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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Intraoperative Parathyroid Autofluorescence Detection in Patients with Primary Hyperparathyroidism

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ABSTRACT

Background. Intrinsic near-infrared (NIR) autofluorescence of the parathyroid gland may improve intraoperative gland identification without the need for contrast agent injection. Compared with patients undergoing surgery for thyroid disease, identification of pathologic parathyroid tissue in patients with hyperparathyroidism is essential. This study analyzed the utility of a novel real-time autofluorescence imaging system in patients with primary hyperparathyroidism enrolled in a prospective feasibility clinical trial.

Methods. Data on patients undergoing surgery for primary hyperparathyroidism by two experienced endocrine surgeons were prospectively collected. Intraoperative imaging was performed with a handheld NIR device, and images were captured for analysis. The collected data included the surgeon's confidence in parathyroid identification, both with ambient light and use of NIR imaging, as well as how the imaging affected the surgical procedure. Images were quantified by Image J software, with autofluorescence reported as mean values ± SD.

Results. From 2017 to 2018, 59 consecutive patients with a diagnosis of primary hyperparathyroidism underwent resection of 69 parathyroid glands. Use of NIR imaging increased the intraoperative confidence of parathyroid identification (on a scale of 0–5) from an average of 4.1 to an average of 4.4 (+0.3, $p = 0.003$), all of which were confirmed pathologically. The addition of autofluorescence helped to identify the parathyroid gland in 12 patients (20%), and to rule out other soft tissue as not parathyroid in an additional 9 patients (15%). The mean autofluorescence for the parathyroid in situ (75.9 ± 21.3) was significantly greater than that for the thyroid (61.1 ± 17.4) or soft tissue (53.3 ± 19.2) ($p < 0.001$ for both). The mean absolute difference in parathyroid versus background thyroid autofluorescence was +15.2 (range, 2.4–53.1).

Conclusion. This is the first prospective trial to examine the utility of parathyroid autofluorescence for identifying glands exclusively in patients with parathyroid disease. Intraoperative identification and localization of parathyroid glands by real-time, NIR imaging using their intrinsic autofluorescence is feasible and may provide a useful adjunct during parathyroid surgery.

Accurate identification and localization of parathyroid glands are vital during thyroid and parathyroid surgery to minimize injury to normal parathyroid glands or their inadvertent resection, as well as to facilitate removal of abnormal or adenomatous parathyroid glands in patients with parathyroid disease. Real-time intraoperative imaging of parathyroid glands may improve localization and decrease morbidity during neck surgery by limiting the amount of dissection necessary for identification of both normal and abnormal parathyroid glands.

Several early studies of intraoperative parathyroid imaging involved the injection of a fluorescence agent such as methylene blue or indocyanine green (ICG) to aid in identifying both the parathyroid glands and their viability.[1–6] Although early results demonstrated some limited success with these techniques, they have not been widely adopted.

The parathyroid gland has been shown to have intrinsic autofluorescence due to the presence of still-uncharacterized endogenous fluorophores that emit a fluorescent signal in the near-infrared (NIR) wavelength range at a peak near

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820 nm, as initially described in 2011.[7] The most commonly used fluorescent dye is ICG, with a maximum peak near 832 nm.[8] Therefore, some of the currently used NIR cameras designed to image ICG also can detect parathyroid autofluorescence.

Several groups have performed preliminary research with the use of handheld intraoperative NIR imaging devices to detect the parathyroid autofluorescent signal with high accuracy.[9–12] A comparison of autofluorescence to ICG for parathyroid detection found that autofluorescence could detect a parathyroid gland earlier than gross visualization with the naked eye in 82% of patients versus only 14% with ICG.[13]

Initial studies with autofluorescence imaging technology demonstrated encouraging preliminary results among small heterogeneous cohorts, including patients with various thyroid and parathyroid pathologies.[11,14,15] The majority of studies to date have focused largely on the feasibility of intraoperative detection of the parathyroid gland during thyroidectomy to avoid inadvertent resection of the parathyroid and to prevent postoperative hypocalcemia.[12,16–19] Less is known regarding the utility of parathyroid autofluorescence detection among patients with primary hyperparathyroidism, in whom both pathologic and normal parathyroids are identified. Previous studies have primarily used a handheld device manufactured by Fluoptics (Fluoptics USA, Cambridge, MD), but none have used the PDE-NEO II manufactured by Hamamatsu (Mitaka USA, Inc., Denver, CO).

The current prospective feasibility clinical trial aimed to analyze the potential utility of real-time intraoperative imaging with a handheld NIR autofluorescence device (PDE-NEO II) to aid parathyroid gland identification in patients with primary hyperparathyroidism. Although true fluorescence quantification is challenging, we aimed to semi-quantify the fluorescent intensity of captured images and assess the correlation of autofluorescence findings with histopathologic features. Using this previously undescribed NIR imaging system, we evaluated the influence of autofluorescence on surgeon confidence in parathyroid identification during parathyroidectomy and postoperatively evaluated parathyroid gland autofluorescence semi-quantitatively compared with that of surrounding thyroid and soft tissue among patients with primary hyperparathyroidism.

METHODS

The study cohort comprised a series of consecutive patients enrolled in a prospective clinical trial who were undergoing neck exploration and parathyroidectomy for a clinical diagnosis of primary hyperparathyroidism between June 2017 and February 2018 by two experienced endocrine surgeons at a single institution. Patients with a diagnosis of multiple endocrine neoplasia (MEN 1 or 2) or secondary hyperparathyroidism were excluded from the study.

Preoperative serum parathyroid hormone (PTH) and calcium levels as well as preoperative, intraoperative, and immediate postoperative PTH levels were recorded for each patient. Intraoperative PTH monitoring was used in all cases. Patients with preoperative imaging by ultrasound or ^{99m}technetium-sestamibi nuclear imaging consistent with a parathyroid adenoma underwent a directed parathyroidectomy, and if the intraoperative PTH decreased by more than 50% and reached the normal range in 10 min, then further exploration, including the contralateral neck, was not performed.

The standard histopathologic variables recorded at the final pathologic analysis included the presence of parathyroid tissue in the specimen, the degree of cellularity, gland weight, and gross dimensions. Historically, both endocrine surgeons have routinely obtained intraoperative frozen section analysis of all resected specimens to confirm the presence of hypercellular parathyroid adenoma.

Intraoperative imaging with a commercially available, handheld NIR camera (PDE-Neo II; Hamamatsu, Mitaka USA, Inc., Denver, CO) was performed after the thyroid gland had been mobilized (Fig. 1). The camera emits infrared light at a wavelength of 760 nm using an light-emitting diode (LED)-excitation light classified as a 1-M LED product and captures NIR wavelengths of 790–830 nm.

The camera was sterilely draped and positioned 5 cm above the surgical field for image acquisition. With the operating room lights off, images were taken with ambient light provided by the camera and then at NIR wavelengths with the emitting light as stated earlier (Fig. 2). Once the parathyroid adenoma had been resected, images of the

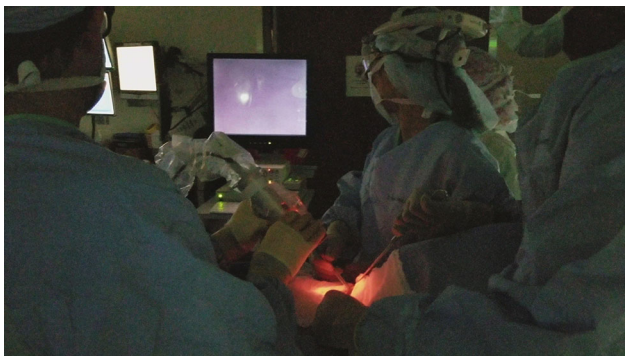

FIG. 1 Intraoperative setup demonstrating handheld, near-infrared camera device for imaging of parathyroid autofluorescence

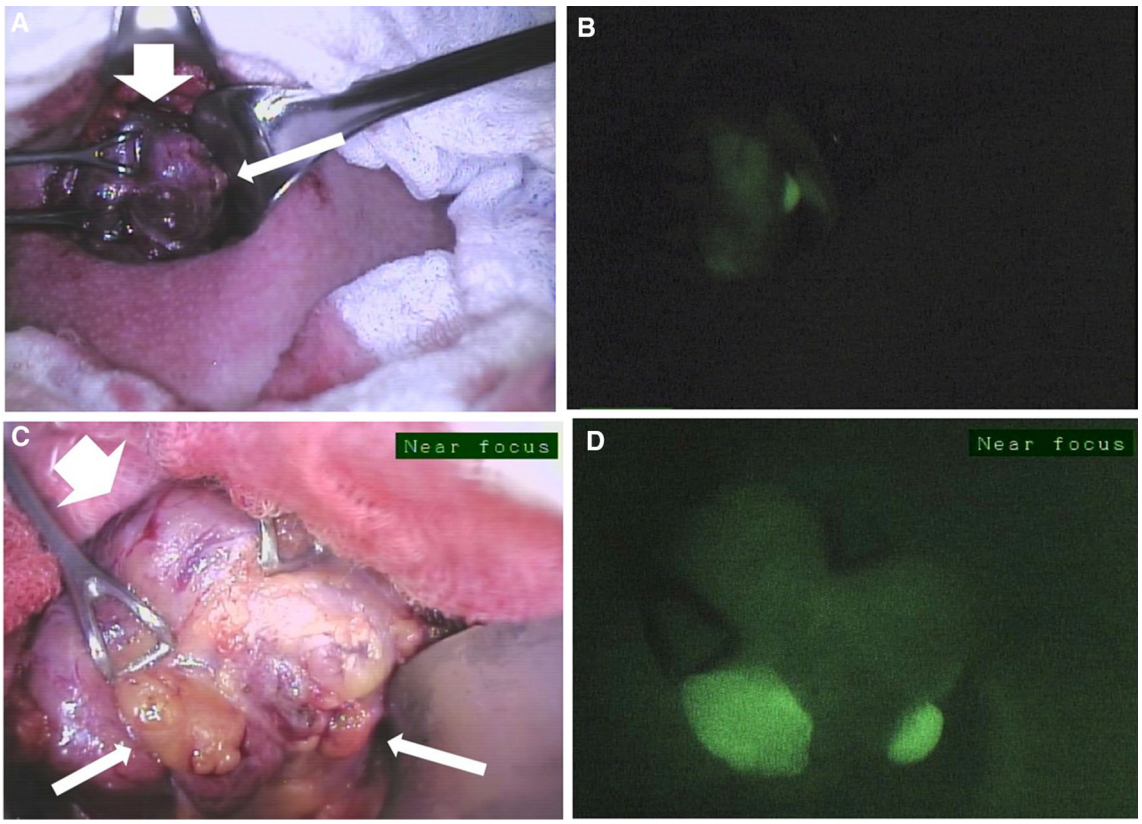

FIG. 2 Intraoperative imaging of patient with primary hyperparathyroidism after mobilization of the thyroid gland demonstrating autofluorescence of parathyroid glands using a handheld, near-infrared (NIR) camera. **a** Patient 1, ambient light. Thyroid gland (thick arrow); parathyroid gland (thin arrow). **b** Patient 1, NIR autofluorescence. **C** Patient 2, ambient light. Thyroid gland (thick arrow); superior and inferior parathyroid glands (thin arrows). **d** Patient 2, NIR autofluorescence

gland also were taken ex vivo with the operating room lights off using the NIR camera at the same distance (Fig. 3).

Images were prospectively collected for all the patients and then retrospectively analyzed using Image J software (National Institutes of Health, Bethesda, MD). Representative regions of equal dimensions (10 × 10 pixels) were selected from the areas of maximum fluorescence of the parathyroid gland, thyroid gland, and surrounding exposed soft tissue and muscle, and fluorescence values were quantified for each tissue type.

Imaging fluorescence calculations were performed in duplicate for each saved image in a blinded fashion, and the values were averaged to minimize subjective observational bias. A positive autofluorescence result was defined as a parathyroid autofluorescence-to-background autofluorescence ratio greater than 1.10. Immediately postoperatively, the surgeon recorded a "parathyroid identification confidence score," namely, a quantified measurement on a scale of 1–5 of the surgeon's confidence in the identification of the parathyroid gland during the procedure by ambient light visualization and then with the addition of NIR autofluorescence.

All statistical analyses were performed using SPSS software version 23 (IBM, Inc., Chicago, IL, USA). Continuous variables were reported as median (range) or as mean ± SD. Differences in autofluorescence intensity among parathyroid, thyroid, and surrounding soft tissue were compared using the paired-samples *t* test. The association of autofluorescence values with continuous clinicopathologic variables was analyzed by the Pearson correlation coefficient. Statistical significance was defined as a *p* value lower than 0.05. All research was undertaken with the approval of the Institutional Review Board.

RESULTS

In this study, 69 parathyroid glands were resected from 59 patients who underwent surgery for a diagnosis of primary hyperparathyroidism. The cohort included 46 women (78%) and 13 men (22%), and the median patient age was 59.5 years (Table 1). The median body mass index (BMI) was 29.9 kg/m^2 [interquartile range (IQR), 26.6–36.5 kg/m^2]. Four patients had undergone previous neck surgery.

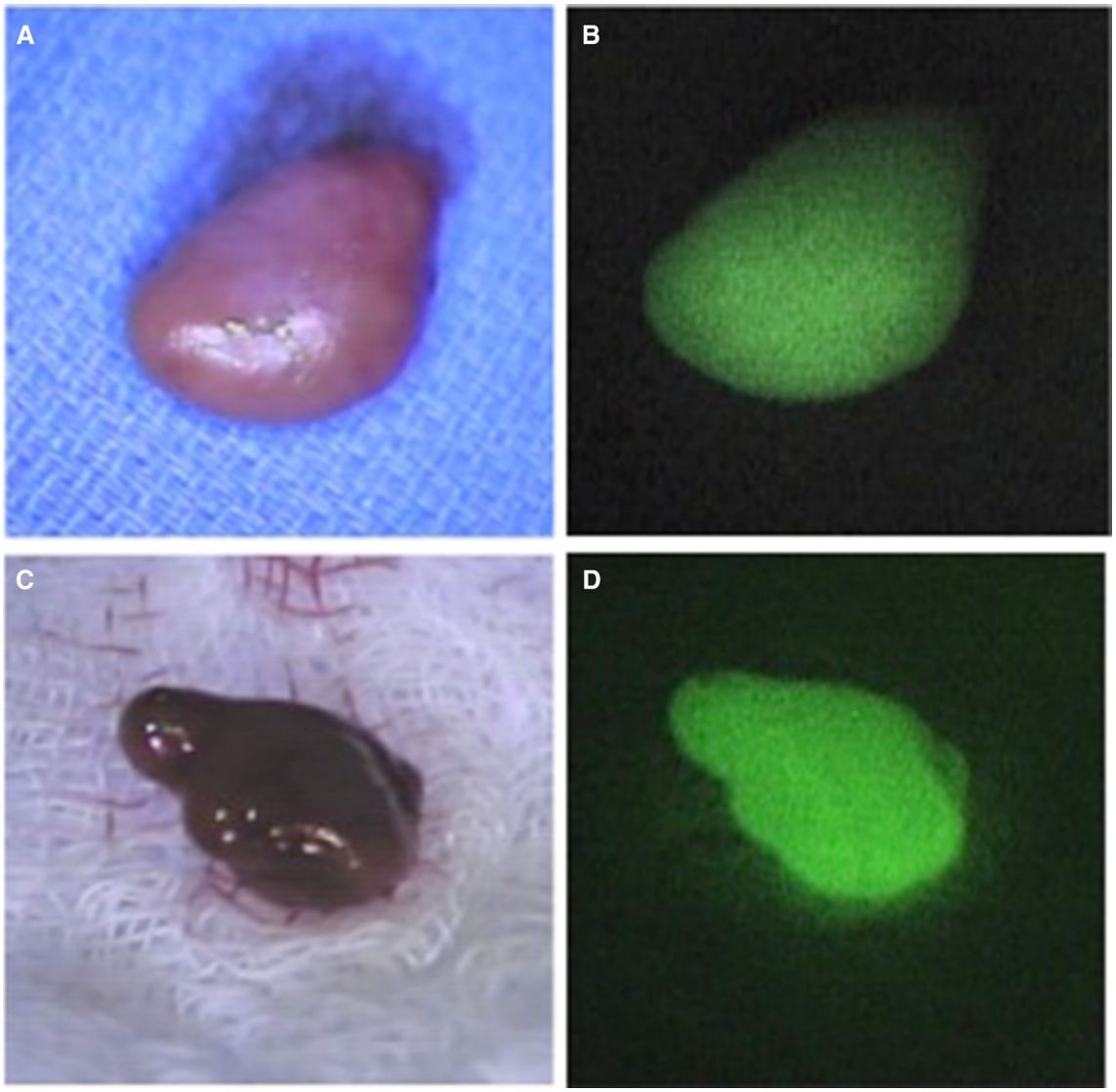

FIG. 3 Intraoperative imaging of ex vivo resected parathyroid glands. **a** Patient 3, ambient operating room light. **b** Patient 3, near-infrared (NIR) autofluorescence. **c** Patient 4, ambient operating room light. **d** Patient 4, NIR autofluorescence

TABLE 1 Demographic and clinical features of 59 patients who underwent neck exploration for diagnosis of primary hyperparathyroidism

Variable	
Female gender: *n* (%)	46 (78)
Median age: years (IQR)	59.5 (53.4–67.1)
Median BMI: kg/m^2 (IQR)	29.9 (26.6–36.5)
Prior neck surgery: *n* (%)	4 (7)
Median preoperative serum PTH: pg/dL (IQR)	110.8 (93.0–159.5)
Median preoperative serum calcium: mg/dL (IQR)	10.9 (10.6–11.3)
Preoperative parathyroid localization: *n* (%)	48 (81)

IQR interquartile range, *PTH* parathyroid hormone

The median preoperative PTH level was 110.8 pg/dL (IQR 93.0–159.5 pg/dL), and the median preoperative serum calcium level was 10.9 mg/dL (IQR 10.6–11.3 mg/dL).

Preoperative imaging localization of parathyroid adenomas by ultrasound or ^{99m}technetium-sestamibi nuclear medicine scan was successful for 48 (81%) of the 59 patients. The remaining 11 patients underwent bilateral

neck exploration. Notably, however, preoperative localization was unsuccessful for six of the nine patients for whom more than one parathyroid gland was ultimately resected. At pathologic evaluation, the median parathyroid gland size was 0.65 cm^3 (IQR 0.34–1.45 cm^3), and the median gland weight was 0.46 g (IQR 0.24–0.93 g; Table 2).

Based on postoperative surgeon debriefing, the average surgeon confidence score for parathyroid identification was 4.1 by direct visualization versus 4.4 by autofluorescence (+0.3; $p = 0.003$), which in all cases was confirmed by histopathology to be parathyroid tissue.

After mobilization of the thyroid, the surgeons found that the use of intraoperative autofluorescence imaging helped to identify parathyroid glands not initially seen by gross visualization in 12 (20%) of the 59 patients. In an additional nine patients (15%), the surgeon identified some tissue they thought could potentially be parathyroid, but found that the lack of autofluorescence helped to rule out the tissue as parathyroid. All this tissue was confirmed at pathology analysis not to be parathyroid tissue. Historically, both surgeons have sent all resected parathyroid tissue for frozen section pathologic analysis.

For 17 patients (29%), a frozen section was not performed because the attending surgeon felt sufficiently confident about both the ambient light identification and the autofluorescence of the presumptive parathyroid adenoma to forego intraoperative histologic confirmation. All these tissues were confirmed to be parathyroid at the final pathology. The criteria for concluding all the surgeries was an appropriate fall in intraoperative PTH regardless of whether a frozen section was sent or not.

At the analysis of the intraoperative imaging results, the mean autofluorescence (AF) value for the parathyroid gland in situ (78.4 ± 21.4) was significantly greater than that for the thyroid gland (63.3 ± 17.6) or the adjacent soft tissue autofluorescence (57.7 ± 19.8) ($p < 0.001$ for both). The mean absolute difference of the in situ parathyroid versus the background thyroid autofluorescence was +15.4 (range, 2.5–53.1).

The mean ratio of the parathyroid/thyroid autofluorescence signal was 1.27 ± 0.22. Based on the a priori definition of a positive imaging result, the overall sensitivity of NIR autofluorescence for detection of the parathyroid gland was 87% (60 of 69). The mean parathyroid gland autofluorescence ex vivo was significantly greater than autofluorescence in situ (89.1 vs 78.4; $p < 0.001$). No difference in autofluorescence of hypercellular ($n = 54$) versus normocellular ($n = 6$) parathyroid glands was observed (in situ: 78.8 vs 73.4, $p = 0.81$; ex vivo: 90.3 vs 78.6, $p = 0.42$).

The value of the ratio of the in situ parathyroid/thyroid autofluorescence signal was significantly associated with increasing parathyroid gland weight (Pearson coefficient, 0.37; $p = 0.015$) and gland volume (Pearson coefficient, 0.41; $p = 0.006$). Similarly, the value of the difference shown by parathyroid AF minus thyroid AF was associated with a trend toward increasing parathyroid gland weight (Pearson coefficient, 0.30; $p = 0.054$) and parathyroid volume (Pearson coefficient, 0.42; $p = 0.005$). The preoperative serum PTH was not associated with the absolute value of in situ parathyroid autofluorescence ($p = 0.95$) or the ratio of the parathyroid/thyroid AF signal ($p = 0.18$).

TABLE 2 Pathologic and autofluorescence imaging features of 59 patients who underwent neck exploration for diagnosis of primary hyperparathyroidism

Variable	
Parathyroid gland size: cm^3 (IQR)	0.62 cm^3 (0.34–1.45)
Parathyroid gland weight: gm (IQR)	0.46 gm (0.24–0.93)
Mean parathyroid AF ± SD	75.9 ± 21.3
Mean thyroid AF ± SD	61.1 ± 17.4
Mean soft tissue AF ± SD	57.5 ± 19.8
Mean parathyroid-thyroid AF ± SD	15.2 ± 10.7
Mean parathyroid:thyroid AF ratio ± SD	1.27 ± 0.21
Mean parathyroid ex vivo AF ± SD	89.7 ± 29.0

IQR interquartile range, *AF* autofluorescence, *SD* standard deviation

DISCUSSION

The current feasibility study reports the results of a prospective clinical trial assessing real-time intraoperative autofluorescence imaging with a novel handheld NIR device to aid identification of parathyroid glands among patients with a diagnosis of primary hyperparathyroidism. Whereas previous studies have focused on the use of intraoperative imaging to improve preservation of the parathyroid glands at the time of thyroidectomy, the current study is the only series to date that used parathyroid autofluorescence detection for patients undergoing neck exploration exclusively for primary hyperparathyroidism. The results demonstrate that parathyroid autofluorescence was consistently greater than that of thyroid gland or background soft tissue fluorescence, suggesting that intraoperative real-time NIR imaging aided in reliable identification of parathyroid glands, as confirmed by correlation with final pathology.

The initial experience with intraoperative real-time imaging of parathyroid glands during neck surgery relied on intravenous injection of contrast agents such as methylene blue or ICG to generate fluorescence.[1–4,13] Intraoperative ^{99m}-technetium Sestamibi (MIBI) imaging

with a portable gamma camera also has been investigated as a real-time adjunct for patients undergoing exploration for primary hyperparathyroidism, but similarly requires preoperative injection of a radiotracer contrast agent and may visualize only MIBI-avid parathyroid adenomas.[20]

Discovery of intrinsic autofluorescence of the parathyroid gland in the NIR range has led to investigation of handheld, real-time intraoperative imaging methods for noninvasive localization and identification of parathyroid glands.[9,21] This autofluorescence allows for visualization of both normal parathyroid glands and parathyroid adenomas, as well as for detection in situ and confirmation ex vivo. Improved intraoperative parathyroid identification has the potential to minimize unnecessary dissection around the parathyroid and thyroid glands, decreasing the risk of recurrent laryngeal nerve injury and improving the safety of parathyroid and thyroid resections.

Recent studies have shown the efficacy of NIR autofluorescence imaging during total thyroidectomy for improving the ease and safety of parathyroid identification, with less dissection and less potential for inadvertent injury to the parathyroid, thereby decreasing the rates of parathyroid autotransplantation and postoperative hypocalcemia.[12,16–19] The gold standard for fully determining the accuracy of autofluorescent imaging is through correlation of images with final pathology.

The current feasibility study focused on the utility of a novel NIR imaging device among parathyroidectomy patients, which in all cases removes parathyroid tissue that can then be analyzed and correlated with intraoperative imaging results. In contrast, parathyroid tissue is almost never removed during thyroid surgery, making imaging correlation with histopathology more problematic.

All of the patients in the current study underwent surgical resection for primary hyperparathyroidism, allowing for uniform analysis of histopathologic features and correlation of these variables with intraoperative autofluorescence imaging results. The results of intraoperative autofluorescence imaging with the current handheld NIR imaging system have never been previously reported. Increasing parathyroid gland size and weight were associated with increasing magnitude of the parathyroid-to-thyroid autofluorescence ratio as well as the absolute value of the difference in parathyroid minus background in situ autofluorescence. Similar to previous series, no significant difference in the intrinsic autofluorescence of the parathyroid was observed between hypercellular adenomas and normocellular parathyroid glands.[22] Although not specifically examined in the current study, previous analyses have suggested that intraoperative autofluorescence imaging may be particularly helpful in the setting of prior neck surgery or thyroiditis, in which chronic inflammation may obscure the parathyroid glands and make visual identification of the parathyroids more challenging.[14]

The magnitude of both intrinsic parathyroid autofluorescence and the parathyroid-to-background thyroid autofluorescence ratio observed in the current study was less than in previously reported series, in which fluorescent intensity was measured directly from the tissue and not based on image software.[9,12] The quantified background autofluorescence of the thyroid gland in particular appeared greater than in previous series, which likely shows an inherent limitation of the image processing software and post hoc analysis of fluorescence imaging.

In this study, what appeared intraoperatively as subjectively clear identification and delineation of parathyroid gland autofluorescence against a background of the darker thyroid gland often correlated with a calculated ratio of only 1.5 to 2.0. Obtaining quantitative data real-time from this NIR imaging system or other camera systems is not possible, so a predetermined intraoperative cutoff value is not obtainable during surgery. We found that the intensity of parathyroid autofluorescence also decreased significantly with increasing distance of the NIR camera probe from the surgical field.

Incorporation of intraoperative autofluorescence imaging helped to identify parathyroid glands that had not been found by gross visualization at that time by the surgeon in 20% of the patients in this study. In these patients, NIR imaging suggested a potential parathyroid gland that at further dissection was thought to be more conclusively identified and resected, with final pathology confirming parathyroid histology. Intraoperative NIR imaging also helped to rule out a potential gland as nonparathyroid tissue in an additional 15% of patients, for whom the surgeon thought certain tissue could potentially be parathyroid gland by gross visualization and removed this tissue despite its lack of autofluorescence, sending it for permanent pathology. In all these cases, the pathology confirmed that this nonfluorescent tissue was not parathyroid gland.

In this era of increased emphasis on health care outcomes and efficient care delivery, with the value of an intervention defined as the quality of the provided care divided by the cost, intraoperative parathyroid localization by autofluorescence detection for patients with primary hyperparathyroidism may provide significant value by improving the safety, accuracy, and speed of parathyroid gland identification. Simultaneously, intraoperative autofluorescent localization may decrease costs by decreasing operative times and potentially obviating the need for routine frozen section pathologic confirmation of parathyroid histology. The image acquisition time was routinely 2–3 min with the use of the handheld camera and did not contribute significantly to the overall duration of the case.

In 17 patients (29%), confidence in the autofluorescence imaging findings of the presumptive parathyroid adenoma allowed the surgeon to forego frozen section pathologic analysis of the specimen, saving expense.

As experience with the described technology increases, the number of patients for whom intraoperative frozen section analysis may potentially be unnecessary is likely only to increase. The current findings were limited by the single-institution nature of this study. Ongoing refinement of imaging techniques and further analyses to confirm these results in a randomized, controlled trial and a larger, multi-institutional cohort are warranted.

CONCLUSION

Intraoperative identification and localization of parathyroid glands during parathyroidectomy for primary hyperparathyroidism with real-time NIR imaging of intrinsic parathyroid gland autofluorescence is feasible and may prove to be a useful adjunct for the parathyroid surgeon.

DISCLOSURES The authors report no conflicts of interest in this work.

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