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# Impact of fluorescence and autofluorescence on surgical strategy in benign and malignant neck endocrine diseases



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Fluorescence and autofluorescence have been shown by several recent studies to be valuable adjuncts in identifying parathyroid glands during thyroidectomy and parathyroidectomy. The aim of this chapter is to review the impact of this new technology on surgical strategy concerning identification and preservation of parathyroid glands during thyroidectomy, identification of parathyroid glands in hyperparathyroidism, and the potential role in thyroid cancer surgery.

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## Introduction

Endocrine surgery has a rich history of discovery to better understand endocrine disorders. Over the years, our understanding of anatomy, constant refinement of surgical technique and postoperative management had a positive impact on outcomes and quality of patient care.

Correct identification and preservation of critical planes and structures during the operative procedure relies on the experience of the surgeon with visual and tactile feedback serving as the main tools. Despite this, there are associated complications and operative failures which result in negative outcomes and reduced quality of life for patients. The incidence of permanent hypoparathyroidism after total thyroidectomy has been reported to be 0.9–6.6% [1]. Failure to identify an abnormal

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parathyroid during a parathyroidectomy can lead to unnecessary reoperations and increased risk of nerve injury [2].

New imaging techniques have been recently studied in endocrine surgery to determine the utility, assess the impact on patient outcomes and reducing complications. These modalities include Indocyanine green (ICG) near-infrared imaging (NIFI) and parathyroid autofluorescence (AF) NIFI.

### **Indocyanine green**

Indocyanine green (ICG) ( $C_{43}H_{47}N_2NaO_6S_2$ ) is an amphiphilic tricarbocyanine dye with a molecular mass of 776 Da which was originally developed by Kodak research laboratories for use in near infrared photography in 1955 and later approved by FDA for clinical use in 1959 [3].

After intravenous administration, ICG is avidly bound to plasma proteins and mainly stays in the intravascular space. ICG is rapidly extracted and exclusively excreted by the hepatic parenchymal cells without modifications, appearing in the bile approximately 8 min after injection [3,4].

ICG becomes fluorescent once excited with NIFI light spectrum at approximately 800–820 nm [5]. The emitted fluorescence can be detected by specially designed cameras and scopes with projection to a standard monitor. The relative distribution and vascularity of different tissue are the main factors of varying ICG uptake in different tissues and the resulting intensity of imaging fluorescence. This property is especially useful in identification of endocrine glands given their increased vascularity.

In addition, ICG has been utilized extensively in ophthalmology, cardiology, hepatology and more recently in flap reconstructions, intestinal anastomosis, coronary artery bypass graft, lymph node mapping, and intraoperative bile duct identification [4,6,7].

Given its extensive use, ICG has been determined to have a relatively safe drug profile. However, adverse reactions and a few deaths have been reported in literature [8]. Hope-Ross et al. used intravenous ICG for video angiography in 1226 patients and reported an incidence of mild, moderate, and severe complications to be 0.15%, 0.2%, and 0.05% respectively. ICG solution has sodium iodide which along with the molecule itself been implicated in these reactions, and therefore, ICG should be avoided in patients with an iodine allergy. The typical dose for standard clinical use (0.1–0.5 mg/mL/kg) which is well below the toxicity level.

### **Indocyanine green imaging: parathyroid localization**

Majority of parathyroid localization is currently achieved in the preoperative setting using ultrasound and sestamibi. Although these imaging modalities can be used to guide parathyroidectomy, the sensitivity of ultrasound is around 69–75% and 49–70% for sestamibi [9]. Dedicated CT scans and MRI are typically reserved for re-operative cases.

There are other localization techniques that have been evaluated in the past and most are not used today. Historically, Dudley described intravenous injection of methylene blue one hour prior to operative exploration for intraoperative localization, however, this technique was not better than visualization and associated with adverse effects [10,11]. Another technique described includes the use of aminolevulinic acid that accumulates in parathyroid glands with resultant fluorescence, however, it was found to be heterogenous in 50% of cases and required patient shielding from light for 48 h [12]. Finally, radio-guided technique using 99-technetium-methoxybutylisocyanide has been used in the past, however, it is associated with increased radiation exposure [13].

Cleveland Clinic endocrine surgery group first reported using ICG for intraoperative parathyroid localization in 3 re-operative cases. In this study, patients had intravenous administration of ICG and a NIFI camera was used for signal detection. Fluorescence was noted approximately 2 min after ICG administration and continued for up to 20 min in all parathyroid glands [14].

Subsequently, the same group did a prospective study and analyzed the use of ICG in 33 patients undergoing surgery for hyperparathyroidism [15]. A four-gland exploration was done in patients with first-time primary hyperparathyroidism and a focal approach was used in patients with persistent or recurrent disease. Thyroid and parathyroid ICG uptake were assessed. After adequate exposure of the central neck compartment, 5 mg of ICG was administered IV. If patients underwent a subtotal parathyroidectomy, an additional dose of ICG was administered to assess the perfusion of the remnant

parathyroid tissue. Of 112 glands identified with visual inspection first, 92.9% demonstrated ICG fluorescence. More intense fluorescence was noted in patients less than 60 years of age, parathyroid glands larger than 10 mm and preoperative serum calcium above 11 mg/dl. The utility of the ICG in detection of parathyroid glands was limited by the concomitant ICG uptake by the thyroid. However, ICG NIFI was useful in assessing parathyroid remnant vascularity in subtotal thyroidectomy patients and those with prior thyroidectomies [14].

In 2016, a group in Switzerland described the use ICG to assess vascular status of the parathyroid gland in patients undergoing subtotal parathyroidectomy, however, there was no comparison of surgical outcomes [16]. The same group later evaluated the vascularity of the parathyroid remnants in 13 subtotal parathyroidectomy patients by using intraoperative ICG to determine postoperative remnant function [17]. They found a correlation between parathyroid gland perfusion and postoperative parathyroid function.

Overall, the use of ICG with NIFI for intraoperative localization of parathyroid glands in primary hyperparathyroidism has been limited by the concomitant ICG uptake by the thyroid gland. There is potential utility for ICG to localize ectopic parathyroid glands, to assess remnant vascularity in subtotal parathyroidectomy and to help identify parathyroid adenomas in a re-operative field.

### **Indocyanine green imaging: identification and assessment of parathyroid glands during thyroidectomy**

Failure to identify and preserve parathyroid glands (PG) during total thyroidectomy can lead to complications including postoperative hypocalcaemia and permanent hypoparathyroidism. The incidence of transient hypoparathyroidism can occur in up to 30% of cases and permanent hypoparathyroidism after total thyroidectomy has been reported anywhere from 0.9 to 6.6% [1,18].

The utilization of ICG for parathyroid gland identification during thyroid surgery was used in dogs by Suh et al. in 2014, which proved that the parathyroid glands could be visualized by ICG NIFI [19].

In 2016, intraoperative ICG was used in patients undergoing total thyroidectomy to characterize parathyroid vascularization and predict postoperative function. In this study of 36 patients, normal postoperative PTH levels were observed in patients with at least one well vascularized parathyroid gland. Transient postoperative hypoparathyroidism was noted in two of the six patients without a well-perfused gland on angiography [20].

Another prospective study by Cleveland Clinic group reported on the use of ICG for assessment of parathyroid perfusion during total thyroidectomy. In this study, 27 patients had intravenous ICG administration with NIFI imaging. There was a total of 85 parathyroid gland identified with 84% showing ICG uptake. The parathyroid gland perfusion was scored and there was a correlation with ICG uptake and postoperative PTH. The mean POD#1 PTH of those patients with at least two PGs exhibiting <30% fluorescence was 9 pg/mL and patients fewer than two demonstrating <30% fluorescence had a POD#1 PTH of 19.5 pg/mL [21]. These results are similar to a recent retrospective study by Rudin et al. evaluating postoperative parathyroid function after total thyroidectomy [22]. In this study of 210 patients underwent total thyroidectomy, 86 patients had ICGA; while, 124 did not. The authors found that patients with at least two well vascularized glands were more likely to have normal postoperative parathyroid gland function [22].

In 2017, Lang et al. evaluated the correlation between fluorescent light intensity of parathyroid tissue after total thyroidectomy and postoperative hypocalcaemia. There were a total of 94 patients with 324 parathyroid glands evaluated by intraoperative ICGA after total thyroidectomy. The parathyroid gland intensity ratio was expressed as the fluorescence intensity between the parathyroid gland and anterior trachea. The average and greatest fluorescence intensity (GFI) was recorded for each patient. GFI was found to be a good predictor of postoperative hypocalcaemia. When GFI >150%, no postoperative hypocalcaemia was noted, compared to 9 (81.8%) patients with a greatest fluorescent light intensity  $\leq$ 150% that did [23]. No permanent hypocalcaemia was observed in the cohort.

Another study reported lower rate of incidental parathyroidectomies with the use of ICG in patients undergoing robotic thyroidectomy through axillo-breast approach, however, no difference between rates of transient or permanent hypocalcaemia was noted [24].

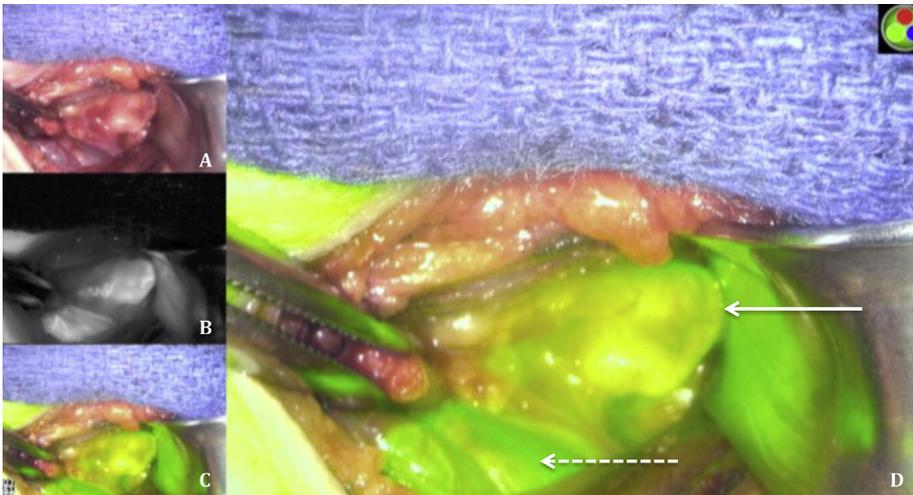
Some limitations of assessing parathyroid function with ICGA after thyroidectomy include discordance between visual and ICGA assessment of parathyroid glands. Rudin et al. found a small percentage of parathyroid glands that visually appeared normal, but, had no vascularity on ICGA. On the other hand, glands that appeared visually non-viable, had adequate blood supply on ICGA. This finding may represent transient ischemia and can pose decision making dilemmas, especially when considering autotransplantation [22]. Overall, the utility of ICGA angiography in evaluating parathyroid gland function is limited and may be best evaluated by randomized control trials.

### Autofluorescence: identification of parathyroid glands

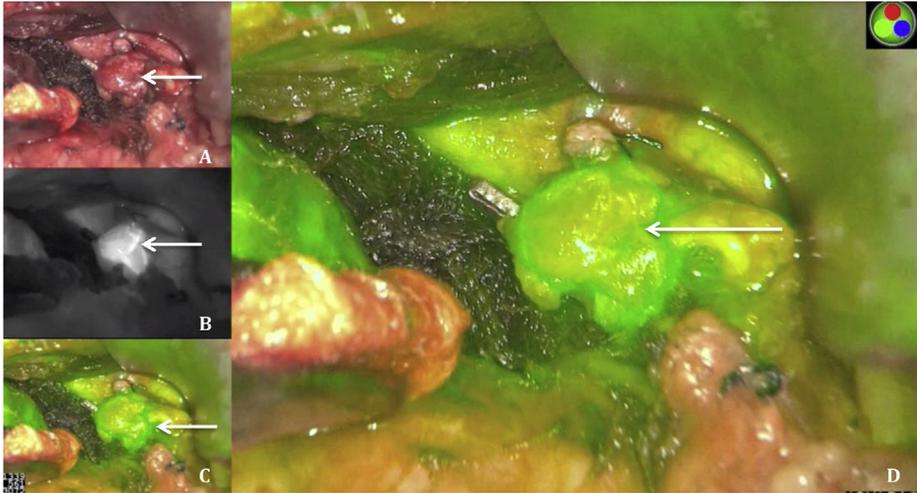
Fluorescence spectroscopy (FS) relies on presence of fluorophores naturally occurring in tissues, and removes the need for use of exogenous agents such as ICG. FS has been used for identification and analysis of various tissues across multiple disciplines [25]. The exact biology of fluorescence signal is not currently known, however, calcium-sensing receptors and vitamin D receptors are possible candidates. The levels of these proteins in tissue has been shown to correlate with intensity of parathyroid fluorescence signal [26]. There has been reports of lower signal intensity in parathyroid adenomas and which may be observed due to down regulation of the aforementioned proteins [27].

Parathyroid autofluorescence is a relatively new entity in endocrine surgery and was reported in a pilot study done in Vanderbilt University [28]. In this study, 785-nm U- type diode laser was used for tissue excitation in 21 patients. Fluorescence intensity was measured from multiple locations, including thyroid, parathyroid, fat, muscle, and lymph nodes. Among the tissues measured, fluorescence intensity of the parathyroid was found to be the strongest, followed by thyroid and then the surrounding muscle and adipose tissue. Thyroid and the parathyroid glands were found to have a peak emission at 820 nm [28]. Since the peak emission is the same for both thyroid and parathyroid, presence of the same fluorophore in both tissues has been implicated, however, in greater concentrations in parathyroid tissue. There have been multiple clinical studies that have examined the implications and utility of this technology in clinical practice.

McWade et al. investigated parathyroid AF using NIFI in 2015 by a group in. They looked at AF in 264 parathyroid glands from 137 patients and found the accuracy of AF to be between 94 and 100% across a variety of disease states. However, a lower accuracy was reported in patients with secondary hyperparathyroidism, where NIFI detected only 54% of parathyroid glands [26]. In addition, they noted



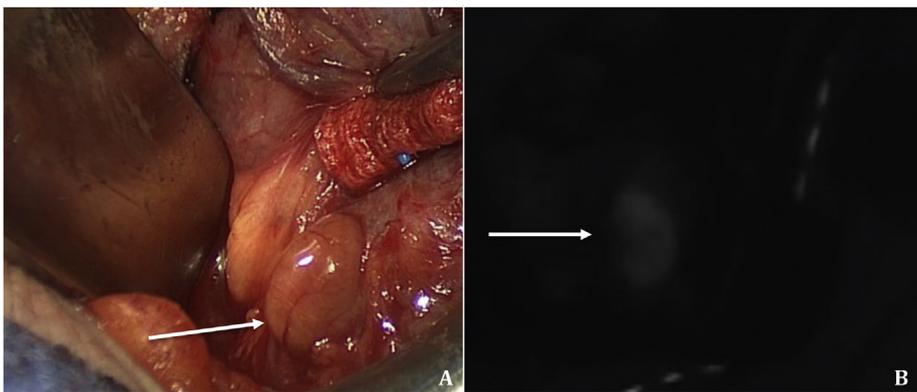
**Fig. 1.** Patient with primary hyperparathyroidism and right lower parathyroid adenoma. ICG was injected after mobilization of thyroid lobe. (A) No Fluorescence (B) ICGA with grey scale view, showing right lower adenoma with vascular pedicle. (C/D) Green ICGA fluorescence, solid arrow showing parathyroid and dashed arrow showing thyroid lobe.



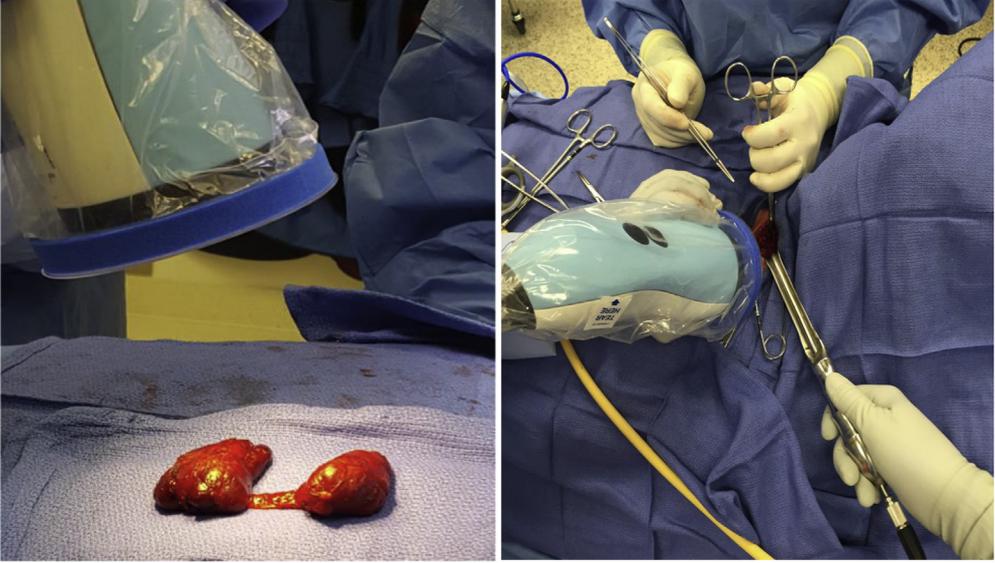
**Fig. 2.** Patient underwent subtotal parathyroidectomy. (A) Remnant parathyroid (arrow) gland (B) ICGA with grey scale view showing good remnant perfusion (C/D) Green ICGA fluorescence of remnant parathyroid.

variability in signal intensity, which was influenced by body mass index, disease state, vitamin D, and calcium levels. The heterogeneity of parathyroid gland signal intensity was noted in a study by Kose et al. They assessed 199 parathyroid glands in 50 patients undergoing parathyroidectomy and found that hyperfunctioning parathyroid glands had a lower mean normalized AF intensity and higher rate of signal heterogeneity compared to normal parathyroid glands [29].

The AF property of parathyroid glands using NIFI has been evaluated by multiple centers. An Argentinian group evaluated 28 patients and reported high rates of parathyroid gland identification with higher intensity parathyroid fluorescence compared to surrounding tissue [30]. Another study evaluated parathyroid AF both ex vivo and intraoperatively. NIFI was used to assess surgical specimens from 28 patients to detect iatrogenically resected parathyroid glands. When used ex vivo NIFI was found to have 94.1% sensitivity and 80% specificity for parathyroid gland identification [31]. Intraoperative evaluation of parathyroid glands in vivo was found to have a sensitivity of 98.8%. In addition, they reported 5 cases where no parathyroid tissue was visually identified and NIFI assisted in correctly



**Fig. 3.** Left upper parathyroid gland. (A) Intraoperative view, (B) Intraoperative view with NIFI demonstrating parathyroid gland AF.



**Fig. 4.** Images showing how the intraoperative near infrared probe is used to detect fluorescence signal intraoperatively. Ideally, it should be held 15–20 cm from the specimen or surgical field.

localizing the parathyroid gland [31]. Other studies in literature had similar results with improved localization and identification of parathyroid glands using NIFI [32,33].

One of the largest parathyroid gland AF studies was conducted at Cleveland Clinic (in press). The aim of this prospective study was to determine both the accuracy of NIFI to detect parathyroid glands in patients undergoing thyroidectomy and parathyroidectomy. A total of 550 specimens were imaged with NIFI and then sent to pathology for confirmation. The sensitivity, specificity, and positive and negative predictive values to predict parathyroid tissue were found to be 98.5%, 97.2%, 95.1% and 99.1%. Assessment of total thyroidectomy specimens, incidentally resected PGs were identified with AF in 5% of cases, leading to auto transplantation. In patients with primary hyperparathyroidism and negative preoperative localization studies, NIFI was able to detect 21% of abnormal glands before visual identification.



**Fig. 5.** (A) Intraoperative NIFI demonstrating incidentally found parathyroid AF (arrow) on total thyroidectomy specimen. (B) Parathyroid gland (arrow) has been removed from the main specimen for autotransplantation.

Overall, NIFI of parathyroid gland AF enables visualization of the parathyroid glands with relatively high sensitivity, and without significant interference from the thyroid or surrounding tissue. NIFI allows recognition of parathyroid glands *ex vivo* and allows immediate auto transplantation. In addition, there may be utility in using NIFI to confirm parathyroid gland tissue instead of frozen section, however, further investigation is warranted. Also, no intravascular contrast agents are necessary for imaging. These properties offer a significant benefit over ICG imaging. However, AF NIFI cannot evaluate perfusion.

## Fluorescence and autofluorescence in thyroid cancer surgery

The use of ICG has and NIFI AF has not been evaluated in with respect to thyroid cancer surgery and assessment of margins during resection. Nevertheless, ICG and NIFI AF can be useful in parathyroid gland localization in thyroid cancer patients and preservation as described previously. One utility of AF is that the thyroid gland and central neck dissection contents can be imaged in the sterile field to rule out incidental parathyroidectomy. Our group at the Cleveland Clinic has also looked at whether ICG could be used to identify sentinel lymph nodes, both in the central and lateral neck. In our unpublished experience, we did not observe that ICG could serve that purpose with either systemic or peri-tumoral injection. This attempt was limited by false positives and false negatives.

### Practice points

#### Dosage of ICG

- ICG is typically available power form consisting of 25 mg of ICG. This is usually dissolved in 10 mL of sterile injectable saline, resulting in a 2.5 mg/mL injectable solution.
- The toxic level for ICG is considered to be 5 mg/kg. The typical administration of 5–10 mg in multiple doses during a course of an operation is generally considered safe and well below the toxic level.

#### Administration of ICG

- Parathyroidectomy
  - Exposure of the central neck is obtained and the ipsilateral thyroid lobe is retracted medially
  - 5 mg ICG (2.5 mg/mL solution) is administered intravenously by anesthesiology.
  - After approximately 30 s to 1 min, an uptake in the parathyroid and thyroid gland(s) can be observed with the NIFI camera (Fig. 1).
  - The same dose can be repeated for the contralateral side once adequate exposure is achieved.
  - The parathyroid glands should appear more vascular than the thyroid gland, however, this distinction can vary depending on the proximity of the parathyroid glands to the thyroid.
- Subtotal parathyroidectomy
  - ICG can be utilized to aid with localization of parathyroid glands and assessment of remnant vascularity. ICG angiography is used before remnant creation to assess the perfusion of each candidate gland. This could then guide the selection of the remnant. Before removal of the other glands, another injection of the dye can be done to confirm vascularization of the remnant (Fig. 2), which could be followed by resection of the other abnormal glands.
- Total thyroidectomy or thyroid lobectomy cases.
  - The same dosage as described above is recommended.
  - ICG should be administered after mobilization of the ipsilateral thyroid lobe to help with localization and after lobectomy to assess perfusion of parathyroid glands.

### Autofluorescence with NIFI

- Parathyroidectomy
  - Exposure of the central neck is obtained and the ipsilateral thyroid lobe is retracted medially
  - Operating room lights are turned off, and NIFI is performed, by holding the camera 20 cm from the surgical field to identify potential parathyroid glands (Fig. 3, Fig. 4).
  - Parathyroid gland should have higher signal intensity compared to surrounding tissue
  - If no parathyroid gland tissue identified, operative dissection of the central neck continues in the usual fashion. NIFI can be repeated any time to aid with identification of suspected parathyroid glands.
  - The same technique used for the contralateral side.
- Total thyroidectomy and thyroid lobectomy
  - Exposure of the central neck is obtained and thyroid lobe is mobilized
  - After thyroid exposure is attained, NIFI is performed as described above to identify any bright autofluorescence signals that could represent parathyroid glands.
  - After completing a total thyroidectomy or thyroid lobectomy, the specimen can be examined in the field using NIFI to identify any focal autofluorescence signal which can represent parathyroid gland tissue (Fig. 5). This tissue should be sent to for confirmation of parathyroid tissue before autotransplantation.
  - Any specimen (i.e. lymph node, central neck dissection contents) removed can also be imaged NIFI to determine presence of parathyroid tissue.

### Research agenda

There is a need to perform a multicenter randomized study comparing ICG or AF technology to conventional thyroidectomy technique to objectively document whether the use of these technologies reduce permanent hypocalcemia. This would require a large patient sample and a multicenter collaboration. In addition, future research could also focus on the utility of AF to differentiate hypersecreting from suppressed parathyroid glands.

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