

The use of Indocyanine green in endocrine surgery of the neck

A systematic review

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Abstract

Background: The insufficient reliability of preoperative imaging technology and limited convenience of intraoperative visualizing techniques have been associated with difficulty in surgical navigation in neck endocrine surgery. Indocyanine green (ICG) fluorescence imaging has stood out as the real-time intraoperative guide amidst research for novel modalities, with an emerging use in endocrine surgery.

Methods: We performed a systematic review of the PubMed, Scopus and Embase databases, to identify published studies on parathyroid and thyroid operations employing ICG. Well-described articles were selected according to 7 criteria and analyzed per operation type and organ structure.

Results: Twenty-one articles matched our selection criteria. Dosage, equipment, and techniques are well-described in literature. ICG was found to significantly enhance the surgical experience and outcomes. Occasional discrepancy among studies was attributed to the lack of standard quantification of values and divergence of study designs.

Conclusion: The most successful applications of ICG are:

1. delineation of hyperplastic or adenomatous or ectopic parathyroids,
2. decision making during subtotal parathyroidectomy,
3. preservation of parathyroid function in thyroid operations and
4. reoperation after failed past neck exploration.

Future research is needed for standard quantification of fluorescence intensity and objective comparisons.

Abbreviations: 5-ALA = 5-aminolevulinic acid, BABA = bilateral axillo-breast approach (robotic thyroidectomy), BMI = body mass index, CEA = carcino-embryonic antigen, CT = computed tomography, DTC = differentiated thyroid cancer, FI = fluorescence intensity, ICG = indocyanine green, ioPTH = intraoperative parathormone, ISPG = remaining in situ parathyroid gland, MB = methylene blue, NIRF = near-infrared fluorescence, PG = parathyroid gland, PH = postoperative hypoparathyroidism, PHPT = primary hyperparathyroidism, POD = post-operative day, PTH = parathormone, PTX = parathyroidectomy, RCT = randomized clinical trial, SHPT = secondary hyperparathyroidism, SPTX = subtotal parathyroidectomy, TIGMA = ^{99m}Tc-macroaggregated human serum albumin and indocyanine green, TPTX = total parathyroidectomy, TT = total thyroidectomy, US = ultrasound.

Keywords: endocrine surgery, indocyanine green, parathyroid gland, thyroid gland

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1. Introduction

Real-time intraoperative identification and functional maintenance of structures are of major importance in endocrine surgery, with a critical role in clinical outcomes and patients' quality of life. Limitations of naked eye inspection and subjectivity of palpation are imposing challenges even for the most experienced surgeons, and despite the advances in preoperative imaging techniques, there is still need for precise intraoperative visualization.^[1–3] In thyroid surgery, the use of loops magnification as a microsurgical tool for the visualization of parathyroid glands and the recurrent laryngeal nerve is one of the most common tools.^[4] A novel technique has been proposed for the intraoperative localization of parathyroid adenomas involving Tc99m-sestamibi.^[5]

Recently, attention has been focused on intraoperative imaging with near infrared fluorescence (NIRF) and endogenous or exogenous contrast agents, which are attractive due to their high penetration depth and low scattering in human tissue.^[2] Among exogenous fluorophores, indocyanine green (ICG) has taken the forefront, bringing promising results in clinical trials.

ICG is an inert, non-radioactive and non-toxic water-soluble molecule that rapidly binds plasmatic lipoproteins upon intravenous administration, infilling the intravascular compartment. When excited with NIR light at a wavelength of ~800 nm, it emits a strong, fluorescent signal, detectable by devices that contain a charge-coupled camera. Thus, it acts as a real-time contrast agent for perfusion assessment and detailed identification of hyperperfused anatomic structures. ICG was approved for clinical use by the Food and Drug Administration in 1959 and has long been applied in a wide spectrum of medical interventions, including cholangiography, gastrointestinal operations, lymph node dissection and evaluation of skin flaps perfusion.^[6–9] Clinical research with ICG has been gaining momentum because of the compound's excellent pharmacokinetic properties. The short half-life of 3 to 5 minutes in the bloodstream and elimination after 15 to 20 minutes allow consequent injections and inspection of a gland without interference from a previously visualized area. ICG is completely excreted into the bile, with a very low incidence of serious adverse effects (estimated 0.05%).^[2]

As the endocrine glands are richly vascularized structures, they can be easily delineated with the help of ICG, due to their intricate capillary network. Our aim is to provide a cumulative review of technical details of ICG visualization (dosing, technique, encountered shortcomings etc.) and results obtained by each type of operation.

2. Methods

In our initial bibliographic screening, the greatest volume of encountered articles and most consistent applications of ICG in endocrine operations pertained to the thyroid and parathyroid, except for a small number of articles on adrenal gland surgery (4 articles). Therefore, since this also preserves a better coherence of topographic anatomy, we saw greater utility in focusing our review on endocrine surgery of the neck.

From November 15th, 2017 to May 20th, 2018, we conducted a bibliographic search in PubMed, Scopus and Embase,

employing the search terms: Indocyanine green AND (thyroid OR parathyroid).

Only well-described studies were included in analysis. In order to be characterized as well-described, a study had to include a documented outcome concerning the intraoperative use of ICG and fulfill at least 5 of the following 7 criteria:

1. research question regarding intraoperative use of ICG on the thyroid or parathyroid glands,
2. individual dosage or dosage range,
3. operative course of ICG administration,
4. excluded patients,
5. scaled visualization results,
6. comparative results of other imaging methods and
7. specified presence or absence of complications.

A few articles not fulfilling these criteria (6 articles) and not included in the analysis are mentioned in the discussion for the purpose of future directions.

We then categorized the suitable and selected articles by operation type.

3. Results

There were 52 records identified in these databases. Of these, duplicates (1 article) and irrelevant studies (28 articles) were removed. Only studies in humans were considered relevant, except for one included in the introduction,^[10] for historical purposes. The remaining articles were assessed for eligibility. Table 1 shows general characteristics of all articles included in our review.

Twenty-one articles matched our search criteria. Of these, 9 articles applied to thyroid operations, 6 to parathyroid operations and 6 to both categories. The articles were thereby divided for analysis by operation type (thyroid or parathyroid surgery), with the latter 6 being discussed in both sections. The aim of ICG employment was mostly to visualize the parathyroid gland (PG). As far as thyroid visualization is concerned, only 2 studies were encountered, one of which is a case report of a

Table 1

General characteristics of articles included in our review.

Author	Article type	Sample size (number of patients)	Endocrine Gland
Chakedis ^[15] (2015)	Case report	1	Parathyroid
De Long ^[6] (2017)	Prospective clinical study	60	Parathyroid
Sound ^[7] (2015)	Case series	3	Parathyroid
Vidal Fortuny ^[8] (2018)	RCT	196	Parathyroid
Alesina ^[9] (2018)	Case series	5	Parathyroid
Yu ^[10] (2017)	Prospective clinical study	22	Parathyroid
Chernock ^[11] (2017)	Case report	1	Thyroid
Jung ^[12] (2014)	Prospective clinical study	7	Thyroid
Ladurner ^[13] (2017)	Prospective clinical study	30	Parathyroid
Sadowski ^[16] (2017)	Review	N/A	Parathyroid
Lang ^[17] (2017)	Prospective clinical study	70	Parathyroid
Zaidji ^[20] (2016)	Prospective clinical study	27	Parathyroid
Zaidji ^[24] (2016)	Prospective clinical study	33	Parathyroid
Vidal Fortuny ^[21] (2016)	Prospective clinical study	36	Parathyroid
Vidal Fortuny ^[23] (2016)	Prospective clinical study	13	Parathyroid
Vidal Fortuny ^[22] (2016)	Review	N/A	Parathyroid/thyroid
Kahramangil ^[26] (2017)	Review	N/A	Parathyroid/thyroid
Kahramangil ^[29] (2017)	Prospective clinical study	44	Parathyroid
Jitpratoom ^[1] (2017)	Review	N/A	Parathyroid/thyroid
Lavazza ^[16] (2016)	Review	N/A	Parathyroid/thyroid
Cui ^[25] (2017)	Prospective clinical study	29	Parathyroid

potential adverse effect of ICG and the other reports combined results with a utilized radioactive element.^[11,12] Overall, ICG was found to enhance the surgical experience auxiliary to traditional imaging options. Occasional discrepancy was observed among studies with the same objective, which was attributed to the small sample sizes and variations in the quantification of values among different studies. We saw greater utility in organizing our discussion in a systematic review form without meta-analysis, to avoid biased numerical conclusions due to the small sample sizes and to present the variety of surgical experiences obtained through synthetic logical interrelations. The cumulative dosage schemes, contraindications and drug interactions are discussed, followed by an operative course analysis per gland and type of surgery.

3.1. ICG visualization per structure and operation type

3.1.1. Challenges in parathyroid gland localization. Due to their small size, similar colorization and varying position, even PGs that are preoperatively well-located can be hard to distinguish from surrounding adipose, thyroid and lymphatic tissue. The most common tools to rely on are palpation, frozen sections, intraoperative parathormone (ioPTH) assay and discoloration occurring after disrupted perfusion.^[13] However, even the global visual assessment standards of discoloration have been shown unreliable in a study on 111 patients.^[14]

Consequently, ischemic injury or inadvertent removal are common and difficult to foresee and prevent, especially by inexperienced and low-volume surgeons. Exhaustive 4-gland exploration is neither desirable, as it can increase invasion, operative times, and the risk of failure or damage to the recurrent laryngeal nerve.^[6,15] Additionally, reoperation entails the obstacle of distorted anatomy and presence of scar tissue.^[15] Therefore, hypoparathyroidism resulting in hypocalcemia is the most common complication in endocrine neck surgery, appearing after up to 30% of total thyroidectomies. There are limited ways to predict whether this hypocalcemia will be transient or permanent, defined as hypocalcemia for more than 6 months (1–10% of patients).^[16] In operations where identification of PGs is essential (usually in thyroidectomy and parathyroidectomy procedures), ICG imaging has been tested to assist in overcoming these adversities.

3.1.2. Parathyroid gland preservation during thyroid surgery.

The Reported incidence of postoperative hypoparathyroidism (PH) with resulting hypocalcemia after total thyroidectomy (TT) varies between 0 to more than 60%, depending on the definition of PH. Although causes of PH can be multifactorial, the 2 most common are inadvertent removal or ischemic injury due to surgical manipulation, which distorts blood supply of the PGs left in situ (ISPGs).^[17] Moreover, TT has been shown to impair PG function even in cases of no clinical postoperative hypocalcemia.^[18]

The successful delineation of PGs was first shown in canine models, in which the glands are located cranial to the thyroid and external to its capsule. This position entails relatively explicit boundaries and low interference with the thyroid, contrarily to humans, where the PGs are normally found embedded in the thyroid parenchyma.^[19]

A primary look at ICG fluorescence in evaluating PG function in humans was performed in 2016. Zaidi et al studied 27 patients undergoing TT to investigate whether intraoperative PG fluorescence level could be associated with postoperative day (POD) #1 PH and hypocalcemia, and assist in intraoperatively identifying patients at risk of these complications.^[20]

There were 2 notable findings: First, mean PTH levels on POD #1 were significantly higher in patients with at least 2 PGs with >30% fluorescence (19.5 pg/mL), compared to the rest (9 pg/mL). Secondly, of the 85 glands visually identified, the majority (84%) exhibited some PG fluorescence. This finding led to the hypothesis that PGs could be demarcated prior to thyroid dissection, but background signal from the thyroid, which intensely fluoresced after ICG administration, prohibited PG isolation. Unlike sestamibi, thyroid uptake did not precede PG uptake, and therefore the authors did not see an advantage of ICG in this regard.

In a case control study, ICG angiography was used to preserve the inferior parathyroid during bilateral axillo-breast approach (BABA) robotic thyroidectomy, to compare the 2 groups (ICG vs traditional operation) in terms of PG-related results.^[10] Afterward, 22 patients with papillary thyroid carcinoma were matched to 2 control subjects each, providing a total of 66 subjects. Sex, age, tumor size, and surgery type (TT or thyroid lobectomy) were the parameters for matching. The authors claim that slow administration of ICG will allow PG discrimination from the thyroid and eliminate the simultaneous signaling.

Nine patients of the intervention group were subjected to an ioPTH assay before resection, which proved that all 13 illuminating structures were PGs, whereas surrounding tissue evaluated for reference was never found to be PG. However, the authors reported no biochemical or histological confirmation testing of the remaining 13 patients of the intervention group. The results showed similar rates of transient and permanent PH between the 2 groups, but a significantly lower rate of inadvertent PTX in the intervention group. Given that the causes of PH can vary, and the vascularization of only the inferior PGs was monitored with ICG (which are more difficult to identify and can, therefore, get injured more easily than the superior glands), the results are interpreted as favorable towards the utility of ICG.

Lang et al adopted a different approach, performing a large study to assess the residual PG perfusion and function not concurrently, but directly after TT, before closure.^[17] Seventy patients, all with 4, paraffin section-confirmed glands, underwent ICG angiography after TT. Glands with an identified vascular pedicle were left in situ, while glands with no pedicle preserved or unintentionally removed were autotransplanted to the ipsilateral sternocleidomastoid. The (FI) was calculated, defined as the contrast ratio of PG to the anterior trachea (set as 100%). The inferior glands showed a significantly lower FI (mean and maximum value) than the superior.

Interestingly, while normal-looking and discolored glands had similar FI values, there was a notable difference of outcomes. No patients with a maximum FI over 150% experienced postoperative hypocalcemia, while the majority of rest did. In fact, FI was found more prognostic than POD#0 hypocalcemia and % drop of PTH between POD#0 and 1 in predicting the development of PH. These results suggest that ICG angiography may offer a more coherent link between the surgeon's assessment of viability and the actual incidence of PH, which can be a result of combined causes.^[17] In case of discordance between the surgeon's assessment and ICG angiography, a number of studies have proposed performing a diagnostic parenchymal incision. In lack of active bleeding, the gland is autotransplanted.^[9,21,22]

In a study evaluating the perfusion of PGs following TT in 36 patients, at least 1 well-vascularized parathyroid was identified with ICG angiography in 83.3% of the patients, none of which developed PH on POD #1.^[10] Following thyroid resection, a grading scale was used for visual evaluation from grade 0

(absence of vascularity) to grade 2 (excellent vascularity), which was retrospectively linked to FI. Discrepancy of grades between visual assessment and ICG angiography was the case for 5 patients, in which a diagnostic parenchymal incision was performed on each gland. As predicted by ICG, active bleeding occurred in none of them, a fact that indicated distorted gland function. Consequently, the gland was autotransplanted to the sternocleidomastoid. Hence, in 13.8% of the patients, the visual evaluation resulted in false-negative error. In all cases of discordance, the incision assessment favored ICG superiority, whereas false-positive results were never obtained. A limitation of this study is that not all 4 glands were identified in every patient, which is not uncommon during neck surgery. Therefore, the perfusion of unidentified glands remained unknown, and this prohibited a direct conclusion based on individual postoperative PTH results.

Vascularity of PGs has been also tracked both before and after TT in a single study with 4 patients undergoing TT, with 12 out of 16 PGs being reported as visually overt before ICG administration.^[9] A first confirmation was made by evident autofluorescence after NIR light excitement at 700 to 900 nm without ICG. The intrinsic autofluorescence of the PGs is further discussed in Future Directions. According to ICG fluorescence, one PG was autotransplanted, although the specific FI findings are not reported. The lack of background thyroid signal is attributed to low-dose consecutive injections. There was neither postoperative PH nor hypocalcemia.

Finally, Vidal Fortuny et al recently performed the first relevant RCT, showing that ICG can preclude the need for standard postoperative follow-up and calcium supplementation by reliably predicting PH after thyroid surgery.^[8] Of the 196 patients undergoing ICG angiography, 146 had at least 1 well-perfused PG (ICG score = 2) and were randomized to receive either PTH-calcium measurement on POD #1 and systematic supplementation (control group), or no blood test and no supplementation (intervention group). In all patients, PTH and calcium levels were measured on the primary endpoint, set at POD #10–15. The 2 groups were similar regarding surgical diagnosis and operation length, and the visual scale of 0 to 2 was employed, with the lowest grade among 3 surgeons being taken into account.

The study had 2 notable findings. First, the intervention group was statistically non-inferior to the control group, indicating that ICG is a reliable predictor of function. Second, 34% of the 50 patients who were not randomized because of absence of an ICG-confirmed well-perfused gland developed PH either on POD #1 or by the end of the 15-day tracking period. Nonetheless, POD #1 measurement alone was found unreliable, as temporary disorders are often normalized in due time. Indeed, typical symptoms of hypocalcemia appeared in 2 patients of the intervention group, but were eliminated on POD #10, without supplementation.

As is evident from this study, a limitation with applying ICG in thyroidectomy is the fact that in most patients, not all 4 PGs are detected. Therefore, in those patients, a clear correlation between individual gland perfusion and postoperative PTH levels cannot be established.^[16] To overcome this and allow for comparable results, the authors limited their research question to patients with at least 1 well-perfused gland. Their results substantiate the claim made by Lang et al's group, that having one well-perfused PG will be more functional than having several less well-perfused ones.^[17]

3.1.3. Subtotal and total parathyroidectomy. Concerning subtotal parathyroidectomy (SPTX), a well-known defect of the established ioPTH assessment for evaluating PG function is

the inability to extract safe conclusions on individual glands, as circulating PTH is a result of the combined 4-gland excretion. Hence, the selection of a well-perfused gland to be left in situ may be challenging. Moreover, in secondary hyperparathyroidism (SHPT) of renal origin, which is one of the most common indications for SPTX, PTH levels decrease more slowly compared to patients with normal renal function. Therefore, the ioPTH assay can be even less representative of real-time PG function. Even in 4-gland hyperplasia (also indicative of TPTX or SPTX), ioPTH assay is problematic due to their possible uneven function. Crucial for a successful outcome are the correct localization of all 4 glands, the excision of 3 or 3.5, and confirmation of adequate function of the remnant.

Vidal Fortuny et al described the application of ICG angiography in SPTX in 13 patients. One patient underwent a simultaneous TT and 2 others a thyroid lobectomy.^[23] All 4 glands were successfully visualized, and ICG angiography was also used to select the best perfused remnant. Ten patients had 3.5 and 3 patients had 10 glands excised, respectively. Two cases of hypocalcemia were observed on POD #1, both eradicated after 48 hours. All POD #1 complications were shortly normalized, proving adequate remnant PG function.

Overall, this study shows that decision guidance with ICG is possible in selecting the most normal-looking PG for the subtotal excision (either an integral gland or half of it). If a gland is not well perfused, another can be chosen to be left in situ, which was the case with 1 patient. In all cases, the surgeons created “virtual remnants” using clips for all 4 glands and then through ICG angiography assessed the most suitable to undergo SPTX, which seems a promising strategy in this type of surgery. However, postoperative PTH as an absolute proof of result may be misleading in this small sample with SHPT of different origins. Hence, a larger or better perfused remnant will produce more PTH, whereas a remnant of the same size may produce different levels of PTH depending on the underlying disease.

The use of ICG has also been described in total parathyroidectomy (TPTX) for primary hyperparathyroidism (PHPT) because of a single or double adenoma, or 4-gland hyperplasia. Sound et al first described a three-case series of successful identification and excision of PGs with ICG fluorescence imaging.^[7] A parathyroid adenoma was resected in a patient with a past TT, an ectopic adenomatous gland in the thymic tissue was removed in a patient with a failed past neck exploration, while another ectopic PG adenoma was identified and removed in a patient with a history of thyroid lobectomy. In all cases, a much more intense PG signal was detected, compared to the surrounding tissue. These results can be explained as in none of the patients were the adenomas embedded within or surrounded by thyroid tissue, interference of which has been well described in surgery with ICG imaging.

Another study engaged 33 patients undergoing PTX, most (30 cases) had a first-time, sporadic disease and underwent a 4-gland exploration.^[24] Two patients had persistent disease after failed past exploration and one had recurrent disease. Of the 112 glands identified by naked eye, 104 fluoresced upon ICG administration. As expected, the majority (57.1%) demonstrated an FI over 70%. Although a simultaneous signal of over 70% was observed by the thyroid interfering with approximately half of the glands, in all 6 patients who underwent subtotal (3.5 gland) excision, adequate perfusion of the remnant PG tissue was ensured by ICG fluorescence, and none of them developed postoperative hypocalcemia. Interestingly, from the 66 removed glands, only 29% had been detected with sestamibi scan preoperatively.

Again, the authors conclude that ICG may be more advantageous in reoperative neck surgery or in patients with ectopic glands, due to minimized background signal.

Very consistent results were obtained in a study by DeLong et al on conventional TPTX.^[6] Of the 60 patients, 71.6% showed strong vascular enhancement, 21.7% moderate fluorescence, and only 6.7% demonstrated little or no uptake. In a study on neck surgery including one patient suffering from a right-upper PG adenoma, focused PTX with ICG was performed after the right enlarged PG was identified by US and sestamibi.^[9] Notably, the authors state that the FI did not differ between normal glands and the adenoma, which gives rise to the concern whether or not the adenoma would have been identified intraoperatively, in case it had not been successfully located in preoperative imaging.

3.1.4. Thyroid gland visualization. A challenging procedure in thyroid surgery is reoperation for tumor excision. Apart from the distorted anatomy, some types of cancer such as differentiated thyroid cancer (DTC) have been associated with a high rate of complications. Jung et al performed a study combining ICG with ^{99m}Tc macroaggregated human serum albumin (TIGMA) in 7 patients undergoing preoperative DTC surgery.^[12] Thus a dual radiofluorescent technique was formulated, which was well tolerated and had a 100% success rate. Using both a NIRF camera and a gamma probe for navigation, the surgeons completely resected all 10 recurrent lesions, and the postoperative scans showed no remnant tumors. A major difference to ICG administration is that the TIGMA (0.1 mL) was injected directly on the lesion before incision, and ultrasound (US) and a gamma probe were used to determine the site of the injection and tumor borders. Macroaggregated albumin was reported to prevent diffusion into surrounding tissues, and TIGMA generated brighter and more precise visualization compared to ICG alone. Nevertheless, this method involves exposure to radiation, and further studies are needed to demonstrate reproducible results.

A case-report associated intraoperative ICG administration with the black-brown discoloration of the thyroid referred to as “black thyroid”, an asymptomatic condition usually discovered incidentally during surgery for another cause.^[11] “Black thyroid” has previously been attributed to long-term treatment with the antibiotic minocycline. As this patient was not taking any medications and all other causes were excluded, the finding was attributed to ICG. The reasons for this were the fact that the thyroid is known for iodine uptake, while ICG uptake by the thyroid has been reported in other studies, and in this patient a follicular thyroid nodule was under-colored (similar to hypofunctional neoplasms identified with ICG).^[11,12,20,25] Only a moderate dose of 7.5 mg was administered. The authors speculate there is probably no significant clinical impact, and caution against misinterpretation for other underlying conditions.

3.2. Clinical variables of ICG uptake

Some of the available studies investigate the ability of certain clinical variables to influence ICG uptake. In PTX operations, Zaidi et al found no significant correlation between ICG uptake and gender, BMI, vitamin D, preoperative PTH, thyroid size, and histology of PGs.^[24] There was a tendency towards increased fluorescence in patients younger than 60 years old. Significantly higher fluorescence was also observed in patients presenting with preoperative calcium levels over 11 mg/dL and in these tumors larger than 10 mm.

In regard to SHPT, Cui et al also examined potential uptake factors in 20 patients, with somewhat different results.^[25] In

particular, preoperative PTH over 1900 pg/mL was associated with increased FI, whereas age and preoperative serum calcium were insignificant factors. Increased FI was also observed in PGs (but not PG neoplasms) over 10 mm. Therefore, dialysis time, calcitriol pulse therapy and histology were examined and showed no relationship with FI. In PG monitoring during thyroid surgery, Zaidi group in their relevant study found no correlation of patient age, sex, BMI, thyroid pathology, and parathyroid size to ICG uptake.^[20] Nevertheless, these statistical samples do not suffice to provide definitive conclusions on general population.

3.3. Comparison to other modalities and preoperative imaging

Until recently, the proposed intraoperative localization techniques did not involve NIRF. Of these, sestamibi scintigraphy is probably the most established, with a sensitivity of 69% to 75%.^[26] However, beside the exposure to radiation, it is unclear whether this method can delineate normal PGs without adenomas.^[13] Also, Optical Coherence Tomography can provide high-resolution imaging in 2 mm depth, but with unproven efficacy in clinical trials.^[13] Intraoperatively, classic options in parathyroid surgery are PTH assessment, the defects of which have been already discussed, and frozen sections, which are time-consuming and can be harmful to the vascular integrity of structures.^[2] Intraoperative US is also an option, but often provides insufficient assistance, especially in obese patients and in areas with multiple adhesions.^[26] In the aforementioned comparative study on TPTX by Cui et al, the sensitivity of CT, sestamibi scan and US were 85.7%, 62.3%, and 81.8%, respectively.^[25] Other studies have found it to be even lower.^[2] ICG was found superior, with a sensitivity of 91.1%, and was also associated with reduced operative times and increased complete resection rate.

ICG superiority over sestamibi was also observed in PTX by DeLong group.^[6] Among 54 patients who underwent a preoperative sestamibi scan, a parathyroid adenoma was detected in 66.7%, while localization failed in the rest (18 patients). Contrariwise, ICG angiography revealed a distinct, fluorescent adenoma in all patients. In general, these imaging techniques (sestamibi, CT, and US) have been reported to be of poor or inconsistent accuracy.^[2]

Surgeons would agree that the optimal intraoperative imaging compound should be safe, convenient and with reproducible results, which has led to a tendency to avoid other previously used staining agents. Among the first studied, methylene blue (MB) was associated with neurologic complications such as toxic encephalopathy. Another intraoperative dye, 5-aminolevulinic acid (5-ALA), was eventually characterized cumbersome due to the requirement for lengthy photosensitizing preparation and inhomogeneous fluorescence.^[7,20] Ostensibly, ICG appears to be the safest, most serviceable and consistent intraoperative dye due to the extremely rare adverse effects, high accuracy, convenient administration, fast elimination and stability of the fluorescent effect.

3.4. Contraindications to ICG usage – drug interactions

Certain conditions are contraindicated with this drug. These are thyroid disorders such as hyperthyroidism, hypothyroidism and thyrotoxicosis (intercurrent in parathyroid operations), primary or secondary sickle cell anemia, uncontrolled hypertension, pheochromocytoma, pregnancy, extreme dehydration, seizures,

Table 2**ICG dosage and equipment used in thyroidectomy operations.**

Group	Visualizing Equipment	Individual Dose (mg)	Number of doses/ patient
Alesina ^[7] (2018)	Endoskope, Karl Storz	2.5	3+, repeated
Chernock ^[8] (2017)	Unspecified	7.5	Unspecified
Vidal Fortuny ^[10] (2016)	PINPOINT, Novadaq	8.75	Unspecified
Yu ^[12] (2017)	Firefly, Intuitive Surgical	10	1
Lang ^[13] (2017)	SPY, Novadaq	2.5	1
Zaidi ^[21] (2016)	PINPOINT, Novadaq	5	2
Kahramangil ^[27] (2017)	PINPOINT, Novadaq	5	1

asthma and severe renal impairment. Also, as the substance contains 5% iodine, patients with known allergies to iodine/iodide containing compounds are not eligible for ICG administration. Finally, heparin solutions containing sodium bisulfate reduce the absorption peak of ICG in the bloodstream and therefore the use of anticoagulants other than heparin should be preferred in collecting samples for analysis, as recommended by the manufacturer (Akorn Pharmaceuticals, Lake Forest, IL).

3.5. Dosage

The optimal total dose for ICG administration has not been well defined. In most studies, the dose and frequency of injections are decided at the discretion of the operating surgeon. The toxic level dose for an adult is 5 mg/kg of body weight circulating in the unit of time.^[21,23] Other groups have restricted this to a more conservative maximum of 2 mg/kg.^[7] However, in all cases, the doses administered are well below these limits, even in multiple administrations of 2.5 to 10 mg in total during the course of a typical operation. Individual doses of up to 30 mg ICG are characterized as safe for a 60 kg adult, as indicated by the liver excretory function test.^[10]

Usually, 25 mg of ICG, commercially available in powder form, are dissolved in 10 mL of saline or sterile water, forming a 2.5 mg/mL injectable solution. The reported time interval between injection and fluorescence ranges from 15 seconds to 5 minutes.^[7,10,11,17,24] Maximum fluorescence has been observed approximately at 5 minutes after visualization, lasting for 20 minutes in most studies. This means that successive injections may be required for longer-lasting visualization.

Upon excitement with NIR light, images appear in shades of grey depending on ICG flow in the bloodstream, thereby reflecting the vascular integrity of the visualized gland. Integer grading scales from 0 to 2 or 0 to 3 are often used for quantification of fluorescence intensity (FI). Percentage ranges of fluorescence (fluorescent volume out of total volume of the gland), are usually matched to these integers at the discretion of the authors. A gland appears black (no remnant vascularity),

grey or heterogeneous (partial vascularity), or white (good vascularity).

To prevent spillage of ICG in the operative field due to vessel damage and consecutive loss of imaging clarity, careful dissection and blood loss minimization is highly advisable.^[10] The dosage schemes and visualizing equipment used in each study are summarized in Table 2, for thyroid operations and in Table 3, for parathyroid operations.

4. Discussion

Indocyanine green fluorescence imaging has stood out as the real-time intraoperative guide in endocrine surgery. According to our findings, the most successful applications of ICG are:

1. delineation of hyperplastic or adenomatous or ectopic parathyroids,
2. decision making during subtotal parathyroidectomy,
3. preservation of parathyroid function in thyroid operations and
4. reoperation after failed past neck exploration.

4.1. Limitations/future directions

One of the limitations of ICG imaging is the subjectivity of FI scoring, which makes the assessment of FI inconsistent among studies. Different researchers define FI with respect to different quantities, such as fluorescent volume out of total gland volume or contrast ratio of the PG to the anterior trachea, which prohibits direct comparisons.^[17,20] Additionally, even if they agree on the quantity measured, researches usually employ grading scales that match the integers 0, 1, 2, and 3 (obtained by visual inspection) to percentage ranges arbitrarily, as no universal standard exists yet. This implies that, a percentage of FI in 1 study may not necessarily correspond to the same percentage in another. As current camera systems allow for qualitative evaluation only, new technologies are being developed to help quantify ICG fluorescence in absolute values, which is necessary

Table 3**ICG dosage and equipment in parathyroidectomy operations.**

Group	Visualizing equipment	Individual Dose (mg)	Number of doses/ patient
DeLong ^[4] (2018)	PINPOINT, Novadaq	7.5	1+, repeated
Sound ^[5] (2015)	PINPOINT, Novadaq	5	2
Alesina ^[7] (2018)	Endoskope, Karl Storz	2.5	3+, repeated
Vidal Fortuny ^[11] (2016)	PINPOINT, Novadaq	8.75	Unspecified, repeated
Zaidi ^[14] (2016)	PINPOINT, Novadaq	5	2
Chakedis ^[17] (2015)	PINPOINT, Novadaq	7.5	1
Cui ^[23] (2017)	AISERY Co.	0.5 mg/kg	1

to enable objective comparison among future studies.^[23] Pixel/color analyzing computer programs may be an option for this.^[18]

In comparative studies, a similar pitfall arises because of the subjectivity of naked eye identification without ICG in control groups. This is inevitably a subjective decision that may involve surgical expertise and can cause frustration in making comparisons and isolating the cases where PGs would have been missed with the other methods alone. Therefore, designing larger and standardized comparative studies is challenging. However, the case-control by Vidal Fortuny et al showed that this setback can be eliminated.^[8]

Moreover, as not all 4 glands are usually identified, a direct correlation between FI and postoperative result is obscure, unless cases are made comparable by a research question limited to the identification of at least 1 well-perfused PG, or by including only patients with 4 histologically confirmed PGs.^[8,17,23]

Also, there is concern on the shortcoming of thyroid interference, due to the general lack of the molecule's histospecificity.^[20,25] A proposed solution is chemical coupling of ICG to a protein uniquely expressed at the organ or structure under examination. This has been performed in colorectal metastases, by coupling ICG with carcino-embryonic antigen (CEA).^[20] Antibody coupling of ICG to integrin, HER-2 and VEGF proteins, which are overexpressed on the surface of tumor cells, has achieved promising results in tumor visualizing.^[20,25] However, to our knowledge, trials in endocrine surgery have not been reported yet. Future research is needed to provide more comprehensive input on these so far successful techniques.

Beyond exogenous fluorophores, intrinsic autofluorescence of the PGs (natural emission of light by endogenous protein molecules on organ surfaces) has also been utilized in endocrine surgery. The hypothesis is that autofluorescence emerges from a calcium-sensing receptor protein which is found at maximum concentration in PG tissue.^[2] Recently, Ladurner et al identified the PGs in minimally invasive thyroid and PG surgery using a NIR/ICG endoscopic system (Karl Storz, Tuttlingen, Germany) modified at a shorter wavelength of 690 to 770 nm to expose the glands' auto-fluorescence capacity.^[13] Of the 42 PGs examined, 34 exhibited a fluorescent signal, which was similar among adenomas, hyperplasia and normal glands. The 8 undetected PGs were embedded inside fatty tissue. This tissue exhibited no considerable fluorescence, similar to the thyroid and lymph nodes. Although the fluorescent "signature" of PGs has been previously observed elsewhere, further adaptation of ICG imaging systems is needed to detect autofluorescence, which is substantially weaker than ICG.^[13,27,28] Nevertheless, plausible advantages are clearer identification due to lack of interference by the thyroid and equal suitability for demarcating adenomas, hyperplasia and normal glands.

A comparison between ICG and autofluorescence was made by Kahramangil and Berber using a spectrometer to expose autofluorescence of the PG.^[29] The subjects were 2 groups of 22 patients each, who underwent either TT or thyroid lobectomy. Both of the techniques had similar detection rates (98% for autofluorescence and 95% for ICG), as well as postoperative hypocalcemia rates (9% and 5%), but differed in regard to time of detection: autofluorescence identified the PGs before naked-eye detection more frequently than ICG imaging (52% and 6%, respectively). However, the clinical importance of this finding is not clarified yet.

As a limitation of our study, we report the absence of Web of Science as a database in our research. We have included three databases (PubMed, Scopus, and Embase) in our bibliographic

search, achieving validity according to international guidelines for reviews.^[30]

5. Conclusion

ICG has demonstrated a high safety and convenience profile. It is able to assist the surgeon in tracking the effects that mechanical manipulation has on the viability of organ structures with greater accuracy and allow timely prevention or fixation of otherwise inevitable surgical complications. Thereby, lengthy and invasive neck explorations can be reduced in practice. However, ICG imaging must not be considered a panacea, as it cannot outperform critical decision making by an experienced surgeon. Standard preoperative and intraoperative imaging should be appropriately performed, to prioritize the patient's best interest (maximal diagnostic information versus minimal risk). The compound's excellent properties render it a very competent adjunct for navigation in the common cases of discordance or doubt.

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