importantly, in all 15 patients IOPTH was correct in predicting cure in 6 (true positive) or prompting further exploration in 9 (true negative) patients. Costs were calculated in two hypothetical scenarios using the new tariffs (US £100, MIBI £1000, and IOPTH £400). Using all three modalities, we have cured 203 out of 208 patients at a cost of £1500 per patient. Using classic combination of US and MIBI would have cured 196 out of 208 patients at a cost of £1100 per patient but combination of US and IOPTH would have cured 202 out of 208 patients at a cost £500 per patient [83-113].

Summary

Diagnosis and criteria for cure of the PHPT are biochemical and it is anachronism that during the operation surgeon has to rely on surrogate information such as size, weight or histopathology of parathyroid glands. IOPTH has potential to re-establish biochemical continuum in pre, intra and post-operative reasoning.

Intra-operative PTH monitoring accurately defines cure in whole spectrum of patients with sporadic and familiar PHPT regardless of their age, renal function, vitamin D status, weight and number of affected glands. It consistently outperforms pre-operative imaging tests in predicting cure and by doing so shows potential to reduce reliance on multiple scans, radiation exposure, patient's inconvenience and overall costs and increase number of minimally invasive procedures while maintaining high cure rate.

Current methods used to monitor PTH concentration are too slow, expensive and logistically difficult. Development of novel "Lab on a chip" ultrafast, cheap and simple devices which can perform all steps automatically without need from human interference, will reduce time, cost, improve logistics, and un-clutter operating theatre, and by doing so place surgeon at the center of decision making by giving him access to vital information in real time and encourage wider utilization of this beneficial technology.

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