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Limited clinical utility of intraoperative frozen section during parathyroidectomy for treatment of primary hyperparathyroidism

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ABSTRACT

Background: This study's objective was to evaluate the utility of intraoperative frozen section (IFS) performed during parathyroidectomy for treatment of primary hyperparathyroidism (PHP), and to identify patients for whom it is most helpful.

Methods: A retrospective chart review was carried out for all patients who underwent parathyroidectomy for treatment of PHP between January 2013 and June 2018.

Results: 262 patients made up the final study population. Overall, IFS provided information that influenced the operative plan in 46 patients (17.6%). IFS altered the operative plan in 10.2% of cases that were correctly preoperatively localized, and in 41.5% of cases that were either incorrectly or not preoperatively localized.

Conclusions: IFS did not provide information that influenced the operative plan during parathyroidectomy for treatment of PHP for the majority of patients. Patients that present with normal PTH and hypercalcemia, or those who do not localize preoperatively, are most likely to benefit from IFS.

Introduction

Individuals who are diagnosed with primary hyperparathyroidism (PHP) most commonly present with hypercalcemia and an elevated parathyroid hormone (PTH) level. These cases are usually caused by a solitary parathyroid adenoma, but may also result from multiple adenomas, four gland parathyroid hyperplasia, and least commonly parathyroid carcinoma.[1] Cure of PHP requires surgical removal of the overactive parathyroid gland(s), or parathyroid tumour(s) (PTs). During parathyroidectomy intraoperative frozen section (IFS) is often performed to confirm PT removal. IFS performed during parathyroidectomy has been reported to have an overall accuracy of 99.2% for identifying parathyroid tissue.[2] However, IFSs are time-consuming, costly, may potentially impact the viability and function of biopsied normal parathyroid glands that are left in situ, and thus may negatively impact patient outcomes. In addition, experienced parathyroid surgeons claim that by gross inspection alone they can differentiate normal from abnormal parathyroid glands, and also distinguish them from adjacent lymph nodes, fat, and thyroid tissue. The development and refinement of preoperative localization imaging studies, such as technetium-99 m sestamibi with single positron emission CT (CT-MIBI) scans, high resolution ultrasound, Dual Energy CT scans (DE-CT), and Four Dimensional CT (4D-CT) scans have allowed for the detection and preoperative localization of PTs, and have permitted a more focused surgical approach, that reduces the need for performance of a bilateral neck exploration (BNE). During a BNE all 4 parathyroid glands must be definitively identified, and this operation is associated with increased morbidity relative to the more focused procedure.[3] IFS has remained an essential part of a BNE when carried out for treatment of PHP because it provides the only objective evidence that normal parathyroid glands have been identified and/or PT(s) have been removed. It is because calcium plays such a central role in many different essential human physiological processes, its blood level must be tightly controlled, and this has largely been made possible by the short half-life of PTH (between 3 and 5 min).[4] Capitalizing on its short half-life, intraoperative PTH (IOPTH) assays have facilitated a focused surgical

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approach by accurately (98%) and rapidly predicting a postoperative cure after PT removal.[2] The utilization of IOPTH to guide the extent of surgical exploration calls into question the need for routine IFS during parathyroid operations. The study's objective was to evaluate the utility of IFS during parathyroidectomy that is performed for treatment of PHP, and to identify the subsets of patients for whom it is most beneficial.

Material and methods

Study design

This study was carried out with the approval of our institutional research ethics board. The medical records of all patients who underwent a parathyroidectomy for the treatment of primary hyperparathyroidism by a single surgeon, at a Canadian tertiary care centre (St. Paul's Hospital, Vancouver Canada) between January 2013 and June 2018, were retrospectively reviewed. Patients were included in the study population if IFS and IOPTH were utilized during their operations. Patients with missing data or a follow up calcium level (or PTH level for normocalcemic PHP cases) measured less then 6 months postoperatively, those who had undergone prior central neck surgery, or those who presented with recurrent PHP (defined as an elevated calcium measured 6 months or longer after surgery, or an elevated PTH level measured 6 months or longer after surgery for normocalcemic PHP patients), inheritable forms of PHP, lithium associated PHP, or secondary or tertiary hyperparathyroidism, were excluded.

Variables evaluated

Retrospective chart review was carried out for all study patients and the information that was collected included: age, sex, preoperative calcium level, preoperative PTH level, preoperative localization studies performed and their findings (correct or incorrect/nonlocalizing), whether the patient underwent a focused parathyroidectomy (single parathyroid gland removed by a unilateral procedure through a small central transverse cervical incision) or a BNE (bilateral 4 parathyroid gland exploration), IOPTH levels, number of intraoperative frozen sections performed, whether the focused parathyroidectomy was converted into a BNE, the final pathological diagnosis, and postoperative calcium level normalization at a minimum of 6 months after operation. For the normocalcemic PHP subgroup normalization of PTH levels at a minimum of 6 months after operation was also evaluated. At our centre IFS is utilized to determine if parathyroid tissue has been either sampled or removed, and not to distinguish specific gland pathology (ie. adenoma versus hyperplasia). Thus, the diagnosis of cases of multiple adenomas versus 4 gland hyperplasia were based on intraoperative findings, with final pathological confirmation. Biochemical cure was defined as a normal calcium level measured at 6 months after surgery for all patients except the normocalcemic PHP subgroup for which cure was defined as PTH normalization at a minimum of 6 months postoperatively. A patient was considered to have their PT correctly preoperatively localized if the preoperative localization test(s) that directed the exploration were concordant with intraoperative findings, and confirmed by postoperative histopathological assessment.

Data analysis

IFS was considered helpful if it provided information that impacted the extent of operative exploration, specifically if the IOPTH level did not drop by 50% or greater from the highest pre-excision level following removal of a suspected PT and a focused procedure was converted into a BNE, or if multiple IFSs were sent during the operation for identification of a normal parathyroid gland(s) or PT(s). The proportion of cases for which IFSs were considered helpful was determined for the entire study population, and also for each of the 3 study subgroups that were separated based upon preoperative laboratory testing: high calcium and high PTH (HCAHPTH) group, normal calcium and high PTH (NCAHPTH) group, and high calcium and normal PTH (HCANPTH) group. Subgroups were compared according to the helpfulness of IFS using the two-tailed χ^2 test. All data was collected using Excel Version 14.0.0 (Microsoft WA, USA) and statistical analysis was performed in Graphpad 7 (GraphPad Software CA, USA).

Results

Entire study population

Over the 5.5 year study period (January 2013 to June 2018) 262 PHP patients met study inclusion criteria, and made up the final patient population. IFS was found to be helpful during surgery, or impacted the operative plan, in 17.6% of the cases that made up the entire study population. Patients were further separated into 3 subgroups based upon their preoperative laboratory testing: 191 patients with high calcium and PTH (HCAHPTH), 52 patients with normal calcium and high PTH (NCAHPTH) and 19 patients with high calcium and normal PTH (HCANPTH). IFS was found to be helpful in 13.6% (26/191), 28.8% (15/52) and 26.3% (5/19) of cases in each of these three groups, respectively. Fig. 1 summarizes study patient characteristics and these results. The comparative reduction in the helpfulness of IFS during parathyroidectomy was significant when comparing all three subgroups ($P = 0.02^*$), and the HCAHPTH vs. HCANPTH subgroup ($P = 0.009^{**}$), but not the HCAHPTH vs. NCAHPTH subgroup ($P = 0.14$) or the NCAHPTH vs. HCANPTH subgroup ($P = 0.83$).

Overall, there were 234 cases (89.3% of study population) in which the IOPTH decrease predicted cure, and the IFS concordantly confirmed PT removal. The intraoperative PTH decrease also accurately predicted postoperative biochemical cure, and was concordant with the final pathology, in 260 cases (99.2%). In one of the discordant cases, IOPTH decreased by 50% or more, but final pathological assessment revealed a normal parathyroid gland, and there was a persistently elevated calcium level measured at 6 months postoperatively. In the other discordant case IOPTH decreased by 50% or greater during parathyroidectomy but final pathological assessment revealed a lymph node. However, at 6 months postoperatively the patient had a normal calcium level. Overall, there were 35 cases (13.4%) where a planned focused parathyroidectomy was converted into a bilateral neck exploration, and all were based on IOPTH levels. Among those patients with PTs correctly localized by preoperative imaging, IFS was only helpful in 10.2% of cases, whereas it was helpful in 41.5% of cases when PTs were either not preoperatively identified or incorrectly localized. Table 1 summarizes these results for the entire study population.

Elevated calcium and elevated PTH (HCAHPTH) subgroup

191 (72.9%) patients had both an elevated calcium level and an elevated PTH level that were measured preoperatively. Of this study population subgroup, 165 individuals (86.4%) ended up undergoing a focused parathyroidectomy and 26 people (13.6%) underwent a BNE. Overall, IFS was helpful in 26 (13.6%) of these cases. 176 (92.1%) patients were found during surgery to harbour a solitary PT, of which 158 (89.8%) were correctly localized preoperatively. 15 (7.9%) patients were found to have multi-gland disease. Fig. 2 summarizes the cases in which IFS was helpful during

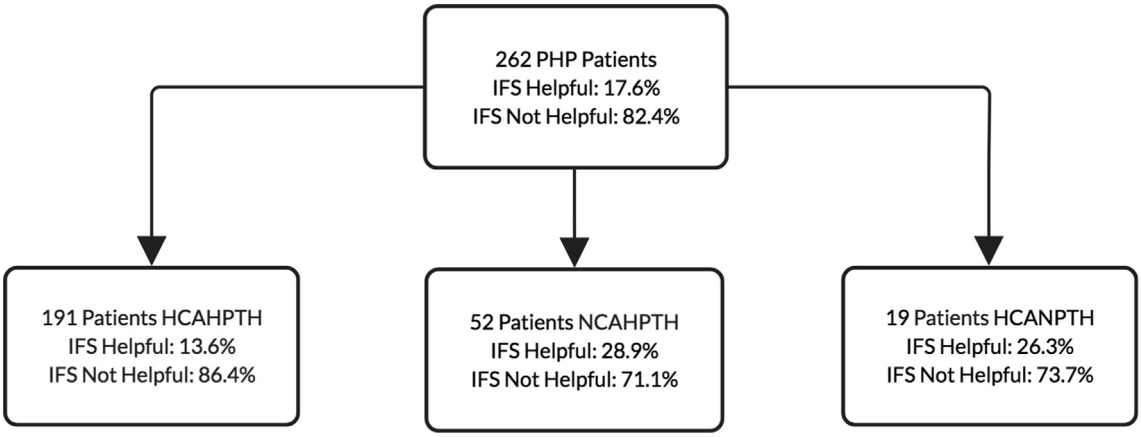

Fig. 1. Flowchart depicting final study patient population, utility of IFS, and separation into subgroups based on preoperative PTH and calcium levels. Abbreviations: IFS: intraoperative frozen section, PHP: primary hyperparathyroidism, PTH: parathyroid hormone, HCAHPTH: high calcium and high PTH PHP patient subgroup, NCAHPTH: normal calcium and high PTH PHP patient subgroup, HCANPTH: high calcium and normal PTH PHP patient subgroup.

parathyroidectomy in this study population subgroup.

Normal calcium and elevated PTH (NCAHPTH) subgroup

There were 52 (19.8%) patients who presented with normocalcemic primary hyperparathyroidism (normal calcium and elevated PTH). Of these cases, 36 (69.2%) underwent a focused parathyroidectomy and 16 (30.8%) underwent a BNE. Overall, IFS was helpful in 15 (28.8%) of these cases. 50 (96.2%) patients were found at surgery to harbour a solitary PT, of which 20 (40%) were correctly preoperatively localized. There were 2 (3.8%) patients who had multi-gland disease. Fig. 3 summarizes the cases in which IFS was helpful during operation in this patient subgroup.

Elevated calcium and normal PTH (HCANPTH) subgroup

There were 19 (7.3%) patients who presented with an elevated calcium level and a normal PTH. In this study population subgroup, 13 individuals (68.4%) underwent a focused parathyroidectomy and 6 people (31.6%) underwent a BNE. IFS was helpful in 5 (26.3%) of these cases. There were 17 (89.5%) patients who were found to have a single PT, of which 11 (64.7%) were correctly preoperatively localized. In addition, 2 patients (10.5%) had multi-gland disease. Fig. 4 summarizes the cases in which IFS was helpful during operation in this patient subgroup.

Table 1
Summary of study population characteristics.

Variable	Value
Sex, N (%)	
Male	63 (24)
Female	199 (76)
Average Age (Years)	63.5
Preoperative Localization Tests Utilized, N (%)	
Ultrasound	257 (98.1)
CT-MIBI Scan	261 (99.6)
DE-CT Scan	157 (59.9)
Preoperative PT(s) Localization, N (%)	
Localized	233 (88.9)
Correctly Localized	197 (75.2)
Incorrectly Localized	36 (13.7)
Not Localized	29 (11.1)
Operation, N (%)	
Focused Parathyroidectomy	212 (81)
Planned Bilateral Neck Exploration	15 (6)
Focused Converted To BNE	35 (13)
Pathology, N (%)	
Single Gland Disease	243 (92.7)
Multigland Disease	19 (7.3)
Cases for Which IFS Was Helpful, N (%)	
Overall	46 (17.6)
Correctly Preoperatively Localized	20 (10.2)
Incorrectly or Not Preoperatively Localized	27 (41.5)

Discussion

Due to the widespread adoption of a focused IOPTH guided operative approach, the role of IFS during parathyroid surgery has changed. During a BNE that is being performed for treatment of PHP, information regarding the pathology of the underlying PT (ie. adenoma versus hyperplasia) can provide knowledge that influences approach and expectations during the operation. The objective of IFS during a focused IOPTH guided parathyroidectomy is primarily to distinguish parathyroid from non-parathyroid tissue, because the operation is dictated by parathyroid function, and not on inferences made based upon the underlying pathological diagnosis.[3] IFS has a very high reported overall accuracy rate (99.2%),[5] which is similar to what was observed in our study. However, in recent years, with the advent of improved preoperative localization testing, and utilization of IOPTH, the routine requirement for IFS during parathyroidectomy has become debatable. The utilization of IOPTH measurement to guide the extent of surgical exploration during parathyroidectomy, and placing it within the context of IFS, was first reported in 1993 by Madira et al. in a series of 12 patients.[6] While their study showed that PTH levels fell within 15 min of excision of the last PT, and correlated with postoperative cure, the technique was limited by a very long IOPTH level measurement turnaround time.[6] In this study the mean time for the IOPTH level measurement was 105 min, compared to 22 min for IFS, while the average operative time was 70 min for a focused parathyroidectomy, and 96 min for BNE.[6] Since this early report, assays with more rapidly available IOPTH measurements have been developed, with some assays providing results within 20–25 min including transport and processing time.[7] This has led to the adoption of IOPTH measurement, and abandonment of routine IFS by surgeons at many centres, to facilitate focused parathyroid operations. However, the specific utility of IFS in the current setting of focused parathyroidectomy, facilitated by rapid IOPTH, has remained poorly defined.

In our study, use of the 'Miami Criterion,' a decrease by 50% or more in the IOPTH level from the higher of either the baseline or

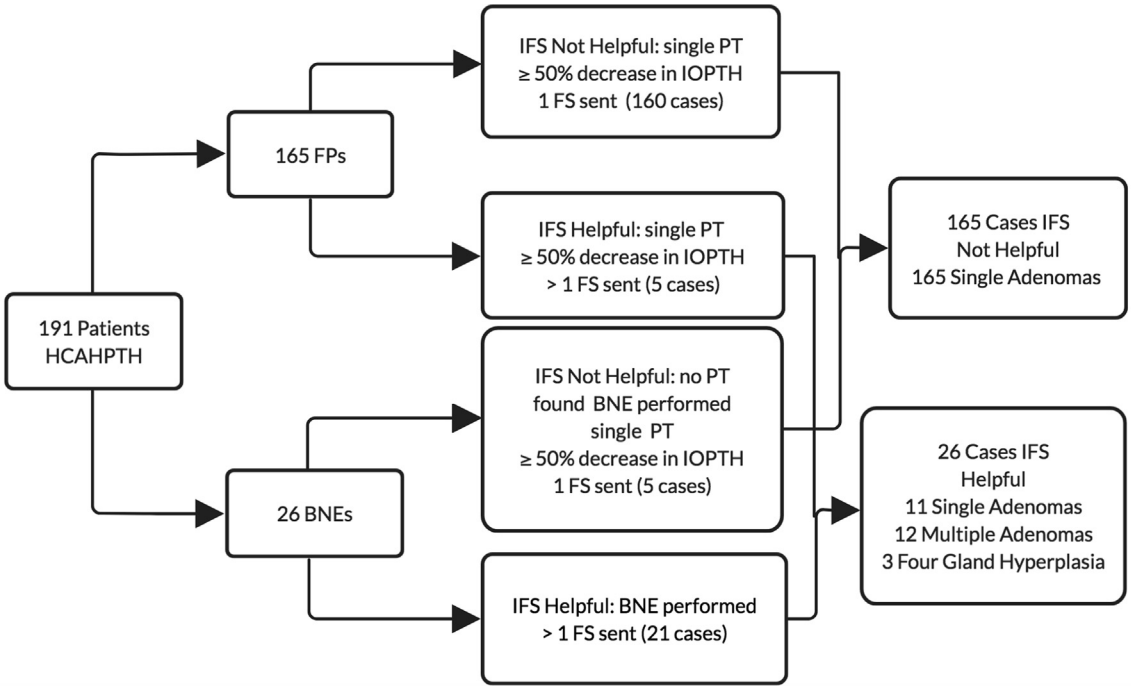

Fig. 2. Flowchart depicting the parathyroid operations during which IFS was helpful versus unhelpful in the subgroup of patients that preoperatively presented with elevated calcium and elevated PTH levels. Abbreviations: BNE: bilateral neck exploration, FP: focused procedure, FS: frozen section, IFS: intraoperative frozen section, PT: parathyroid tumour, PHP: primary hyperparathyroidism, PTH: parathyroid hormone, IOPTH: intraoperative PTH, HCAHPTH: high calcium and high PTH PHP patient subgroup.

pre-excision IOPTH levels, successfully predicted biochemical cure 6 months or longer following surgery in 99.2% of the cases. This finding is comparable to the reported accuracy rates for IOPTH decreases in predicting cure, that range from of 83.8%–97.3%, in the current literature.[8–10] This high accuracy suggests that IOPTH measurement can reliably confirm complete removal of pathologically hyperfunctioning parathyroid tissue, and is an accurate technique for predicting cure, and thus when the operation should be considered completed. We observed that for the majority of cases the surgical endpoint of a parathyroidectomy carried out for

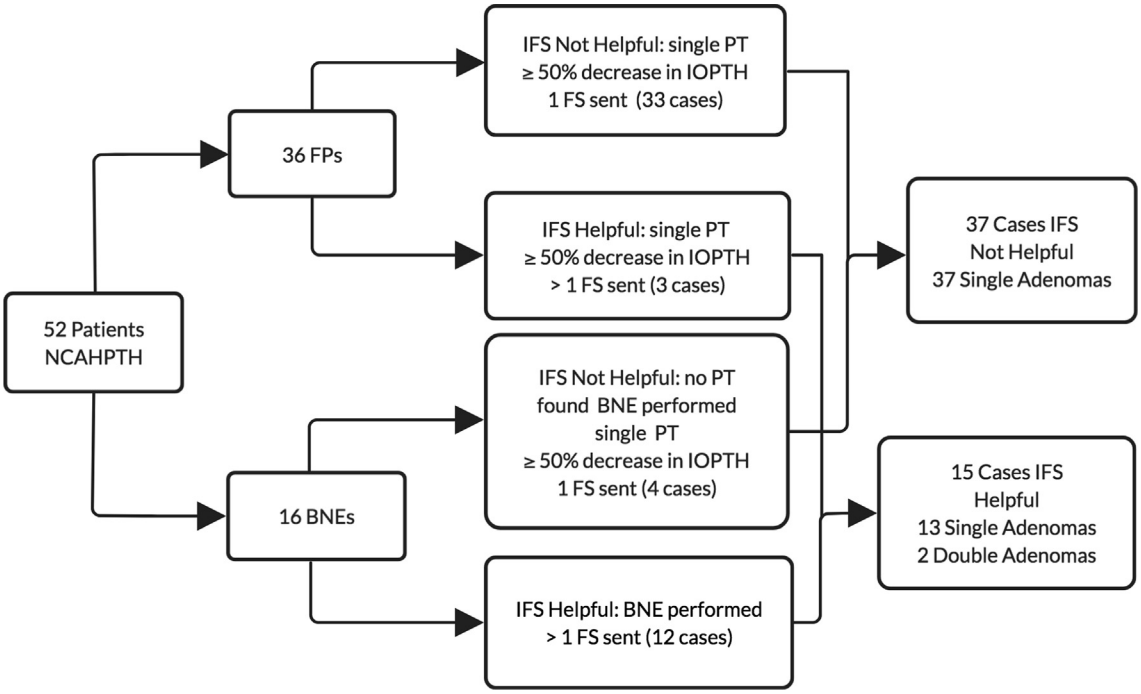

Fig. 3. Flowchart depicting the parathyroid operations during which IFS was helpful versus unhelpful in the subgroup of patients that preoperatively presented with normal calcium and elevated PTH levels. Abbreviations: BNE: bilateral neck exploration, FP: focused procedure FS: frozen section, IFS: intraoperative frozen section, PT: parathyroid tumour, PHP: primary hyperparathyroidism, PTH: parathyroid hormone, IOPTH: intraoperative PTH, NCAHPTH: normal calcium and high PTH PHP patient subgroup.

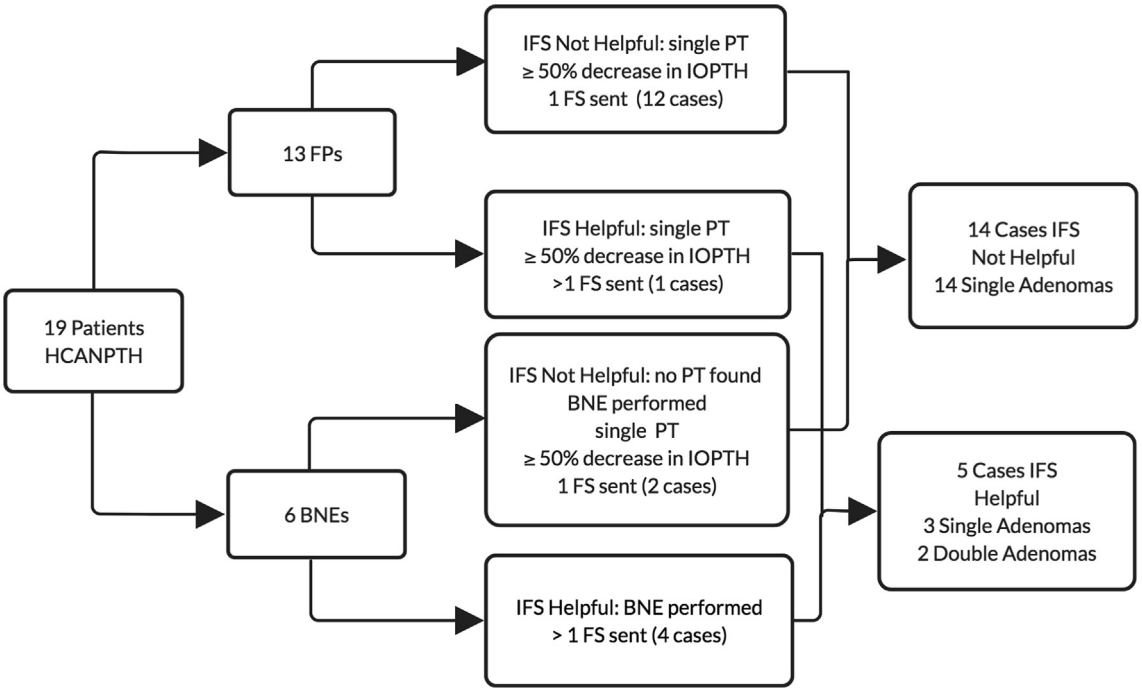

Fig. 4. Flowchart depicting the parathyroid operations during which IFS was helpful versus unhelpful in the subgroup of patients that preoperatively presented with elevated calcium and normal PTH levels. Abbreviations: BNE: bilateral neck exploration, FP: focused procedure, FS: frozen section, IFS: intraoperative frozen section, PT: parathyroid tumour, PHP: primary hyperparathyroidism, PTH: parathyroid hormone, IOPTH: intraoperative PTH, HCANPTH: high calcium and normal PTH PHP patient subgroup.

treatment of a preoperatively localized solitary PT is usually straightforward. Once the suspected PT has been identified by the surgeon and removed, and IFS confirms the specimen is parathyroid, and the IOPTH level suggests biochemical cure, the incision may be closed, and the operation is finished. For these cases, performance of an IFS to confirm that a PT has been removed had no additional value, and should not routinely be carried out. Our findings are similar to those reported by Guarda et al. who reviewed 125 parathyroid operations that were performed for treatment of PHP, who concluded that routine IFS was not required because IOPTH was an accurate predictor of PT removal and cure.[11] Similarly, in 2005 Lacobone et al. reported that IOPTH monitoring was reliable for predicting postoperative normocalcemia, and had both a lower turnaround time, and cost, than IFS.[12] For the cases in which removal of a PT did not result in a 50% or more decrease in the highest pre-excision IOPTH level (13% of cases in our study) and the contralateral neck was explored, IFS was helpful and served as a useful intraoperative adjunct to IOPTH measurement. However, even for these cases, IOPTH was better at predicting biochemical cure, as it indicated the absence of a remaining hyperfunctioning PT, whereas IFS only confirmed that a PT had been removed.

In the study population, among all cases in which IFS was considered to be helpful, 41.3% of patients had multigland disease, suggesting utility for IFS in this patient subgroup. However, multigland disease is not necessarily preoperatively predictable. Similarly, the higher proportion of cases in which IFS was helpful in the HCANPTH groups when compared to the HCAHPTH group, suggests that IFS may be more useful in this clinical setting, and based on calcium and PTH levels, be preoperatively predictable. This is likely related to the lower rate of accurate preoperative localization for solitary adenomas in the NCAHPTH group (40%) when compared to the HCAHPTH group (89.8%). The relationship between the utility of IFS and preoperative localization is also important, with IFS being helpful in 41.5% of cases that had either no PT localization or incorrect PT localization, compared to 10.2% of cases in which the PT was correctly localized. In a study that evaluated the factors that influenced the time required to observe a 50% or greater decrease in the IOPTH level during parathyroidectomy, Bhutiani et al. found that lower baseline and pre-excision IOPTH levels were associated with a significantly longer (greater than 15 min) time that was required to achieve a 50% or greater decrease in IOPTH.[13] Similar to the observations made in our study, this report suggests that IFS may remain a valuable test in this patient subgroup.

Some investigators have argued that gross examination of parathyroid tissue by an experienced parathyroid surgeon and pathologist can replace IFS analysis. In a study that evaluated 50 patients undergoing parathyroidectomy, 35 with a solitary adenoma, and 15 with multigland hyperplasia, only 3 cases were misidentified when only grossly examined by both the surgeon and pathologist.[2] Nevertheless, other studies have shown that even experienced surgeons may have difficulty in distinguishing parathyroid adenomas from other tissues, and IFS may be helpful during certain cases.[14] In our study we identified 8 cases (3.1%) in which IFS was helpful, despite an adequate drop in the IOPTH level after removal of a preoperatively localized PT. In 7 of these cases IFS assisted the surgeon in identification of a PT, helping to distinguish it from fat, lymph nodes, and thyroid. In a single case the pathologist commented on unusual features within a suspected PT, and adjacent fat and lymph nodes were subsequently sent for IFS to evaluate for malignancy, and the extent of surgery was influenced (en bloc resection of parathyroid carcinoma with adjacent thyroid, fat and lymph nodes). As has been previously reported, IFS can be used as an adjunct to IOPTH during focused parathyroidectomy in the uncommon circumstance when parathyroid malignancy is suspected.[12]

The current study has several limitations that must be reviewed. The retrospective single-centre and single-surgeon design of this study may increase risk of bias, and thus the results may not be

generalizable. Cure after parathyroidectomy that is performed for treatment of PHP, and the utility of IFS, may be influenced by many different factors that include: surgeon and pathologist experience/volumes, centre volumes, performance metrics of the preoperative localization studies utilized, characteristics of the IOPTH assay utilized, and PHP patient clinicopathological characteristics. In the current study we have shown that variation in the proportion of the patients in groups defined by their preoperative PTH and calcium levels impacts IFS utility. In addition, our findings also cannot be generalized to patients with inheritable forms of PHP, lithium-related PHP, recurrent PHP, and secondary or tertiary hyperparathyroidism, as these cases were excluded from the study population. However, such patients tend to more commonly have multigland disease, and require a BNE, and thus would more likely benefit from an IFS when compared to the current study patient population, though further investigation is required. Finally, all patients at our centre undergo preoperative ultrasound not only for PT localization, but also to evaluate their thyroid gland for the presence of underlying nodular disease that warrants further evaluation by fine needle aspiration biopsy. This allows for comprehensive preoperative surgical planning, helps to avoid future reoperation, and usually eliminates the need to carry out IFS to evaluate thyroid lesions that are unexpectedly encountered during parathyroidectomy. Thus, at some centres IFS may also have added value if it is employed during parathyroidectomy to investigate concurrent thyroid disease.

In conclusion, we have found that IFS is not required for the vast majority (82.4%) of patients during parathyroidectomy when performing a focused operation, guided by IOPTH and preoperative localization studies, for the treatment of PHP. Unlike IOPTH, in most cases during parathyroidectomy IFS does not provide the surgeon with information that changes their operative plan, or leads to performance of a bilateral neck exploration when a focused procedure is anticipated. Thus, carrying out an IFS during cases in which a solitary adenoma is removed, and the decrease in IOPTH suggests cure, is not necessary, and may add time and expense to the operation. After this study was completed and we became aware of its results, we stopped carrying out routine IFS during focused parathyroid operations performed at our centre. However, there are clinical settings where IFS may be helpful to the surgeon during parathyroidectomy. Such cases may be predictable (normal PTH with elevated calcium PHP patients and for individuals that do not have their PT preoperatively localized) or unpredictable (multigland disease or cases with incorrect PT localization) preoperatively. Even though performance of IFS is not needed during most IOPTH guided focused parathyroid operations, there do remain unpredictable cases for which it does have value, and so it must remain readily available to surgeons who perform this often perplexing endocrine operation.

Author disclosure statement

The authors of this manuscript declare no competing financial interests exist.

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