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Parathyroid Gland Autofluorescence Characteristics in Patients With Primary Hyperparathyroidism

Richard H. Law
Henry Ford Health, rlaw1@hfhs.org

Katherine A. Larrabee
klarrab1@hfhs.org

Meredith Van Harn
Henry Ford Health, mvanhar1@hfhs.org

Michael C. Singer
Henry Ford Health, MSINGER1@hfhs.org

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Parathyroid Gland Autofluorescence Characteristics in Patients With Primary Hyperparathyroidism

Richard H. Law, MD; Katherine A. Larrabee, MD; Meredith Van Harn, MS; Michael C. Singer, MD

Objective: Near-infrared imaging for intraoperative parathyroid gland (PG) detection has recently commanded significant attention. The PTeye (Medtronic, Minneapolis, MN) is a probe-based system for near-infrared autofluorescent evaluation of PGs. This study was designed to evaluate the capabilities of the PTeye in the setting of surgery for primary hyperparathyroidism.

Study Design: Prospective, Cohort study.

Methods: This single-institution, prospective cohort study included all patients undergoing parathyroidectomy for primary hyperparathyroidism with presumed single gland disease from June 2020 to December 2020. Absolute intensity and intensity ratios, with the thyroid as the control tissue, were obtained for the adenoma, ipsilateral normal PG, and adjacent tissue. The ability of the PTeye to function when not in direct contact with tissue was measured.

Results: Twenty-two patients were included. The median intensity ratio for the in situ adenomas was 4.38 (interquartile range [IQR]: 2.03–5.87), ipsilateral normal PGs 6.17 (IQR: 3.83–7.67), strap muscle 0.47 (IQR: 0.30–0.60), and fat 0.20 (IQR: 0.17–0.47). All normal PGs and 21/22 adenomas demonstrated autofluorescence above the detection threshold. The PTeye functioned at a maximum distance of separation of 10 mm through saline medium and 6 mm through clear solid medium.

Conclusion: This study confirms the PTeye's ability to recognize PGs with a high degree of precision. The device was found to function properly even with the probe not in direct contact with the tissue. Although adenomatous PGs appear to demonstrate altered autofluorescent properties from normal PGs, additional research is required to determine if these differences are clinically useful.

Key Words: PTeye, primary hyperparathyroidism, parathyroid gland, parathyroidectomy, autofluorescence.

Level of Evidence: 3

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INTRODUCTION

Finding and recognizing parathyroid glands (PGs) is a fundamental skill required for positive outcomes in both thyroid and parathyroid surgery. For thyroidectomy, this is the first step in preserving these glands, necessary to avoid postoperative hypoparathyroidism and hypocalcemia.[1,2] In parathyroidectomy, identifying the PGs is compulsory for surgical success. However, this can be a challenging and time-consuming endeavor, for even highly experienced surgeons.[3–8]

The use of fluorescence imaging technology to facilitate thyroid and parathyroid surgery has garnered significant clinical and research interest over the last several years. The ability to view and evaluate PGs with near-infrared (NIR) light seems to offer the prospect of overcoming some of the persistent challenges encountered during these surgeries.

Near-infrared imaging (NIRI) is currently being utilized in a number of ways to assess PGs. PGs possess a particularly intense intrinsic fluorescent nature that when stimulated with the proper wavelength of light can be seen with no augmentation or injected agent.[1,2] Although the fluorophore responsible for this autofluorescent (AF) quality has not yet been identified, near-infrared autofluorescence (NIRAF) has been shown to be effective at identifying PGs in the setting of both thyroid and parathyroid surgeries.[1,2]

NIRI not reliant on AF, in which a contrast material is injected to view the fluorescence generated by blood vessels of tissues, has also been investigated with PGs. For visualization of the vascularity of PGs, indocyanine green (ICG) is the preferred injection agent. In addition to allowing for evaluation of the perfusion of the PGs, ICG-enhanced NIRI can aid in their recognition.[1,2]

Several devices are available to surgeons to perform NIRAF or NIRI. Camera-based systems, such as Fluobeam (Fluoptics, Grenoble, France), offer a wide view of the surgical field and require limited pre-identification knowledge of the location of the PGs. As an alternative, a probe-based system has been developed. The PTeye device (Medtronic, Minneapolis, MN) is the only probe-based system currently available. Rather than an image on a screen showing varying degrees of brightness, the PTeye provides an absolute measure of the degree of AF of tissue (detection level) and a relative measurement of AF compared to the AF of the thyroid gland (detection

From the Department of Otolaryngology—Head and Neck Surgery (R.H.L., K.A.L., M.C.S.), Henry Ford Hospital, Detroit, Michigan, U.S.A.; Department of Public Health Sciences (M.V.H.), Henry Ford Health System, Detroit, Michigan, U.S.A.

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Send correspondence to Michael C. Singer, MD, Department of Otolaryngology, Henry Ford Hospital, 2799 W Grand Blvd, K-8, Detroit, MI 48202. E-mail: msinger1@hfhs.org

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TABLE I.
Descriptive Statistics for All Variables.

Variable	Response	Mean (SD) or N (%)	Median (Min, Max)
Total, N	22		
Age (yr)		62.3 (13.6%)	64 (25, 83)
Sex	Male	3 (13.6%)	
	Female	19 (86.4%)	
Body mass index (kg/m^2)		29.7 (5.0)	28.1 (22.6, 40.8)
History of radioactive iodine	No	22 (100%)	
	Yes	0 (0)	
History of kidney stones	No	15 (68.2%)	
	Yes	7 (31.8%)	
DEXA T < −2.5 forearm	N/A	4 (18.2%)	
	No	6 (27.3%)	
	Yes	12 (54.5%)	
Concurrent thyroid surgery	No	19 (86.4%)	
	Yes	3 (13.6%)	
Preoperative intact PTH (pg/mL)		125.9 (75.0)	115.0 (35.0, 357.0)
Preoperative vitamin D2 (ng/mL)		31.4 (15.0)	28.5 (13.0, 74.0)
Preoperative ical (mmol/L)		1.39 (0.10)	1.38 (1.21, 1.62)
Corrected serum calcium (mg/dL)		10.9 (0.6)	10.8 (9.9, 12.6)
Pre-incision ioPTH (pg/mL)		193.5 (140.1)	156.1 (116.4, 208.8)
Postexcision ioPTH (15-min)		26.6 (10.9)	28.5 (8.4, 49.7)
Maximum gland weight (mg)		1,270.7 (1,311.8)	595.0 (170.0, 5,000.0)

DEXA = dual-energy X-ray absorptiometry; ical = ionized calcium; ioPTH = intraoperative parathyroid hormone; Max = maximum; Min = minimum; N/A = not available; PTH = parathyroid hormone; SD = standard deviation.

ratio [DR]).[1,2] Tissue demonstrating a ratio of 1.2 or greater has been shown with a high degree of sensitivity and specificity to represent parathyroid tissue.[6]

Although the PTeye received Food and Drug Administration approval in November 2018, there is still limited data available on the precise capabilities of the device. Still even fewer studies have examined quantifiable differences between normal and adenomatous PGs. The primary aim of this study was to further explore the abilities and limitations of the PTeye. This included assessment of the PTeye's capacity to measure AF when not in direct contact with the tissue being interrogated. A secondary aim of this study was to begin to evaluate possible quantifiable AF differences between normal and pathologic PGs.

MATERIALS AND METHODS

This was a single-institution, prospective cohort study of 22 patients undergoing parathyroidectomy for primary hyperparathyroidism from June 2020 to December 2020. The study was approved by the Henry Ford Health System's Institutional Review Board (#14143). This study conforms to the ethical principles for medical research involving human subjects as described in the Declaration of Helsinki.

All patients were confirmed to have primary hyperparathyroidism with a range of indications for surgery. Inclusion criteria for the study included co-localizing, preoperative imaging studies highly suggestive of a single adenoma as the cause of the primary hyperparathyroidism. All patients underwent focused parathyroidectomy. Patients discovered to have multi-gland disease intraoperatively were excluded from the study.

TABLE II.
Six-Month Postoperative Metrics.

Variable	Response	Mean (SD) or N (%)	Median (Min, Max)
Total, N	15		
Postoperative intact PTH (pg/mL)		59.3 (29.9)	58.8 (28.0, 129.0)
Postoperative vitamin D25 (ng/mL)		31.6 (10.9)	32.5 (12.0, 58.0)
Postoperative ical (mmol/L)		1.18 (0.05)	1.18 (1.07, 1.25)
Postoperative corrected calcium (mg/dL)		9.6 (0.3)	9.6 (9.1, 10.2)
Outcome	Cure	15 (100%)	
	Incomplete	7 (46.7%)	

ical = ionized calcium; Max = maximum; Min = minimum; PTH = parathyroid hormone; SD = standard deviation.

TABLE III.
Autofluorescence Intensities: Absolute and Ratios.

Variable	Response	Mean (SD)	Median (Min, Max)
Thyroid AI baseline median		31.1 (13.5)	33.0 (9.0, 56.0)
In situ adenoma AI	Absolute	127.3 (67.5)	123.5 (3.3, 242.0)
	Ratio	4.7 (2.8)	4.4 (0.0, 12.4)
In situ normal parathyroid gland	Absolute	197.6 (84.0)	201.8 (35.7, 334.3)
	Ratio	6.5 (3.0)	6.2 (2.3, 14.8)
In situ strap muscle AI	Absolute	13.8 (6.0)	12.7 (5.3, 27.0)
	Ratio	0.7 (1.3)	0.5 (0.1, 6.3)
In situ fat AI	Absolute	10.2 (5.7)	8.8 (1.7, 26.7)
	Ratio	0.3 (0.2)	0.2 (0.0, 0.8)
Ex vivo adenoma AI (1-min)	Absolute	175.0 (111.2)	150.5 (19.0, 443.0)
	Ratio	6.3 (4.4)	5.2 (0.4, 19.1)
Ex vivo adenoma AI (15-min)	Absolute	192.4 (127.9)	171.8 (20.7, 539.3)
	Ratio	7.1 (5.3)	5.4 (0.5, 21.7)

1-min = 1-minute postexcision; 15-min = 15-minute postexcision; AI = autofluorescence intensity; Max = maximum; Min = minimum; SD = standard deviation.

Information collected via chart review included patient demographic information, symptoms, history of radioactive iodine treatment, prior neck surgeries, preoperative, intraoperative, and postoperative laboratory values, and pathology reports. All patients had fluorometric readings taken via the PTeye, which was used in the prescribed manner. The thyroid median baseline intensity served as baseline comparison from which the intensity ratios were calculated by the device. Both detection level and DR were obtained for the following: Adenoma in situ, the normal, ipsilateral PG, strap muscle, fat, and the adenoma ex vivo 1 minute after excision and 15 minutes after excision.

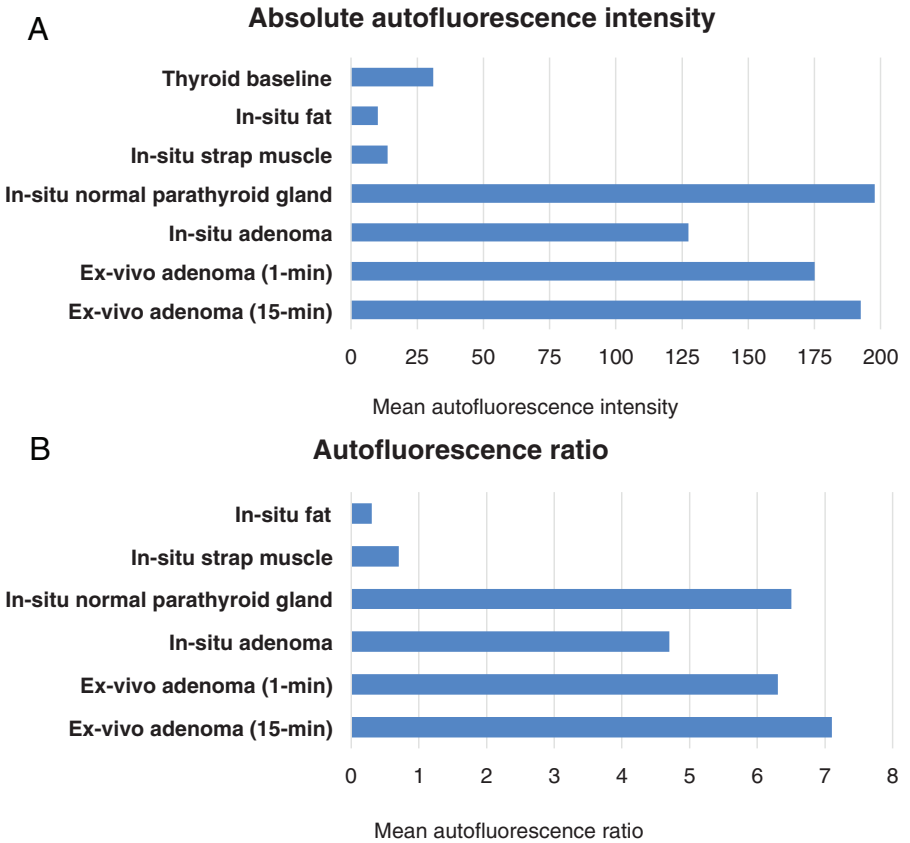

Fig. 1. (A) Mean autofluorescence intensity of examined tissues. Ex vivo adenoma is measured at 1-minute postexcision (1-min) and 15-minute postexcision (15-min). Thyroid tissue is measured at baseline prior to excision of the adenoma. (B) Ratio of autofluorescence compared to thyroid tissue. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

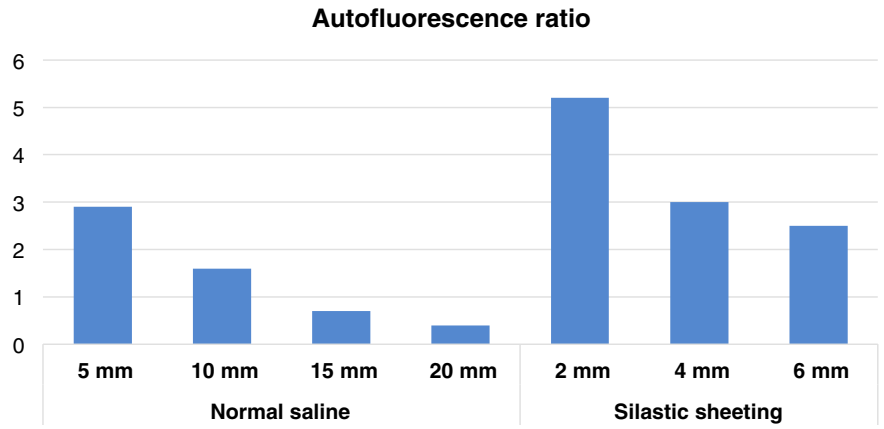

Fig. 2. Mean autofluorescence ratio of the excised adenoma in various settings. (1) The adenoma was submerged in saline of varying depths (5, 10, 15, and 20 mm), (2) the adenoma was placed under clear silastic sheeting of varying depths (2, 4, and 6 mm). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

To assess the ability of the PTeye to work when not in direct contact with the PG, a second data set was collected in 10 patients. In this phase of the study, the detection level and DR of the excised adenoma were determined by the PTeye when 1) a blue surgical drape was placed directly in between the probe and the adenoma, 2) the adenoma was submerged at the bottom of a graduated cylinder with saline of varying depths (5, 10, 15, and 20 mm) separating the surface of the gland and the tip of the probe, and 3) the adenoma was placed under clear silastic sheeting of varying depths (2, 4, and 6 mm).

Surgical Technique

All patients included in the trial underwent a minimally invasive (focused) parathyroidectomy. After the adenoma was identified and assessed with the PTeye probe, it was excised. The ipsilateral, normal PG was then found and interrogated with the probe. Adjacent fat and strap muscle were subsequently tested with the probe. In all cases, intraoperative parathyroid hormone (ioPTH) levels were used to determine cure. The ioPTH criteria employed were a drop of ≥50% from baseline, into the normal range, and to a level less than 40 pg/mL. If the ioPTH levels did not meet these standards, the remainder of the PGs were sought and assessed.

Determination of Postoperative Cure

Cure was defined by becoming eucalcemic and maintaining calcium (ionized, serum, and corrected serum calcium) levels in the normal range for ≥6 months from time of surgery.[9] Persistence was defined by continued hypercalcemia postoperatively that did not normalize. Recurrent disease was characterized by a period of eucalcemia that lasted at least 6 months following surgery, followed by a return of the hypercalcemia.[9]

Statistical Analysis

Continuous data are described using medians with 25th and 75th percentiles, whereas categorical data are presented using counts and percentages. Univariate associations between continuous variables are carried out using Spearman's rank correlation coefficients due to the small sample size and non-Gaussian distribution of the variables, which was examined using histograms, Q-Q plots, and Shapiro–Wilk tests. Paired variables are compared using the nonparametric sign test. Statistical significance is set at $P < .05$. Measures of associations were performed for the AF intensities/ratios of the adenomas and normal PGs to the other variables. All analyses are performed using SAS 9.4 (SAS Institute Inc, Cary, NC). The study was conducted with a sample size commensurate with previous studies.

RESULTS

There were 22 patients included in the study, of which 86.4% (19) were female. The median age was 64 years (interquartile range [IQR]: 57–74) and body mass index was 28.1 kg/m^2 (IQR: 25.0–33.6) (Table I).

All patients met ioPTH criteria for cure after removal of a single adenoma. Adenomas were confirmed by histopathology. At 1-month follow-up, all patients achieved eucalcemia. Fifteen patients remained cured >6 months from time of surgery, whereas seven patients have not yet reached their 6-month follow-up window (Table II). At 6 months, the patients demonstrated a mean PTH level at the high-end of the normal range. Critically, however, all patients continued to be eucalcemic.

The median preoperative intact PTH level was 115 pg/mL (IQR: 83–150), vitamin D level was 28.5 ng/mL (IQR: 18–41), and ionized calcium was 1.38 mmol/L (IQR: 1.32–1.42). The median pre-incision ioPTH was 156.1 pg/mL (IQR: 116.4–208.8) and the median postexcision ioPTH at 15 minutes was 28.5 pg/mL (IQR: 19.1–34.2). The median adenoma weight was 595 mg (IQR: 250–2,000).

The median thyroid baseline NIRAF detection level was 33 (IQR: 19–39) (Table III). The median DR for the parathyroid adenoma in situ was 4.38 (IQR: 2.03–5.87), ipsilateral normal PG 6.17 (IQR: 3.83–7.67), strap muscle 0.47 (IQR: 0.30–0.60), fat 0.20 (IQR: 0.17–0.47), ex vivo adenoma at 1 minute 5.15 (IQR: 3.03–8.43), and ex vivo adenoma at 15 minutes 5.35 (IQR: 2.67–11.13). The detection levels were also recorded (Fig. 1). The median differential in DR between the adenoma and normal PG in situ was 1.85 (IQR: 0.33–3.77). The overall sensitivity and specificity of the device for normal and abnormal PGs was 97.7% and 100%.

All nonpathologic PGs demonstrated AF DR > 1.2 (minimum of 2.3), which is the threshold for detection of parathyroid tissue. Twenty-one of 22 adenomas also showed AF ratios >1.2. These AF levels were maintained ex vivo. One adenoma demonstrated almost no AF response. In 5/22 (22.7%) cases, the adenoma AF response was greater than the normal, ipsilateral PG.

Univariate correlations were made between the NIRAF level or ratio and clinical measures as shown in Supporting Table S1.

The median DR of the adenoma under the blue surgical drape was 1.10 (IQR: 0.63–1.47). The median DR of the adenoma under 5, 10, 15, and 20 mm of saline was 3.30 (IQR: 1.47–4.20), 1.10 (IQR: 0.83–1.90), 0.60 (IQR: 0.23–0.73), and 0.42 (IQR: 0.20–0.50), respectively. The median DR of the adenoma with 2, 4, and 6 mm of intervening silastic sheeting was 4.17 (IQR: 2.50–5.93), 2.88 (IQR: 2.20–3.70), and 2.00 (IQR: 1.30–3.50), respectively (Fig. 2).

DISCUSSION

The use of NIRI with or without ICG injection for intraoperative PG detection and assessment has gained popularity in recent years. Although the technology is not new, its application in the setting of thyroid and parathyroid surgery is relatively novel. The potential to reduce the rates of post-thyroidectomy hypoparathyroidism and ease the challenge of finding PGs and achieving cure in parathyroidectomy has elicited much excitement among surgeons performing these surgeries. However, there are many nuances in the applications of these technologies that are yet to be discovered and research is required to better understand their precise capacities and benefits.[10]

Much of the available research on NIRI has been performed utilizing camera-based systems. These camera-based systems, such as the Fluobeam devices, provide a wide view and can be used with ICG enhancement to not just detect PGs but also evaluate their vasculature and perfusion. As with any new technology, surgeons require some training to understand how to interpret the acquired images. One significant current limitation of the camera-based systems is they do not allow for real-time quantification of fluorescence. In the absence of quantification, a subjective scoring system of the degree of fluorescence, described by Vidal Fortuny et al., is widely employed when using ICG injection for PGs.[11–13]

The PTeye is the only Food and Drug Administration-approved, probe-based system for NIRAF evaluation of PGs. As the device does not provide a broad NIRI "view" of the field, it does require surgeons to have a greater knowledge of the likely location of PGs. One significant advantage of the PTeye is that it provides quantified data, allowing a more objective measure of NIRAF. Earlier studies by the research group at Vanderbilt University have established a reference DR threshold for parathyroid tissue.[14] McWade et al. showed that a NIRAF ratio ≥ 1.2 compared to the thyroid was highly indicative of parathyroid tissue.[6] A second benefit of the PTeye compared to the camera-based system is its small profile. Unlike a camera-based system, wide exposure is not needed for the PTeye, making it more user-friendly, particularly for minimally invasive cases.

Several studies have shown the accuracy of the PTeye at identifying parathyroid tissue. The sensitivity, specificity, and overall accuracy of the PTeye in these studies has been reported to be >90%.[2,4,15]

In regard to sensitivity and specificity, our results are consistent with earlier studies. The PTeye accurately identified all normal PGs, fat, and strap muscles. All fat and muscle demonstrated almost no AF response. An interesting finding brought up in prior studies is that there can be a high false positive rate due to colloid nodules.[16] That was not the case in this series, as the false positive rate was 0%. Although a small series, the positive predictive value in this study was 100%. Despite previous reports that abnormal PGs do not demonstrate the same degree of NIRAF as normal PGs, in our series 21/22 (95.5%) of adenomas produced an AF DR above the threshold for parathyroid tissue.

This high degree of accuracy of the PTeye system raises several important considerations. Currently, the gold standard to intraoperatively confirm tissue as parathyroid is frozen section biopsy. Alternatively, some surgeons will aspirate the tissue in question and send this for ioPTH levels. Both of these approaches have associated costs and require time to be processed. Some have suggested the possibility of using NIRAF as an "optical biopsy" of the PGs. Given the findings of this and prior studies, surgeons can consider employing the PTeye as a more rapid, less invasive manner of confirming the presence of parathyroid tissue. This could potentially have a significant impact on both parathyroid and thyroid surgeries. Given the real-time feedback of this device, bilateral neck explorations for parathyroid disease, for example, may be performed in a faster manner. Anecdotally, surgeons have reported this experience although this possible time saving has not yet been studied rigorously.

One major concern that has been raised about the capability of NIRAF for PG identification is the penetrating ability of the technology. PGs are often covered by fat, fascia, or other soft tissue. The capacity of the PTeye (or any NIRAF device) to adequately stimulate and receive an AF response when tissue is overlying the PG is unknown. Unfortunately, trying to rigorously quantify this ability in a surgical field, while eliminating confounding factors, is difficult. To begin to evaluate this question, we examined the PTeye's ability to measure AF when separated from the PG by known depths of saline and heights of silastic sheets. This experiment clearly does not replicate genuine surgical conditions. However, to our knowledge this is the first study that reveals that the PTeye does not need to be in direct contact with the PG to function appropriately. The maximum distance at which proper detection still occurred in a normal saline medium was found to be around 10 mm and about 6 mm through a clear solid medium (although larger thicknesses were not tested). Although these materials do not represent the equivalent scenario in situ, these findings give surgeons additional knowledge of how to best use the device and how to interpret the intensities and ratios. This ability to function at a distance (at least through

clear mediums) may significantly impact how this device can be used in thyroid and parathyroid surgeries.

Much of the current data on the use of NIRI for intraoperative PG detection have been obtained in the setting of thyroid surgery for various pathologies, with some focus on hyperparathyroidism.[3,6,14,15,17–22] But the potential benefits of this technology in parathyroid surgery are self evident. Identification of PGs during parathyroidectomy, the fundamental requirement for successful outcomes, presents a significant challenge in some cases. In theory, the ability of NIRAF to facilitate intraoperative localization of PGs could represent a major step forward in parathyroidectomy. The ability to discriminate between normal and abnormal PGs, which in some cases can be nuanced and challenging, is a second crucial skill needed in parathyroidectomy. Characterizing the NIRAF qualities of pathologic PGs is needed to understand whether NIRAF can possibly aid as an adjunct to address this challenge of differentiation.

To date, the research on the NIRAF characteristics of pathologic PGs has reported somewhat inconsistent findings. However, a number of studies have reported that pathologic PGs demonstrate lower AF compared to normal PGs.[1,7,14,23,24] This may be due to differences in the concentration of the fluorophore, which has not yet been identified, present in pathologic versus normal PGs. The calcium sensing receptor (CaSR) of PGs has been proposed as the possible fluorophore. Potentially, the lower concentration of CaSRs in adenomas is the explanation for their lower AF responsiveness.

Importantly, most of the investigations of pathologic PGs have been performed using camera-based NIRAF. As previously mentioned, due to the lack of quantitative feedback, these studies are based on subjective reporting. In addition to a possible altered degree of AF, a number of studies have described anecdotally that there appears to be increased AF heterogeneity displayed by adenomatous PGs.

Our results regarding the AF nature of adenomatous PGs are more mixed than prior studies. In this series, many adenomas had lower median and mean DR compared with normal glands. However, the quantitative nature of the PTeye allowed for greater stratification of these results. Interestingly, 22.7% (5/22) of patients had adenomas that had higher NIRAF responsiveness than that of the ipsilateral normal gland. In one patient, the parathyroid adenoma demonstrated almost no AF despite extensive interrogation of the whole surface of the gland. After dividing this gland, the inside of the gland also did not show any AF. No "cap" of tissue with higher AF responsiveness was found.[1] Although a majority of glands in this study did show lower AF compared to normal PGs, a significant minority did not. This is an important finding as it suggests that using a relatively lower DR cannot be used reliably to help discriminate between normal and pathologic glands. As has been reported in prior studies, anecdotally we noted that adenomas tended to demonstrate a significant degree of heterogeneity. Perhaps if quantifiable, this feature of adenomas may be exploited in the future as a tool for differentiation. Research endeavors are ongoing to assess this possibility further.

CONCLUSION

The advancement of NIRAF technology in the setting of thyroid and parathyroid surgeries has been exciting. To fully optimize the use of this technology, the precise capabilities and limitations of these devices and approaches must be delineated. This study provides further evidence of the sensitive and specific ability of the PTeye system to confirm the presence of parathyroid tissue. Given this high accuracy, surgeons can consider using the PTeye in lieu of frozen section biopsy. Importantly, this series also demonstrates that to function properly the probe does not need to be in direct contact with the tissue being assessed.

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