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18-AES-34R1 EDITED BY DR SARR Innovative operative guidance for label-free, real-time parathyroid identification- the PTeye.

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Abstract

Background: Difficulty in identifying the parathyroid gland (PG) during neck operations can lead to accidental PG excisions and post-surgical hypocalcemia. The PTeye (“parathyroid eye”) was developed to guide PG identification using a fiber-optic probe that detects near infra-red auto-fluorescence (NIRAF) from PGs as operating room (OR) lights remain on. An Overlay Tissue Imaging System (OTIS) was designed concurrently to detect NIRAF and project visible light precisely onto PG location.

Methods: The PTeye and the OTIS were tested in 20 and 15 patients respectively, while a modified near infrared imaging system (NIRIS) was investigated in 6 patients. All 41 patients underwent thyroidectomy or parathyroidectomy. System accuracy was ascertained with surgeon’s visual confirmation for in-situ PGs and histology for excised PGs.

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Disclosures

Professor Anita Mahadevan-Jansen and Vanderbilt University have a licensing agreement with AIBiomed Instruments (Santa Barbara, CA) for developing the PTeye. AIBiomed Instruments is the exclusive licensee of the intellectual property on the NIRAF detection technique from Vanderbilt University.

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Results: There was no observable difference between NIRAF of healthy and diseased PGs. The PTeye identified 98% of the PG, while the NIRIS and the OTIS identified 100% and 97% of the PGs respectively.

Conclusions: The PTeye can guide in real-time PG identification even with ambient OR lights. The NIRIS performs PG imaging with high sensitivity, while the OTIS enhances PG visualization directly within the surgical field without requiring display monitors. These label-free technologies can be valuable adjuncts for identifying PGs intraoperatively.

Introduction

Accidental excision or damage to a healthy parathyroid gland (PG) during thyroidectomy and the inability to identify diseased PGs during parathyroidectomy can result in post-surgical complications. Incidental PG removal occurs in 5 – 22 % of the thyroid operations(1) causing transient hypocalcemia (< 6 months) in 15 – 30% of cases or permanent hypocalcemia (> 6 months) in up to 7% of the patients (2). In comparison, failure to identify and remove diseased PGs occurs in 5 – 10% of parathyroidectomies and can lead to persistent hyperparathyroidism (3) necessitating repeat operation that is associated with greater rates of complication and costs (4, 5). Although preoperative imaging modalities, such as ultrasonography imaging, Technetium-99m sestamibi scintigraphy, and computed tomography (CT), can aid in localizing diseased PGs with varying success (6), many surgeons still identify PGs intraoperatively using visual examination where the accuracy can vary depending on experience (7, 8). PG tissue is ultimately confirmed by frozen section analysis and indirectly by intraoperative parathyroid hormone (IOPH) assays that are invasive, require repeat sampling and need a wait time of 20 – 30 minutes per sample (9, 10). Therefore a non-invasive, label-free, rapid, yet highly accurate intraoperative tool would be very valuable in identifying PGs.

Paras *et al.* was the first to demonstrate non-invasive and label-free PG identification regardless of disease state using near-infrared (NIR) auto-fluorescence detection. This finding was subsequently validated with high accuracy by McWade *et al.* (11, 12). The phenomena is based on the fact that PGs emit a stronger NIR auto-fluorescence (NIRAF) signal compared to adjacent neck tissues, which has been investigated with promising results by several other groups (13–16). Among the various systems that have been explored for NIRAF-based PG identification, the spectroscopy-based systems with hand-held fiber-optic probes present tissue NIRAF as spectral data, while NIR imaging systems depict grey-scale images on remote display monitors. Despite high accuracy in PG identification, both these modalities present data in a format not easily utilized by surgeons. Although NIR imaging systems provide valuable spatial information about the PG, the images may be subject to erroneous interpretations, because alignment of anatomic structures observed in NIR images may not be easily translated easily to what is visualized directly in the operative field (17, 18). Both these modalities are also prone to interference from NIR components in operating room (OR) lights during tissue NIRAF detection, requiring OR lights to be switched off frequently causing surgical work-flow interruption.

To address the described challenges, we optimized our previous fiber-based spectroscopy system (11, 12) and developed a handheld surgical guidance device called the PTeye (AIBiomed Inc., Santa Barbara, CA and Vanderbilt University, Nashville, TN) that can optimally function with ambient OR lights and has a distinct user-interface that can be interpreted more easily by surgeons. In parallel, we developed an Overlay Tissue Imaging System (OTIS) that collects tissue NIRAF signal and projects it as a visible image directly onto the operative field, thus minimizing the need for remote display monitors and incorrect image interpretations.

In this study, we sought to evaluate the performance of these two novel devices in accurately identifying or visualizing PGs in comparison with a modified commercial NIR imaging system. Because most available NIR imaging systems are designed primarily for detecting NIR fluorescence from contrast agents such as indocyanine green, this system was modified for label-free PG visualization as described earlier (19). This study eventually aims to showcase the various technologic innovations that could ensure rapid, non-invasive, label-free intraoperative PG identification with minimal work-flow disruption, while assessing merits and limitations for all the three devices.

Methods

Patient selection.

Patients (18–99 years of age) who presented at the Vanderbilt Endocrine Surgery Center for thyroidectomy and/or parathyroidectomy were recruited based on the eligibility as assessed by the respective surgeon during preoperative assessment. Informed written consent was obtained from all patients recruited for this study which was approved by the Institutional Review Board (IRB) of Vanderbilt University (IRB# 070795, 141648). Forty one patients were recruited: 20 for the PTeye, 6 for the modified NIR imaging system, and 15 for the OTIS. Patient data were acquired and stored in compliance with the HIPAA privacy rule.

NIRAF detection with the PTeye.

The PTeye (Figure 1) comprises (i) a console encasing a 785 nm laser source and a detector, (ii) a detachable and sterilizable fiber optic probe, (iii) a foot-pedal to activate NIRAF measurements, and (iv) a display panel. The PTeye probe delivers laser light at a power of 20 mW over a spot size of ~ 400 μ m. Although it is based on the earlier system (11, 12), the internal circuitry of the PTeye is designed to detect NIRAF without interference from ambient OR lights. Tissue NIRAF recorded with PTeye is conveyed (i) to the display panel and (ii) to the loudspeaker as auditory feedback. The display panel informs the surgeon on (i) the ‘Detection Level’ – absolute tissue NIRAF intensity, (ii) the ‘Detection Ratio’ – tissue NIRAF normalized to the thyroid NIRAF intensity, and (iii) the ‘Detection Percentage’ – the PTeye confidence in identifying PGs (calibrated to the ‘Detection ratio’). The auditory feedback commences once the ‘Detection Ratio’ reaches a threshold value set for PG identification (11, 12).

The surgeon first confers the degree of confidence in having identified PG tissue as high, moderate, or low, based on visual inspection of the tissue in view. The surgeon then places

the hand-held probe of the PTeye on the tissue site and presses the foot-pedal, following which tissue NIRAF intensity is displayed in real-time with the OR lights remaining on. In each patient, a NIRAF baseline was first established on the thyroid so that subsequent tissue NIRAF measurements in the patient could be normalized to this thyroid baseline for obtaining the 'Detection ratio' described earlier. The auditory feedback volume was kept inaudible and the PTeye display panel was turned away to decrease bias of the surgeon's judgement.

NIRAF imaging with the modified commercial NIR imaging system.

The commercial NIR imaging system is composed of a 3-chip, color camera with an integrated zoom lens (Karl Storz, PDD Camera El Segundo, CA) driven by a control unit (Karl Storz, Tricam SL, El Segundo, CA) (19). The system has a spatial resolution of 170 μm on a surgical field measuring 5 cm $\times$ 5 cm, while the 785 nm laser evenly illuminated the operative field at 1 W/cm². This commercial NIR system was modified to block the 785 nm laser beam used, while allowing white light and NIRAF image capture (Figure 2). On finding a parathyroid candidate, the surgeon degree of confidence was first recorded following which NIRAF images were acquired with the OR lights turned off.

Parathyroid visualization with the OTIS.

The OTIS, seen in Figure 3A, was custom-built consisting of (i) a 785 nm diode laser (Innovative Photonics Solutions, Monmouth Junction, NJ), (ii) a NIRAF image collection unit, (iii) coupling optics, (iv) a visible light projector, (v) focusing optics, and (vi) an image processing laptop. The NIRAF image collection unit includes a filtered NIR camera (Basler AG, Ahrensburg, Germany). At a distance of 50 cm from a operativefield measuring 5 cm $\times$ 6.25 cm, the OTIS has a spatial resolution of 176 μm . When the operative field is diffusely illuminated with the 785 nm laser at an irradiance of 11.5 mW/cm², tissue NIRAF signal is picked by the NIR camera through the coupling optics as seen in Figure 3B. Raw NIR images are then relayed to the image processing laptop and subsequently transmitted to a visible light projector (AAXA Technologies, Irvine, CA) which overlays a visible image through focusing optics precisely onto the operativefield. An additional color camera (Basler AG, Ahrensburg, Germany) is integrated to record the projected overlay images. The components of OTIS are fixed onto a surgical support arm that can be positioned at any required angle by the surgeon using a disposable sterile handle (Figure 3A).

Prior to each patient testing, spatial precision of the OTIS projected image wa assessed using a grid sketched with fluorescent ink and calibrated accordingly. Once a parathyroid candidate ws seen, the surgeon confidence level in visually identifying each parathyroid gland was noted. The OTIS was then positioned by the surgeon above the region of interest with the help of a projected visible white grid. After the OR lights were turned off, NIRAF signals were collected, processed, and projected directly as visible green images onto the surgical site. The surgeon looked away during the OTIS projection to keep surgical decision-making unbiased.

Data Analysis.

NIRAF intensity was normalized to the thyroid NIRAF baseline to generate 'Detection ratio' for the PTeye, while NIRAF intensity obtained with the NIR imaging system and the OTIS was standardized to that of the adjacent tissue (background) to obtain the NIRAF ratios. A 2-tailed Student's t-test was used to compare measured ratios of parathyroid and non-parathyroid tissues with values of $p < 0.05$ being considered statistically significant. Detection rate for each system was determined by correlating the number of tissues deemed PG positive by the system (Threshold: Detection or NIRAF ratio > 1.2) with the number of PG tissues confirmed using histology for excised or biopsied PGs, or visual inspection by participant surgeons. Continuous variables are expressed as mean $\pm$ standard deviations when appropriate.

Results

Table 1 summarizes the demographics of the 41 patients recruited for this study. Measurements were obtained using the PTeye on 55 PGs (107 sites) and 198 non-parathyroid tissues (i.e. thyroid, fat, lymph node, muscle and trachea) in 20 patients. The modified NIR imaging system was tested over 9 PGs in 6 patients while the OTIS was evaluated across 35 PGs in 15 patients.

The hand-held probe of the PTeye was utilized as seen in Figure 4A in the presence of ambient OR lights to first establish a thyroid NIRAF baseline (Figure 4B) and obtain subsequent tissue measurements. Examples of 'positive' and 'negative' measurements for PG as indicated on the PTeye display are represented in Figure 4C and 4D respectively. Detection ratio from PGs measured 3.6 ± 1.6 , when compared to nonparathyroid tissues (i.e. thyroid, fat, muscle, lymph nodes and trachea) that measured 0.7 ± 0.4 . The detection ratios of healthy PGs ($n=33$) was measured to be 3.8 ± 1.7 and that for diseased PGs ($n=22$) was found to be 3.3 ± 1.6 . Based on these ratios, the PTeye yielded a 97% sensitivity (104/107 parathyroid measurements) and 95% specificity (188/198 non-parathyroid measurements). The surgeons found 50 PGs (detection rate: 91%) with high or moderate confidence, using simple visual examination by relying on their individual experience. In comparison, the PTeye identified 54 of 55 PGs with a 98% detection rate.

The modified NIR imaging system was investigated for PG identification as illustrated in Figure 5A with the OR lights off. The operative field with the PG as visualized with the naked eye is represented by Figure 5B and the corresponding NIRAF image as displayed on the system monitor can be seen in Figure 5C. PGs exhibited NIRAF ratios that were approximately 2.1 times greater than that of the non-parathyroid background. NIRAF ratios of healthy PGs ($n = 6$) measured 2.2 ± 0.4 (HAVE THE AUTHORS EXPRESS THIS VALUE AS THE MEAN AND RANGE NO STANDARD DEVIATION), while the diseased PGs ($n = 3$) recorded 1.9 ± 0.3 (SAME EMAN AND RNGE HERE). Both the NIR imaging system and surgeon's visual confirmation yielded a 100% detection rate (9 out of 9 PGs).

Feasibility of enhancing PG visualization with OTIS is depicted in Figure 6A. As described earlier, the OTIS is regularly calibrated with a fluorescent ink grid (Figure 6B) to ensure that

the visible projected image is aligned precisely (Figure 6C). Routine observation of operative field for a healthy PG (Figure 6D) without using the OTIS can be compared with enhanced visualization of the same gland using visible green light (Figure 6E) from the projection overlay of the OTIS. This is also demonstrated with similar precision for diseased PGs (Figure 6F and 6G). NIRAF ratios obtained with the OTIS for healthy ($n = 19$) and diseased ($n = 16$) PGs were measured to be 4.4 ± 1.1 and 6.0 ± 1.7 respectively. Overall, the OTIS successfully visualized 34 out of 35 PGs with a detection rate of 97%, while all PGs were accurately identified by the surgeon on visual examination. In one patient, a tissue suspected to be PG with low confidence by the surgeon was tested with OTIS and did not receive any visible projection overlay. This tissue was later histologically confirmed to be benign thyroid tissue indicating the specificity of OTIS.

All the three optical modalities rely on detecting NIRAF of PGs in real-time and do not require any contrast agent administration. While all the three approaches demonstrate high and comparable PG detection rates when correlated with histologic validation (see Table 2), the modified NIR imaging system and the OTIS provide additional spatial information regarding the PGs with the OTIS enabling direct PG visualization in the operative field. The PTeye scores over the other two modalities with its ability to identify PGs despite ambient OR lights that typically interferes with tissue NIRAF measurements. Quantitative comparison of the 'Detection' ratio (for PTeye) and NIRAF ratio (for the modified NIR imaging system and the OTIS) is represented in Figure 7.

Discussion

Accurately identifying and then preserving PGs can prove challenging during neck operations due to distorted anatomy from previous interventions (20), presence of ectopic or multiglandular diseased PGs (7), extensive thyroid surgery with or without central neck lymph node dissection (21) and varying experience or skillset of the surgeon (8). In such scenarios, rapid and label-free intraoperative guidance to identify PGs would be beneficial for minimizing post-operative morbidity. Here, we showcase various innovative optical approaches that rely on NIRAF detection to provide surgical guidance for intraoperative PG identification. In our study, we evaluated and compared the performance of (i) the PTeye – a device that utilizes a simple, handheld fiber-optic probe to guide PG identification, even in the presence of ambient OR lights, (ii) a modified version of a commercial NIR imaging system, and (iii) the OTIS – an imaging approach that projects visible images directly onto the operative field to enhance PG visualization.

Each system is endowed with a distinct set of features as summarized in Table 3. The main advantage of the PTeye is that it is a compact device ($33 \text{ cm} \times 22 \text{ cm} \times 15 \text{ cm}$) with a simple, hand-held probe that aids in PG identification in the presence of OR lights, ensuring easy usage, portability, and storage. In contrast, the PTeye provides point-based measurements that does not provide spatial information of the structures surrounding the PGs that may be useful for the surgeon. Moreover, the PTeye has a contact-based approach mandating either sterilization of the fiber-optic probe for reusability in each new patient or using cost-effective disposable probes. These limitations are offset when utilizing the NIR imaging systems that can achieve widefield imaging and provide spatial information of the PGs in

relation to adjacent tissue structures. While commercial NIR imaging systems can image a field of view of 900 cm² (22), our modified NIR imaging system covered a field of view measuring 5 cm × 5 cm (25 cm²), which was adequate considering that routine thyroid and parathyroid incisions range from 3 – 6 cm (23). Although tissue contact is not required for this system, the NIR camera would still need to be covered with a sterile barrier material mainly, because most commercial NIR cameras can capture images only at a working distance of 4 – 12 inches (10 – 30 cm) from the operative field (22), which intrudes into the recommended sterile zone of 18 inches (50 cm) from the surgical plane (24). While NIRAF images are highly informative, grey-scaled images as displayed in Figure 5C may be interpreted incorrectly without adequate operative experience. In addition, having to stare at NIRAF images on a remote display monitor and correlate it with the real operative field could be tedious and distracting. The OTIS can circumvent this limitation by projecting NIRAF of PG as a visible image directly onto the operative field, thus providing true spatial context for the signal from PGs (Figure 6E and 6G). With the current system design, the OTIS can successfully function at a distance of 18 inches (50 cm) from the operative field and thus do not need to meet sterility requirements, unlike for the PTeye or the NIR imaging systems.

Ambient OR lights can prove problematic for NIRAF measurements with the NIR imaging system and the OTIS necessitating complete darkness in the OR, thus interrupting the surgical work-flow. The applicability of these two optical modalities may also be limited when multiple PGs are present in a single field of view – a PG with greater NIRAF may obscure other PGs in an acquired image – or when PGs are located at ectopic sites – tracheoesophageal groove or retro-esophageal region – that are not as easily visualized with imaging systems. In such scenarios, the PTeye is more convenient to use as the hand-held probe can be easily positioned onto the target site for NIRAF measurements. The optimal functionality of PTeye during tissue NIRAF measurements even in the presence of OR lights is an added advantage that is currently unmet by standard NIR imaging systems.

It should be emphasized that the PGs needed to adequately dissected and exposed for evaluation with all the three devices described in this study. This implies that NIRAF of PGs is more useful to confirm tissue identity only after the suspect tissue is first visualized by the surgeon. Because all three modalities employ NIR wavelengths that have limited tissue penetration depth (in mm), the potential to locate ‘missing’ or deeply situated PGs is restricted at least using the described approaches at present. While some preliminary work of visualizing NIRAF of PGs below layers of fibrofatty tissue has been reported (14), further investigations are needed to fully understand depth-based parathyroid NIRAF detection. Operative expertise still remains vital in correctly exposing, identifying, and subsequently preserving PGs in these scenarios.

The PG detection rate for the PTeye, the (modified) NIR imaging system and the OTIS stand at 98%, 100% and 97% respectively, suggesting that all three systems are viable operative guidance tools to aid in identifying PGs. Preference for either of the described NIRAF-based approaches would be governed by the surgeon’s choice, ease of use for the OR personnel, effortless integration to the existing workflow, availability, and cost of the device. Among the three systems, the learning curve for intraoperative implementation would be the shortest

for the PTeye, as the instrument handling is very similar to nerve monitoring devices – Nerve Integrity Monitoring System (Medtronic, Dublin, Ireland) or Nerveana (Neurovision Medical Products, Ventura, CA, USA) – frequently used during thyroid operations (25) that most surgeons are already familiar with. Moreover, because this technique does not require OR lights to be switched off, the PTeye is relatively easier to use without disrupting surgical workflow compared to the other two modalities. Despite its inability to function with OR lights, using the NIR imaging system should not be complicated, because surgeons have previously used similar modalities previously for visualization of tumor margins, sentinel lymph node mapping, lymphatic drainage, and blood flow visualization (22).

Notwithstanding the novel results provided by the OTIS, this system would have the longest learning curve of the three, because the device is still in developmental stages and requires a user-friendly format prior to clinical use. Among the three modalities, NIR imaging systems are already commercially available worldwide (22), some of which have already been investigated for intraoperative PG identification with high accuracy (13–16). These systems, however, are not FDA-approved for label-free parathyroid NIRAF detection as yet. Similarly the PTeye is currently under FDA evaluation and yet to become commercially available, while the OTIS needs to be optimized for a more simplistic user-interface and operability inside the OR prior to commercialization. While cost comparison between the three modalities is not presently feasible due to the aforementioned factors, it must be noted that purchasing either of the three systems is eventually a one-time investment for the hospital followed by periodic maintenance costs to ensure optimal performance when compared to recurrent costs incurred per frozen section analysis and prolonged duration of anesthesia maintenance for each patient.

Despite the various innovations for intraoperative PG identification elaborated in this study, these optical tools may only serve as adjuncts to the experience, skill set, and knowledge of the surgeon. Experienced endocrine surgeons can correctly identify PGs without major challenges, by simply relying on visual examination and their experience. Data analysis indicates that our participant surgeons accurately identified PGs by visual confirmation in 91% of the PGs assessed with the PTeye, and 100% for those tested with the NIR imaging system and the OTIS (overall surgeon accuracy: 95%). NIRAF detection modalities for PGs may therefore, stand to be more beneficial for early career or low volume center surgeons who tend to have greater complication rates (8). In procedures with extensive thyroid and associated lymph node dissection, even highly experienced surgeons face the possibility of incidental damage to the PGs or its vasculature, which can be minimized by detecting NIRAF of PGs. This approach can then aid in decision-making to auto-transplant an accidentally excised PG. Although these NIRAF-based modalities may not differentiate between healthy and diseased PGs, these techniques can still be valuable during parathyroidectomies, because surgeons are occasionally challenged in distinguishing between a diseased PG and other tissues, such as benign thyroid nodule or an enlarged lymph node. Nonetheless for parathyroidectomies, these NIRAF-based modalities works best as an adjunct tool along with the existing protocol of IOPTH monitoring. Another prime advantage gained with these real-time devices would be a decrease in the time and expense associated with each unnecessary frozen biopsy sent for PG confirmation. A recent study demonstrated that NIRAF-based PG detection could potentially improve patient outcomes

by minimizing the incidence of postsurgical hypocalcemia after thyroid operations(16). Innovative optical modalities developed for NIRAF detection in PGs could thus be used for label-free surgical guidance to conserve healthy PGs during thyroid operations or aid in removing diseased PGs through parathyroidectomies for decreasing postoperative complications and needless costs.

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Figure 1:

The PTeye system – consisting of 1) the console that encloses the laser and detector, 2) a detachable and sterilizable fiber-optic probe, 3) a foot-pedal that activates tissue near-infrared autofluorescence (NIRAF) detection and 4) a display that intuitively informs the surgeon if the tissue is parathyroid or not.

Figure 2:

A modified commercial near infra-red (NIR) imaging system. The system comprises of 1) a 785 nm laser source (for tissue illumination), 2) a commercial NIR camera (Karl Storz) that has been modified to permit NIRAF and white light capture of the operative field and 3) a control unit with a remote display monitor to visualize the acquired NIRAF images.

Figure 3:

A) Components of the Overlay Tissue Imaging System (OTIS) – 1) a 785 nm laser source output, 2) a near infra-red (NIR) camera, 3) coupling optics 4) a visible image projector, 5) focusing optics for outgoing projection signal and 6) a color camera to image the operative field. B) Workflow in the OTIS - NIRAF detection from tissue followed by visible image projection overlay directly onto the tissue within the operative field.

Figure 4:

A) Hand-held fiber-optic probe of the PTeye being placed onto tissue suspected to be parathyroid. B) Thyroid NIRAF baseline being established for the PTeye with measurements from 5 random spots on the thyroid. C) Display interface when the tissue is identified as 'positive' for parathyroid and D) when the tissue is identified as 'negative' for parathyroid. Detection ratio > 1.2 was set as the threshold for parathyroid identification. The auditory feedback was kept inaudible and display interface was turned away from the surgeons during this study.

Figure 5:

A) Intraoperative workflow when using the modified commercial near-infrared (NIR) imaging system. B) White light image of the surgical field with a healthy parathyroid gland indicated by the black arrow. C) Corresponding NIRAF image showing the same parathyroid gland (denoted by the white arrow) with significantly higher NIRAF intensity compared to adjacent tissues in the background. Note: The surgeons were blinded from the NIRAF images during this study.

Figure 6:

A) Intraoperative workflow while using the OTIS. B) Grid sketched with near infrared (NIR) fluorescent ink. C) The OTIS calibration with the projected image overlay aligning precisely over the actual inked grid. D) Surgical field without the projection overlay. White arrow denotes a healthy parathyroid gland as seen by the surgeon. The projected white rectangle aids in positioning the OTIS over the region of interest. E) With the visible projection, the parathyroid is overlaid precisely with bright green light, with no overlay on the adjacent tissue structures. F) Operative field without projection overlay and G) with projection overlay for a diseased parathyroid gland. Note: The surgeon looked away during the projection overlay.

Figure 7:

Comparison of normalized NIRAF intensities – Detection ratio for the PTeye and NIRAF ratio for the the NIR imaging system and the OTIS – for parathyroid and non-parathyroid tissues. Parathyroid tissue exhibited greternormalized NIRAF intensities than non-parathyroid tissue consistently across all the three optical modalities. (** - p-value < 0.05).

Table 1:

Demographics of patients evaluated with the NIRAF based guidance modalities for parathyroid identification.

Patient Demographic variables	PTeye	(Modified) NIR imaging system	OTIS
Total number of patients	20	6	15
Age (in years)			
Mean $\pm$ Standard Deviation (<i>Range</i>)	46.8 $\pm$ 14.2 (21 – 70)	54.8 $\pm$ 17.6 (29 – 75)	55.6 $\pm$ 12.7 (29 – 70)
Gender			
Male	4 (20.0%)	3 (50.0%)	3 (25%)
Female	16 (80.0%)	3 (50.0%)	12 (75%)
Ethnicity			
Caucasian	17 (85.0%)	5 (83.3%)	14 (93.3%)
Non-caucasian	3 (15.0%)	1 (16.7%)	1 (6.7%)
Body Mass Index (in kg/m²)			
Mean $\pm$ Standard Deviation (<i>Range</i>)	30.6 $\pm$ 7.9 (24.2–50.21)	26.5 $\pm$ 6.9 (16.4–33.1)	29.0 $\pm$ 7.7 (20.5 –47.8)
Disease type			
Benign thyroid disease	8 (40.0%)	2 (33.3%)	4 (26.6%)
Malignant thyroid disease	1 (5.0%)	1 (16.7%)	5 (33.3%)
Graves' Disease			
Primary Hyperparathyroidism	1 (5.0%)	0 (0.0%)	1 (6.7%)
Solitary adenomas	5 (25.0%)	2 (33.3%)	3 (20%)
Multiglandular disease	3 (15.0%)	0 (0.0%)	1 (6.7%)
Secondary hyperparathyroidism			
Concurrent thyroid and parathyroid disease		0 (0.0%)	1 (6.7%)
Primary Hyperparathyroidism	1 (5.0%) *	1 (16.7%) **	0 (0.0%)
Secondary hyperparathyroidism	1 (5.0%) *	0 (0.0%)	0 (0.0%)

* associated with malignant thyroid disease

** associated with benign thyroid disease

Table 2:

Detection rates for the three NIRAF based optical modalities when correlated with histological validation.

	PTEye	(Modified) NIR imaging system	OTIS
Total number of participant surgeons	2	2	1
Tissues identified as parathyroid by visual examination (surgeon's degree of confidence)			
High	46 (83.6%)	9(100.0%)	.35 (97.2%)
Moderate	4 (7.3%)	0 (0.0%)	0 (0.0%)
Low	5 (9.1%)	0 (0.0%)	1 (2.8%)
Number of potential parathyroid glands seen	55	9	36 [‡]
Number of parathyroid glands validated by histology	23	3	16
Accuracy			
Surgeon's detection rate for parathyroid glands (visually identified with high or moderate confidence)	50/55 (90.9%)	9/9 (100.0%)	35/35 (100.0%)
Device detection rate for parathyroid glands (glands left in-situ + excised glands validated by histology)	54/55 (98.2%)	9/9 (100.0%)	34/35 (97.1%)
Device detection rate for parathyroid glands (only excised glands validated by histology)	22/23 (95.6%)	3/3 (100.0%)	16/16 (100.0%)

[‡]one specimen confirmed as benign thyroid tissue

Table 3:

Overview of the features and performance accuracy of the three NIRAF based optical modalities.

	PTeye	(Modified) NIR imaging system	OTIS
Features			
Data output	NIRAF detection intensity, detection ratio, device confidence in parathyroid identification (in %)	Grey scale NIRAF images on display monitor	NIRAF projected as visible image (ill green color) onto surgical field
Functional component	Hand-held optical probe for point-based NIRAF detection	Portable NIR camera	Portable image projector
Spatial information	None	Yes	Yes
Working distance from surgical field	Contact based modality	15 cms	50 cms
Power fluence	20 mW over 600 pm spot size	1 W/cm ²	11.5 mW/cm ²
Spatial Resolution	N/A	170 µm	176 µm
Field of view per measurement	600 µm (point-based measurement)	5 cm × 5 cm	5 cm × 6.25 cm
Auditory feedback	Yes. (Inaudible during study)	No	No
Visual feedback	Device display	Remote display monitor	Direct projection onto surgical field
Sterility requirements	Sterilization for the detachable fiber-optic probe	Sterile barrier medium required for NIR camera	None. Disposable sterile handle attached for system positioning
Contrast agents	Not required	Not required	No required
Ambient OR light interference	No	Yes	Yes
Commercial availability	No	Yes	No
Performance			
	20 patients	6 patients	15 patients
Number of parathyroid glands assessed	55	9	35
Detection rate	98.2% (54/55 parathyroids)	100% (9/9 parathyroids)	97.1% (34/35 parathyroids)
Healthy parathyroid glands	100% (33/33 parathyroids)	100% (6/6 parathyroids)	94.7% (18/19 parathyroids)
Diseased parathyroid glands	95.5% (21/22 parathyroids)	100% (3/3 parathyroids)	100% (16/16 parathyroids)
Sensitivity	97.2% (104/107) *	N/A **	97.1 (34/35)
Specificity	94.9% (188/198)	N/A **	100% (1/1) ***
Overall accuracy	95.7%	N/A **	97.2%
Advantages			
	(i) Compact and portable unit (ii) Hand-held point-based guidance technique (iii) Intuitive user-interface (iv) Functional with OR lights	(i) Wide field imaging technique (ii) Spatial information of parathyroid acquired (iii) Commercial devices available	(i) Spatial information of parathyroid acquired (ii) Enhanced visualization directly in surgical field (iii) No display interface or monitors required
Disadvantages			
	(i) No spatial information provided. (ii) Not commercially available as yet	(i) Affected by OR lights (ii) Interpretative errors due to mismatch between NIRAF image and surgical field of view	(i) Affected by OR lights (ii) User-interface requires further simplification (iii) Not commercially available as yet

* Measurement on 1–2 sites in all parathyroid glands

**
NIR imaging performed only for parathyroid glands and not for thyroid, fat, muscle

single non-parathyroid tissue tested - thyroid

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