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Initial clinical experiences using the intraoperative probe-based parathyroid autofluorescence identification system – PTeye™ during thyroid and parathyroid procedures

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Abstract

Background and Objective: The Food and Drug Administration has cleared a probe-based NIRAF detection system called PTeye™ as an adjunct tool for label-free intraoperative parathyroid gland identification. Since PTeye™ has been investigated only in a ‘blinded’ manner to date, this study describes the preliminary impressions of PTeye™ when used by surgeons without being blinded to the device output.

Methods: Patients undergoing thyroid and parathyroid procedures were prospectively recruited. Target tissues were intraoperatively assessed with PTeye™. The surgeon’s confidence in PG identification was recorded concomitantly with NIRAF parameters that were output in real-time from PTeye™.

Results: A retrospective review of prospectively collected data on 83 patients was performed. PTeye™ was used for interrogating 336 target tissues in 46 parathyroid and 37 thyroid procedures. PTeye™ yielded an overall accuracy of 94.3% with a positive predictive value of 93.0% and a negative predictive value of 100%. An increase in confidence for intraoperative PG identification with PTeye™ was observed by all three participating high-volume surgeons, irrespective of their level of accrued surgical experience.

Conclusions: Probe-based NIRAF detection with PTeye™ can be a valuable adjunct device to intraoperatively identify PGs for surgeons of varied training and experience.

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Disclosures
Dr. Giju Thomas is affiliated with Vanderbilt University who has a licensing agreement for PTeye™ with AiBiomed (now officially acquired by Medtronic).

Keywords

Parathyroid gland; surgical guidance; thyroidectomy; parathyroidectomy; near-infrared; autofluorescence

Introduction

Approximately 150,000 thyroid and at least 100,000 parathyroid operative procedures occur annually in the US [1-3]. For thyroidectomies, post-operative hypocalcemia is an undesirable and unwarranted sequela that may follow due to inadvertent trauma/excision of healthy parathyroid glands (PGs) or unintentional damage to parathyroid vasculature. While postoperative hypocalcemia can be transient as seen in 5-35% of cases or permanent as observed in 2-7% of the patients, this condition can be debilitating for most patients [4-6]. In comparison, a surgeon may fail to localize all diseased/hyperfunctioning PGs in 5-10% of parathyroidectomies [7,8], leading to persistent hyperparathyroidism and unnecessary re-operative procedures thereafter. The root of the aforementioned complications is mainly due to surgeons having difficulty in accurately identifying or localizing PGs during the operations, as PGs may often be mistaken for thyroid nodules, fat, or lymph nodes.

Ultrasound imaging (US), ^{99m}technetium-sestamibi scintigraphy, and computed tomography (CT) are valuable preoperative modalities to localize enlarged PGs [9-11] and the gamma probe can be utilized to locate diseased PGs intraoperatively with varied success [12,13]. However, these techniques are not useful to localize and preserve healthy PGs. More importantly, preoperative localization does not always match with what is observed by the surgeon intraoperatively. Thus, surgeons still tend to visually identify both healthy or diseased PGs by relying on their own accrued surgical experience, which may be highly subjective and variable. Frozen section analyses (FSA) or tissue aspirate parathyroid hormone (PTH) analysis serves as the current gold standard to intraoperatively identify if a tissue is a PG or not, whenever a surgeon is unsure. However, FSA or tissue aspirate PTH analysis is possibly injurious to healthy PGs and requires a waiting period of 20 to 30 minutes per sample [14]. Therefore, surgeons could highly benefit from non-invasive intraoperative tools that can help preserve healthy PGs as well as detect/identify diseased PGs.

About a decade ago, strong near-infrared autofluorescence (NIRAF) was discovered in PGs compared to other soft tissues in the neck [15]. Since the instrumentation required for NIRAF detection was relatively simple [15-17], several studies implemented this technique for PG identification with high success [18-23]. Thus, NIRAF detection proved to be a rapid, non-invasive, and label-free approach that could effectively identify both healthy and diseased PGs, which had not been feasible with conventional intraoperative modalities available to date.

The implemented approaches for NIRAF detection so far can be broadly categorized as (a) imaging-based (Fluobeam) and (b) probe-based (PTeye™). While several studies have been able to evaluate the impact and outcome of the imaging-based approach due to easily accessible commercial near infrared (NIR) cameras [24-30], the scope of probe-based NIRAF detection has only been investigated with surgeons always remaining blinded to the device output [15,17,18,31,32]. Without true feedback from the modality, the actual benefits from a probe-based system for surgical guidance remain only theoretical at best. Given that the probe-based approach can provide real-time quantitative information and was observed to be more sensitive in NIRAF detection from PGs than an imaging-based approach [33], the utility of this approach needs to be further explored in a non-blinded manner. In this study, we present our early clinical impressions upon utilizing PTeye™ as an adjunct device across a range of thyroid and parathyroid procedures, while providing an overview of its merits and demerits. Based on our initial experiences with this device, we sought to elaborate regarding our learning curve to effectively use PTeye™ in the operating room, while highlighting the clinical scenarios where PTeye™ was the most beneficial during neck endocrine procedures.

Methods

Description of PTeye™

PTeye™ (see Figure 1), mainly consists of (i) a display console that also encloses a 785 nm laser source, a photo-diode detector, and relevant internal circuitry, (ii) a foot-pedal to activate the laser source, and (iii) a detachable sterile fiber-optic probe that is placed in contact with the tissue for NIRAF measurements. The distinct internal circuitry of PTeye™ enables NIRAF detection from tissues without interference from ambient operation room lights. Tissue NIRAF measured with PTeye™ is conveyed to the surgeon via display console as (i) Detection level – absolute NIRAF intensity measured from tissue and (ii) Detection ratio – absolute NIRAF intensity of tissue normalized to the baseline NIRAF intensity established in the patient (see equation below).

$$Detection\ ratio\ in\ tissue = \frac{Detection\ level\ (absolute\ tissue\ NIRAF\ intensity)}{Baseline\ NIRAF\ intensity\ from\ thyroid\ or\ neck\ muscle}$$

Based on earlier data, the device threshold was set such that only tissues with a detection ratio exceeding 1.2 were classified as ‘parathyroid’ [18,32]. To obtain a NIRAF measurement, the surgeon places the sterile fiber-optic probe on the tissue and presses the foot-pedal. For tissue measurements with PTeye™, the surgeon first establishes a baseline NIRAF for each patient by obtaining NIRAF measurements on five random sites on the patient’s thyroid (or neck muscle if the thyroid is absent). After establishing the baseline, subsequent NIRAF measurements would indicate detection levels and ratios on the display console as NIRAF measurements are recorded from tissues of interest.

Study Design

A retrospective review was performed of the initial experiences of three high-volume surgeons utilizing NIRAF detection with the probe-based system PTeye™ as part of routine practice. Inclusion criteria for patients that were reviewed and considered for analysis were adult patients (≥18 years of age) who underwent thyroid or parathyroid procedures between February and October 2020 during which PTeye™ was utilized. Patient demographics, body mass index (BMI), operative indication, and procedure type were collected. Procedure types consisted of (i) parathyroidectomy – including focused or bilateral neck explorations (BNE) and (ii) thyroidectomy – including thyroid lobectomy (TL), total thyroidectomy (TT), TT with central lymph node dissection (CND), and TT with CND and modified lateral neck dissection (MLND). It was also noted if the surgery was a primary or re-operative procedure. The number of PGs preoperatively localized with US, ^{99m}Technetium-sestamibi scintigraphy, or CT for parathyroid procedures was also noted.

During the first 19 cases, PTeye™ was arbitrarily used as intended and described in its instruction manual, without following a specific protocol per se. The surgeon relied on the audio-visual feedback from the device simply to determine if the tissue was PG or not. Based on the learning curve obtained with PTeye™ after enrolling 19 patients, a study protocol was designed to standardize the use of PTeye™ across the participating surgeons for subsequent patients to be recruited. The study protocol ensured that the device setup, intraoperative utilization, and interpretation of PTeye™ output, were unanimously adopted and followed by all three surgeons for the remaining 64 patients (Table 1). Detection level, ratios, baseline values, and sources of device error were additionally noted for the subsequent patient dataset.

To quantify the utility of PTeye™, surgeon confidence was recorded for each target PG. The surgeons first recorded their confidence level on whether the tissue is PG as high (>75%), medium (50-75%), or low (<50%) based on their visual examination. The surgeon's confidence was then recorded again after interrogating the tissue with PTeye™ and the detection ratio on the presumed PG was known. Confidence levels of the surgical trainee, if present during the procedure, were also collected. To eliminate the attending’s influence on the surgical resident, they were asked to first identify PGs independently by placing the PTeye™ probe on the tissue that was assumed to be the parathyroid. The resident would then interrogate the target tissue with PTeye™ and interpret the device output again stating their confidence prior to the surgical attending making their judgement. If the resident failed to see the gland or incorrectly placed the probe on a non-parathyroid tissue, their degree of confidence was marked as ‘low’.

Histopathology (FSA or permanent histology) served as the gold standard validation for excised specimens, while the surgeon’s expert opinion was used for the corroborating identity of in situ tissues investigated with PTeye™. It must be noted that while a surgeon’s expert opinion could be subjective and error-prone, it is the only option available to verify the identity of in-situ tissues that are typically left intact and not biopsied. After each case, surgeons quantified their interpretation of the results as true positive (TP), false positive (FP), true negative (TN), or false negative (FN). Definition and determination of TP, FP, TN, and FN are provided in Table 2. The number of PGs identified with high confidence by the surgeons and the residents, before and after PTeye™, were compared and analyzed using a paired 2-tailed student t-test, with a p-value < 0.05 being considered significant.

After testing the device in this preliminary cohort, all three surgeons met to share their initial impressions and examine the perceived advantages and pitfalls during use with PTeye™. Specific scenarios in which the PTeye™ was found to be most helpful and the skills acquired while using the probe-based system in practice were discussed extensively. The quantitative and qualitative data from the three surgeons were pooled together, analyzed, jointly interpreted, and subsequently described below.

Results

A total of 83 cases, 46 (55.5%) parathyroidectomy, and 37 (44.6%) thyroidectomy met the inclusion criteria. Patient demographics and clinical information are included in Table 3. The median age of the cohort was 54 years with the majority of patients being female (n=60, 72.3%). Of the parathyroidectomy cases, 19.6% were focused and 80.4% were BNE. While the majority of parathyroidectomies were performed for primary hyperparathyroidism (95.7%), 13% of the parathyroid cases were performed in a re-operative setting. Of the thyroidectomy cases, 21.6% were lobectomy, 59.5% total thyroidectomy, 5.4% total thyroidectomy with CND, 8.1% total thyroidectomy with CND and MLND, 2.7% completion thyroidectomy, and 2.7% prophylactic thyroidectomy. Indications for thyroidectomy included multinodular goiter/thyroid nodule (37.8%), hyperthyroidism (40.6%), well-differentiated thyroid cancer (16.2%), recurrent thyroid disease (2.7%), and Multiple Endocrine Neoplasia Type IIA syndrome (2.7%)

In this cohort, a total of 336 target PGs were interrogated using the PTeye™. The overall accuracy was 94.3% with a positive predictive value of 93.0% and a negative predictive value of 100%. Table 4 demonstrates the performance of the PTeye™ versus the surgeon’s confidence level. Without the PTeye™, the surgeons themselves exhibited high confidence in 67.2% (226/336), medium confidence in 8.3% (27/336), and low confidence in 22.2% (83/336) on whether the target tissue was PG. When the surgeon reported high confidence in tissue being PG (n = 226), the PTeye™ agreed with the surgeon 100% (226/226) of the time. However, there were 5 (2.2%) FP results in the high confidence group, where 4 were confirmed to be negative for PG by histology. The remaining FP was judged to be a non-PG tissue by the surgeon when the actual PG was found later with an even higher detection ratio in a similar location. Taking this into account, the TP rate in the high confidence group was 97.8% (221/226). In the group where surgeons reported medium confidence (n = 27), PTeye™ indicated PG for 92.6% of those tissues (25/27). Of these 25, PTeye™ exhibited a TP rate of 96% (24/25), with just one FP being found in the medium confidence group. The tissue was deemed as FP when it was later opined to be thyroid tissue based on the surgeon’s judgment after two confirmed PGs were later identified on the ipsilateral side.

When the surgeons gave low confidence in tissue being PG (n=83), the PTeye™ concurred with the surgeons at 74.7% (62/83) that the tissue was not PG. In the remaining 21 cases (25.3%) when the surgeon had low confidence in tissue being PG, the PTeye™ detection ratio was >1.2 indicative that parathyroid tissue may in fact be present. Eight of the 21 were validated to be TP by histology or prompted the surgeon to interrogate further and ultimately confirm the parathyroid. In these 8 cases it was particularly valuable, as the PTeye™ indicated PG tissue even when the surgeon did not think it was likely to be PG. The remaining 13 cases were deemed to be FP by surgeon judgement and/or histology. The overall data set yielded 19 FPs obtained from thyroid nodules, lymph nodes, brown/regular fat, thymus, and paratracheal tissues as indicated in Table 5. 50% of FPs exhibited a ratio from 1.2-2.0, while the remaining FPs gave detection ratios >2.0. There was however a

100% negative predictive value as there were no instances of FN observed with PTeye™, regardless of the surgeon's confidence level. Although it must be mentioned that some adenomatous glands had NIRAF heterogeneity, leading to low detection ratios (or FNs) on the most diseased regions of these glands. These glands were in turn detected due to the high ratios in the healthy-appearing 'cap' of the diseased gland.

Overall, the number of PGs identified with high confidence by the surgeons increased significantly from (i) 2.5 PGs/case to 3.1 PGs/case during thyroid procedures (p=0.00013) and (ii) 3.2 PGs/case to 3.5 PGs/case during BNE parathyroid procedures (p=0.005). While PTeye™ increased the number of PGs identified with high confidence from 1.1 to 1.2 PGs/case during focused parathyroid procedures, the difference was not significant (p=0.35). With respect to resident trainees, a total of 10, were included in the study, the level of surgical training ranged from 1st to 5th year of residency. The level of experience with parathyroid/thyroid surgery and with PTeye™ was variable. In comparison, PTeye™ aided the resident trainee considerably in identifying more PGs with high confidence during thyroid (1.3 PGs/case vs 3.1 PGs/case with PTeye™, $p=1.9\times10^{-6}$), BNE parathyroid (1.2 PGs/case vs 3.4 PGs/case with PTeye™, $p=4.8\times10^{-7}$) and focused parathyroid (0.2 PGs/case vs 1.2 PGs/case with PTeye™, p=0.01).

For focused parathyroid procedures, preoperative imaging (CT, US, and/or ^{99m}Technetium-sestamibi) had visualized 100% of the diseased glands (9/9 PGs) that were also confirmed intraoperatively by surgeon and PTeye™. However, for BNE parathyroid procedures, preoperative imaging found only 42.8% of the diseased PGs (30/70), while PTeye™ detected all these 70 diseased PGs intraoperatively along with the ipsilateral/contralateral additional 58 healthy PGs visualized.

Discussion

With the recent emergence of NIRAF detection as a promising technology for label-free intraoperative PG identification, PTeye™ is currently the only FDA-cleared probe-based NIRAF detection device [23,34]. As a relatively new technology, little has been published about the surgeon's experiences on utilizing PTeye™ in a high-volume endocrine surgery practice (>150 endocrine cases per surgeon per year). This study describes our initial experiences upon using PTeye™ in our thyroid and parathyroid procedures while providing insights into the potential advantages as well as some of the pitfalls encountered while using PTeye™.

In this initial cohort, the overall concurrence of PTeye™ with the surgeons' judgment was 94.1%. When validated with the respective gold standards (surgeon opinion and/or histology), the accuracy for the device was calculated to be 94.3%, which is comparable to 92-98% reported with the prototype version of PTeye™ used in earlier studies [31-33]. It must, however, be noted that the surgeons were always blinded to PTeye™ output in prior studies, while the current study is the first where the surgeon(s) received audio-visual feedback for PG discrimination. The agreement of PTeye™ with the surgeons was highest (97.8%) when the surgeons were highly confident that they had already identified a PG. While it can be argued that in these cases PTeye™ did not provide any added benefit, all surgeons report feeling reassured by PTeye™ as it confirmed their judgment. For target tissues identified with medium confidence, PTeye™ was highly beneficial for further improving the surgeon's confidence and confirming PG tissue in 88.9% of these cases (24/27) and prevented surgeon error in 7.4% (2/27) of times where the surgeon misidentified non-parathyroid tissue as PG. On the contrary, very few PGs (8 out of 21) were identified as TP when the surgeon had low confidence. Importantly a detection ratio with PTeye™>1.2 was more likely to be an FP than a TP in this group. As seen in the Table 6 (for the second dataset of 64 patients), it is clear that if surgeons were to consider a higher Detection Ratio for tissue discrimination when they have low confidence, the number of false positives decreases. One must note that while false positives drop considerably as the Detection Ratio threshold is raised to 2.0 from 1.2, false negatives with PTeye™ on parathyroid glands that the surgeon had high-medium confidence increased from 0 to 2. Therefore, it might be more appropriate to consider a threshold of higher Detection Ratio only when the surgeon has low confidence on the tissue. This also further reiterates that surgeon's judgement should always be considered while interpreting Detection Ratios. Therefore, we conclude that when the surgeon has low confidence about a tissue that gives a detection ratio >1.2 with PTeye™, it should be interpreted with caution and the surgeon should beware of the potential for FP. In these cases when the surgeon has low confidence, consideration of the value of detection ratios may be more helpful. Higher detection ratios > 2.0 are likely to be more indicative of PGs (normal PGs in particular vs. adenomas) than lower ratios i.e., 1.2-2.0. Alternatively, intraoperative FSA or tissue aspirate PTH assay can be considered if accurate identification of the target gland is critical to conclude the case. Another aspect to be considered is that brown fat is a strong source of FP with exceptionally high detection ratios (Table 5). Since brown fat tends to occur in younger and leaner adults (as also observed in our study), the surgeon should be discerning of this finding while operating on these patients.

After using the probe-based approach in practice, we have identified several advantages of PTeye™ utilization during thyroid and parathyroid surgery, which are detailed in Table 7. Overall, we believe there is an advantage in the real-time feedback provided to the surgeon regarding a suspect parathyroid tissue. Whether this advantage offered by PTeye™ could reduce operative time, minimize the number of FSAs, or simply improve a surgeon's confidence in PG identification is yet to be determined. We, however, hypothesize that it may indeed impact all of the aforementioned. Interestingly in our group, all surgeons subjectively reported improved confidence in identifying PGs using the PTeye™, regardless of their level of experience (18, 6, and 2 years of independent surgical practice), particularly for thyroid and BNE parathyroid procedures. While this improved confidence may never translate into a measurable benefit, the ability of such modalities to provide increased certainty in often uncertain surgical environments should not be undervalued, particularly for early-career surgeons and trainees. In addition to improving the operating surgeons' confidence, we have found PTeye™ useful as a teaching tool for our surgical trainees. Trainees gain real-time feedback on their interpretation of the anatomy by placing the probe on a target gland. Based on their feedback, the trainees also reported higher confidence in identifying parathyroid tissue when using PTeye™. From a cost-benefit perspective, it is extremely unrealistic and time-consuming to perform FSAs on every tissue a trainee would want to interrogate. Yet PTeye™ can be used to interrogate tissues rapidly with very little time wasted. However, we have learned that surgical experience matters while interpreting results from new technology such as PTeye™. Trainees seem more likely to accept FP results from PTeye™, particularly when they have low confidence on whether the tissue is parathyroid or not. As a result, trainees would likely trust the device more than their own surgical experience. Thus, it would be important for early-career and trainees to consider using FSA/tissue aspirate PTH analysis when they have low confidence and encounter a detection ratio above the threshold, particularly when they are just learning to use this device. Another aspect to be noted regarding this study was that it was not feasible to track the confidence and learning curve of the surgical trainees over a longer duration since they rotate frequently on the endocrine surgery service. The scope of PTeye™ and similar technologies being able to shorten the learning curve for residents or early career surgeons requires further investigations in a more comprehensive manner.

Although our team has been investigating the feasibility of the probe-based lab-built system since 2009 [15,17,18,35] and the original PTeye™ prototype since 2017 [31,32] to identify PGs, the surgeons involved have always been blinded to the device output in these prior studies. While using the FDA-cleared PTeye™ as intended – without being blinded, we encountered several pitfalls in our initial cohort experience that allowed us to troubleshoot along the way and improve the learning curve to reliably utilize PTeye™ (Table 1). We learned that setting an appropriate baseline is critical to obtaining reliable results. Inappropriately high or low baseline levels can result in misleading FN and FP respectively, arising from the resultant incorrect detection ratios in PTeye™. Low baseline levels are particularly challenging as the rate of FP will increase and can lead to intraoperative confusion. After the device baseline is set, the surgeon should always scan/survey the thyroid (or muscle in absence of thyroid) with the probe to reduce the likelihood of an inaccurate low baseline. If any areas show detection ratios >1.2 after the initial baseline, the surgeon should then re-adjust the baseline to include the thyroid areas with the high ratios. While we did not encounter any FN in this cohort, there is certainly also the risk of an inappropriately high baseline from either unidentified intrathyroidal PGs, a toxic thyroid nodule, or thyroid cancer with very high NIRAF getting included in baseline measurements. Knowledge about the potential sources of high NIRAF within the thyroid can help surgeons have a higher suspicion for an FN, e.g., if the baseline NIRAF is high and a target PG has a detection ratio <1.2 despite high surgeon confidence. PTeye™ is not recommended for use in patients with secondary hyperparathyroidism or parathyroid cysts due to high FN rates observed earlier in these cases [18,23,32].

An additional lesson learned from this cohort study is that there is great intraglandular NIRAF heterogeneity within diseased PGs, as also reported in other studies. [36,37]. This has been encountered when a PG gland has both a normal-appearing portion and an adenomatous portion with higher detection ratios encountered in the normal-appearing ‘cap’ portion of the gland. If only the most abnormal portion of the gland is interrogated with PTeye™, the surgeon may fail to see a detection ratio >1.2 with PTeye™. Therefore, we recommend interrogating the entirety of the target diseased PG with the probe before drawing a conclusion. This can be encountered particularly with large parathyroid adenomas or when the PG has cystic areas. The majority of pitfalls with this technology can be overcome as surgeons learn how to optimally use the modality or as they gain further surgical experience over time with more thyroid and/or parathyroid surgeries (akin to nerve monitoring device). Thus, it is imperative to state that surgeon discretion is essential in the use of this device [23,34].

There are several clinical scenarios in which PTeye™ has proven most beneficial. (Table 8). We anticipate this list will grow and/or change within increased utilization of this device in different clinical situations. In general, the PTeye™ has been most useful in (i) re-operative or non-localized parathyroid procedures, (ii) patients with Hashimoto's thyroiditis with associated reactive lymphadenopathy during thyroid or parathyroid procedures, and (iii) identification/confirmation of at least one residual PG after total thyroidectomy. Furthermore, PTeye™ can assist surgeons to find residual diseased PGs that were not preoperatively localized or when intraoperative PTH levels fail to normalize, while helping preserve the remaining healthy PGs, which can be extremely valuable during BNE parathyroid procedures. Other studies utilizing image-based NIRAF detection cameras have already suggested that the use of this technology to visualize PGs and help avoid postoperative hypocalcemia after total thyroidectomy [24,38]. We are currently investigating the impact of NIRAF detection through two clinical trials to systematically assess the benefits of PTeye™ during thyroidectomy or parathyroidectomy [39,40].

In conclusion, we have found that in practice PTeye™ is highly accurate and overall, greatly improves the surgeon's confidence in PG identification thus allowing the operator to move forward more assuredly. In this manner, the surgeons will need to worry less about whether there was tissue misidentification during a parathyroidectomy or if there were sufficient PGs left behind after thyroidectomy to ensure a euparathyroid state for the patient. This increase in surgeon confidence for confirming PGs was described by all three participating surgeons and felt to occur irrespective of surgeon experience level. As with the implementation of any new technology, there is bound to be a learning curve with PTeye™ as its utility becomes more widespread in the surgical community. Overall, PTeye™ is a user-friendly and easy to interpret platform that can aid surgeons in identifying PGs. More extensive and large-scale studies with feedback from surgeons at other surgical centers will be needed to corroborate our current findings.

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Data Availability Statement

Data that support the findings of this study will be made available from the corresponding author upon reasonable request.

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Synopsis

Near infrared autofluorescence (NIRAF) could be useful for label-free intraoperative parathyroid gland identification during thyroid and parathyroid procedures. This study describes the early clinical impressions of 3 high-volume surgeons who tested the probe-based NIRAF detection system - PTeye™ - for identifying parathyroid glands in 83 prospectively enrolled patients.

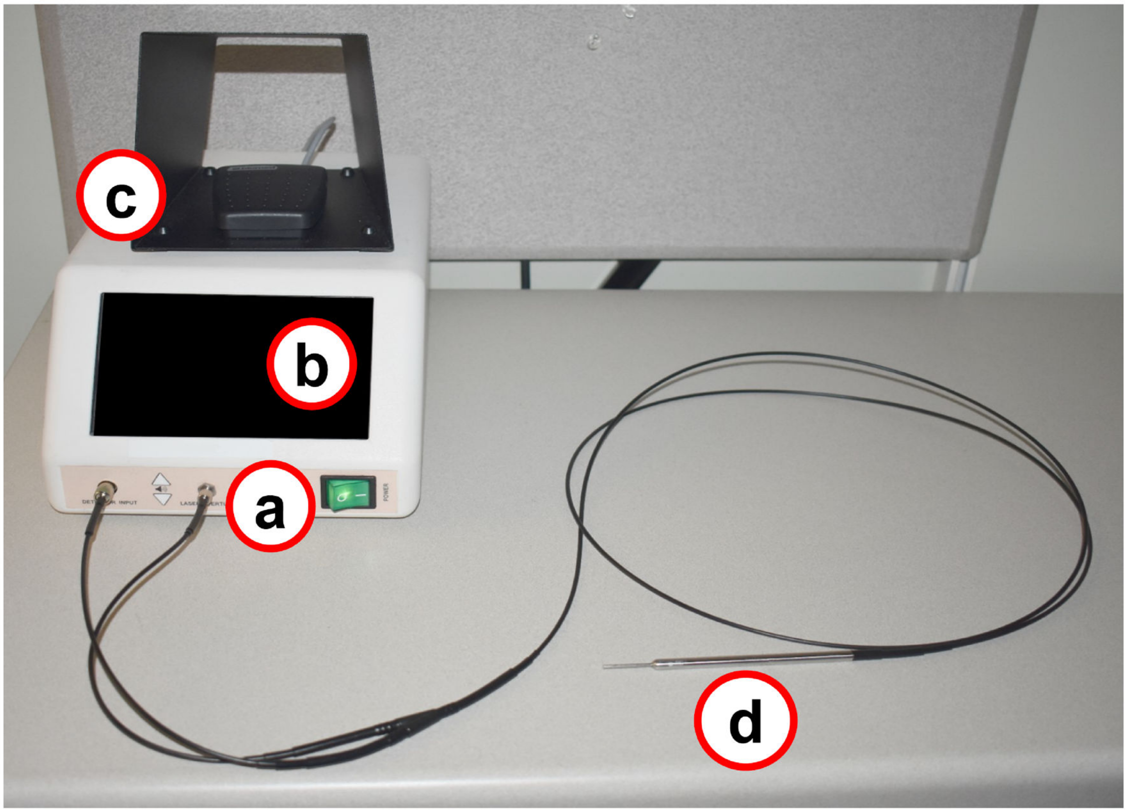

Figure 1:
Probe-based near-infrared autofluorescence (NIRAF) detection system – PTeye™. The device consists of (a) a console that houses a near-infrared (NIR) laser and a detector, (b) a display that informs the surgeon whether tissue is a parathyroid or not, (c) a foot-pedal for activating the NIR laser for tissue measurements and (d) a sterile detachable fiber probe that is placed in contact with the target tissue. (Figure adapted from Solórzano et al.[34])

Table 1:

Protocol designed for PTeye™ after surgeons' learning curve with initial 19 patients.

Step of PTeye™ Use	**Description of Protocol**
Step 1: Set-up	Turn on and set up the device as instructed
Step 2: Thyroid exposure	Expose as much of the thyroid lobe and isthmus as possible. This may not be possible in cases with a substernal component and/or retropharyngeal thyroid extension. Ligation of the middle thyroid vein is recommended.
Step 3: Obtain the baseline	The goal is to assess the highest areas of autofluorescence on the thyroid so that baseline reflects its NIRAF heterogeneity. Place the sterile probe in contact with the thyroid, press the foot pedal to activate the NIR light to detect thyroid NIRAF. Repeat 5 times on the thyroid. After the fifth measurement, the device will automatically set the baseline. * If there is no thyroid the baseline can be set using neck muscle.
Step 4: Double-check the baseline	After the device baseline is set the surgeon should always scan/survey the thyroid/muscle with the probe to ensure accuracy of baseline NIRAF. To double-check the baseline- place the probe on the thyroid lobe and press the foot-pedal to scan the thyroid lobe in as many places as possible. If any areas show "high" detection ratios (ratios > 1.2) after the initial baseline, then the surgeon should aim to re-adjust the baseline to include those thyroid areas with high detection ratio. *Beware of subcapsular parathyroids when obtaining/checking baseline.
Step 5: Readjust the baseline if necessary	Turn the device off and then back on. Repeat Steps 3 and 4 above. The goal is to scan the thyroid with the probe and not detect any areas that give high detection ratios on the thyroid.
Step 6: Expose suspected PG tissue	Properly expose the tissue of interest before obtaining the NIRAF measurement. Obtain measurements at various locations on the possible PG tissue. Parathyroid adenomas tend to have heterogenous NIRAF and could have areas of low detection ratio and areas of very high ratios. *Always ensure that the probe tip is clean and free from tissue/blood residue before and after interrogation.*
Step 7: Interpreting the PTeye™ display	When the probe touches PG tissue, the device should typically display a detection ratio >1.2 and generate high-frequency auditory beep. The surgeon should however question low detection ratios that range from 1.2-2.0 particularly when he/she has low confidence that the tissue is a PG. Or when he/she has high confidence it is a parathyroid adenoma.
(a) During thyroidectomy	*The probe can be used to confirm PGs when the surgeon has high confidence. When the surgeon has lower confidence and the PG has not been visualized clearly, the surgeon can use the probe to interrogate or map suspicious PG, fat, thyroid, thymus, lymph nodes.*
(b) During parathyroidectomy	*The probe can be used to confirm PGs when the surgeon has high confidence. When the surgeon has lower confidence and/or the PG has not been localized or visualized clearly, the surgeon can use the probe to interrogate or map suspicious PG, fat, thyroid, thymus, and lymph nodes.*
(c) Excised specimen(s)	*Any removed specimen can be interrogated/scanned with the probe to look for possible PGs. The excised thyroid should be scanned with the probe to look for incidentally excised PGs. Parathyroid adenomas tend to have heterogenous NIRAF and could have areas of low detection ratio and areas of very high ratios.*

Table 2:

Definition and description of true positive (TP), false positive (FP), true negative (TN), and false-negative (FN) as determined for PTeye™ in this study. (FSA, Frozen section analyses)

	In situ tissues		Excised tissues	
	PTeye™ output	**Gold standard**	**PTeye™ output**	**Gold standard**
True Positive (TP)	Detection ratio > 1.2	The expert surgeon has HIGH/ MEDIUM confidence that tissue is parathyroid	Detection ratio > 1.2	FSA/Permanent histology is POSITIVE for parathyroid tissue
False Positive (FP)	Detection ratio > 1.2	The expert surgeon has LOW confidence that tissue is parathyroid	Detection ratio > 1.2	FSA/Permanent histology is NEGATIVE for parathyroid tissue
True Negative (TN)	Detection ratio < 1.2	The expert surgeon has LOW confidence that tissue is parathyroid	Detection ratio < 1.2	FSA/Permanent histology is NEGATIVE for parathyroid tissue
False Negative (FN)	Detection ratio < 1.2	The expert surgeon has HIGH/ MEDIUM confidence that tissue is parathyroid	Detection ratio < 1.2	FSA/Permanent histology is POSITIVE for parathyroid tissue

PTeye™ has been designed such that when detection ratio > 1.2, the device indicates a high probability of the tissue being parathyroid. Similarly, a detection ratio < 1.2 would suggest a low probability of the tissue being parathyroid.

Table 3:

Patient demographics and operative procedure information (CND, central neck dissection; MLND, modified lateral neck dissection).

Total cases using PTeye™	19 *(initial set)*	64 *(2nd set)*	**83 (overall)**
Age (years, range)	57 (20 – 75)	52 (22 – 83)	54 (20 – 83)
Gender			
Male	5 (26.3%)	18 (28.1%)	23 (27.7%)
Female	14 (73.7%)	46 (71.9%)	60 (72.3%)
Body Mass Index (kg/m^2, range)	28 (22 – 39)	30 (17 – 54)	29 (17 – 54)
Race			
Caucasian	16 (84.2%)	55 (85.5%)	71 (85.5%)
Non-Caucasian	2 (10.5%)	9 (13.3%)	11 (13.3%)
Unknown	1 (5.3%)	0 (1.2%)	1 (1.2%)
Ethnicity			
Hispanic	0 (0%)	2 (3.1%)	2 (2.4%)
Non-Hispanic	17 (89.5%)	62 (96.9%)	79 (95.2%)
Unknown	2 (10.5%)	0 (0%)	2 (2.4%)
Operative procedure			
Thyroidectomy	9 (47.4%)	28 (43.8%)	37 (45.6%)
Parathyroidectomy	10 (52.6%)	36 (56.2%)	46 (55.4%)
Parathyroid specific data			
Procedure			
Focused	1 (10%)	8 (22.2%)	9 (19.6%)
Bilateral neck exploration	9 (90%)	28 (77.8%)	37 (80.4%)
Re-operative surgery			
Yes	4 (40%)	3 (8.3%)	7 (15.2%)
No	6 (60%)	33 (91.7%)	39 (84.8%)
Diagnosis			
Primary hyperparathyroidism	10 (100%)	34 (94.4%)	44 (95.7%)
Tertiary hyperparathyroidism	0 (0%)	2 (5.6%)	2 (4.3%)
Thyroid specific data			
Procedure			
Thyroid lobectomy	4 (44.5%)	4 (14.2%)	8 (21.6%)
Total thyroidectomy	3 (33.3%)	19 (67.9%)	22 (59.5%)
Total thyroidectomy with CND	1 (11.1%)	1 (3.6%)	2 (5.4%)
Total thyroidectomy with CND and MLND	1 (11.1%)	2 (7.1%)	3 (8.1%)
Completion thyroidectomy	0 (0%)	1 (3.6%)	1 (2.7%)
Prophylactic thyroidectomy	0 (0%)	1 (3.6%)	1 (2.7%)
Diagnosis			
Multinodular goiter/thyroid nodule	1 (11.1%)	13 (46.4%)	14 (37.8%)
Hyperthyroidism (Graves/toxic nodule)	5 (55.6%)	10 (35.7%)	15 (40.6%)

Well-differentiated thyroid cancer	3 (33.3%)	3 (10.7%)	6 (16.2%)
Recurrent/residual thyroid disease	0 (0%)	1 (3.6%)	1 (2.7)
Multiple Endocrine Neoplasia, Type IIA *	0 (0%)	1 (3.6%)	1 (2.7)

*Asymptomatic patient underwent prophylactic thyroidectomy

Age, body mass index reported as median, all others n (%)

Table 4:

Concurrence between the surgeons' confidence in identifying parathyroid and PTeye™ output. (PG, parathyroid gland).

Surgeon's confidence in tissue being PG	In-situ (Final surgeon's opinion for validation)	Excised (FSA/ Permanent histology for validation)	Target tissues tested (n)	Device Positive: Detection ratio >1.2 (n)	True Positive: Detection ratio >1.2 (n, %)	False Positive: Detection ratio >1.2 (n, %)	Device Negative: Detection ratio <1.2 (n)	True Negative: Detection ratio <1.2 (n, %)	False Negative: Detection ratio <1.2 (n, %)
19 patients – initial set									
High (>75%)	33	21	54	54	52 (96.3)	2 (3.7)	0	0 (0)	0 (0)
Medium (50-75%)	1	1	2	2	2 (100)	0 (0)	0	0 (0)	0 (0)
Low (<50%)	8	6	14	3	2 (66.7)	1 (33.3)	11	11 (100)	0 (0)
Total	42	28	**70**	**59**	**56 (94.9)**	**3 (5.1%)**	**11**	**11 (100)**	**0 (0)**
64 patients – second set									
High (>75%)	108	64	172	172	169 (98.3)	3 (1.7)	0	0 (0)	0 (0)
Medium (50-75%)	25	0	25	23	22 (95.7)	1 (4.3)	2	2 (100)	0 (0)
Low (<50%)	62	7	69	18	6 (33.3)	12 (66.7)	51	51 (100)	0 (0)
Total	**195**	**71**	**266**	**213**	**197 (92.5)**	**16 (7.5)**	**53**	**53 (100)**	**0 (0)**
83 patients – overall									
High (>75%)	141	85	226	226	221 (97.8)	5 (2.2)	0	0 (0)	0 (0)
Medium (50-75%)	26	1	27	25	24 (96)	1 (4)	2	2 (100)	0 (0)
Low (<50%)	70	13	83	21	8 (38.1)	13 (61.9)	62	62 (100)	0 (0)
Total	**237**	**99**	**336**	**272**	**253 (93.0)**	**19 (7.0)**	**64**	**64 (100)**	**0 (0)**

Number of true positive, false positive, true negative and false negative (see Table 2) was determined by surgeon's judgement (for in-situ tissues) or histology (for excised tissues).

Table 5:

Distribution of non-parathyroid tissues in the dataset that was misclassified by PTeye™ (FP – false positives)

Tissue type	Number of FP readings (n, %)	Mean Detection Ratio	Range of Detection Ratios
Thyroid nodules	10 (52.5%)	3.1	1.4 – 12.3
Lymph node	4 (21.1%)	4.5	1.8 – 9.0
Brown fat	2 (10.5%)	8.4	5.7 – 11.0
Yellow fat	1 (5.3%)	1.5	1.5
Thymus	1 (5.3%)	1.4	1.4
Paratracheal tissue	1 (5.3%)	2.0	2.0
Total	**19 (100%)**	**3.8**	**1.4 – 12.3**

Table 6:

False positives and false negative levels with different thresholds set for Detection Ratios when using PTeye™. A Detection Ratio of 1.2 is the threshold set by the manufacturer of PTeye™ for parathyroid identification.

	Detection Ratio Threshold set in PTeye™ - 1.2	**High confidence**	**Medium confidence**	**Low confidence**	**Total**
83 patients (overall)		**226**	**27**	**83**	**336**
False Positive at 1.2		5	1	13	19
False Negative at 1.2		0	0	0	0
19 patients (Initial set)	***Detection Ratio not recorded***	***54***	***2***	***14***	***70***
False Positive at 1.2		2	0	1	3
False Negative at 1.2		0	0	0	0
64 patients (2nd set)	***Detection Ratio recorded***	***172***	***25***	***69***	***266***
False Positive at 1.2		3	1	12	16
False Positive at 1.5		3	0	9	12
False Positive at 1.8		3	0	6	9
False Positive at 2.0		2	0	6	8
False Negative at 1.2		0	0	0	0
False Negative at 1.5		0	0	0	0
False Negative at 1.8		1	1	0	2
False Negative at 2.0		1	1	0	2

Table 7:

Advantages and pitfalls when utilizing probe-based NIRAF detection system – PTeye™ in thyroid and parathyroid operative procedures (PG, parathyroid gland; FSA, frozen section analyses; PTH, parathyroid hormone).

	Advantages	Possible pitfalls
PTeye™ utilization in neck endocrine operative procedures	**1** Real-time intraoperative feedback on whether tissue is PG or not. **2** May reduce the use of FSA for PG tissue confirmation or before autotransplantation **3** May reduce the use of tissue aspirate for PTH level analysis. **4** Improves surgeon confidence at all levels of surgeon experience. **5** Can serve as a real-time intraoperative educational tool for trainees. **6** May expedite OR time by avoiding FSA or improving confidence on the identification of PG tissue.	**1** Failure in setting up PTeye™: Probe not properly connected or error arising from inaccurate baseline (FP or FN). **2** False positives: thyroid cancer, thyroid nodule, lymph nodes, and brown fat. Baseline set up to be lower than what it should be. **3** False negatives: Baseline set up to be higher than what it should be. The adenomatous region of a diseased gland may have low ratios due to heterogeneity of NIRAF typically observed in diseased PGs - leads to low and high ratios in the same gland. **4** PTeye™ does not assess parathyroid perfusion/ viability. **5** Recurring costs per probe as the sterile probe is meant to be disposed after each patient and is not reusable.

Table 8:

Clinical scenarios in which PTeye™ was found to be most helpful for endocrine surgeons (PG, parathyroid gland; FSA, frozen section analyses; PTH, parathyroid hormone)

Type of operative procedure		The clinical scenario in which PTeye™ was most beneficial
Thyroid procedures	**1**	Thyroid procedures where the surgeon saw only one PG with low confidence: In such scenarios, PTeye™ can help identify at least one PG before autotransplantation, if the gland is found to be devascularized by the surgeon.
	2	Finding incidentally removed PG(s): At the conclusion of each thyroid case, thyroid specimens can be scanned for accidentally excised PGs that can then be autotransplanted.
	3	Graves' Disease: Due to a hypervascular thyroid, PG identification can be challenging and can be aided with PTeye™
	4	Malignant thyroid disease: If the case involves lymph node dissection, PTeye™ can help identify at least one PG that could be autotransplanted, if found to be devascularized following extensive neck dissection.
	5	Hashimoto's thyroiditis with associated reactive adenopathy: PTeye™ can help discern lymph nodes from PG.
	6	Large multinodular/substernal goiters: PTeye™ can help identify PG(s) despite the distortion of anatomy.
Parathyroid procedures	**1**	Non-localized cases: PTeye™ can be used to scan thyroid, thyrothymic ligament, carotid sheath as necessary
	2	Concurrent Hashimoto's thyroiditis with associated lymphadenopathy: To discern lymph nodes from PG.
	3	Re-operative cases: PTeye™ can help identify and confirm PG in a scarred or distorted anatomical field.
	4	Localized and non-localized cases: PTeye™ can improve surgeon confidence at all levels of experience.
	5	PTeye™ may lead to a decrease in the use of FSA/tissue aspirate PTH analysis.