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**INTRAOPERATIVE INDOCYANINE GREEN (ICG) ANGIOGRAPHY FOR
THE IDENTIFICATION OF THE PARATHYROID GLANDS: A
SYSTEMATIC REVIEW AND FUTURE PERSPECTIVES**

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Εισαγωγή/Σκοπός: Πρόσφατα, η απεικόνιση με φθορισμό με το πράσινο της Ινδοκυανίνης , έχει χρησιμοποιηθεί για την αναγνώριση των παραθυροειδών αδένων κατά την διάρκεια επεμβάσεων θυροειδούς και παραθυροειδούς. Πάραυτα, μια συνολική κοινή απόφαση για την βελτίωση της τεχνικής, της δόσης και του χρόνου χορήγησης της ICG και τέλος της ερμηνείας και της κλινικής χρησιμότητας, υπολείπονται δεδομένων. Ο στόχος αυτής της ανασκόπησης, είναι να ερευνηθεί την χρήση της ICG αγγειογραφίας κατά την διάρκεια της θυροειδεκτομής ή και της παραθυροειδεκτομής για την αναγνώριση, όπως και της διαφύλαξης της ακεραιότητας των παραθυροειδών αδένων.

Υλικά και Μέθοδοι: Βάση δεδομένων Pubmed ερευνήθηκε συστηματικά για δημοσιεύσεις που αφορούσαν την διεγχειρητική απεικόνιση με ICG, σε ασθενείς που υποβλήθηκαν σε θυροειδεκτομή ή παραθυροειδεκτομή.

Αποτελέσματα: 18 δημοσιεύσεις που αφορούσαν 612 ασθενείς, εκ των οποίων 71 παραθυροειδεκτομές και 541 θυροειδεκτομές συμπεριλήφθηκαν με βάση τα προαπαιτούμενα κριτήρια. Έντεκα δημοσιεύσεις αφορούσαν την χρήση της ICG αγγειογραφίας για την αναγνώριση των παραθυροειδών αδένων κατά την θυροειδεκτομή και επτά κατά την παραθυροειδεκτομή για πρωτοπαθή και δευτεροπαθή υπερπαραθυροειδισμό.

Συμπεράσματα: Η απεικόνιση με ICG φθορισμό, είναι μια γρήγορη, απλή και αναπαραγωγίσιμη μέθοδος ικανή για διεγχειρητικό εντοπισμό και έλεγχο της λειτουργίας των παραθυροειδών αδένων και μπορεί να βοηθήσει τους χειρουργούς στην λήψη απόφασης. Παρόλα αυτά, η τεχνική της απεικόνισης με ICG φθορισμό για την ανίχνευση των παραθυροειδών αδένων ακόμα ελλείπεται δεδομένων και περαιτέρω μελέτες απαιτούνται για να εδραιωθεί η κλινική της χρησιμότητα.

Λέξεις Κλειδιά:

Πράσινο Ινδοκυανίνης, φθορισμός, παραθυροειδείς αδένες, θυροειδεκτομή, παραθυροειδεκτομή, ανασκόπηση.

Abstract

Background/Aim: Recently, indocyanine green (ICG) fluorescence imaging has been used for the identification of the parathyroid glands (PG) during thyroid and parathyroid surgery. However, an overall consensus on the optimal technique, the dosage, the timing of the ICG administration and finally its interpretation and clinical usefulness is still lacking evidence. The aim of this review is to investigate the use of ICG angiography during thyroidectomy and/or parathyroidectomy for identification as well as for the perfusion integrity of the parathyroid glands.

Materials and Methods: The PubMed database was systematically searched for publications regarding intraoperative ICG imaging in patients that undergo thyroidectomy or parathyroidectomy.

Results: Eighteen publications reporting on 612 patients, namely 71 parathyroidectomy and 541 thyroidectomy patients met the inclusion criteria. Eleven publications reported the use of ICG angiography for the identification of the parathyroid glands during thyroidectomy and seven during parathyroidectomy for primary and secondary hyperparathyroidism.

Conclusion: ICG fluorescence imaging is a simple, fast and reproducible method capable of intraoperatively visualizing and assessing the function of parathyroid glands, and can, therefore, assist surgeons in their decision-making. Despite all this, ICG fluorescence imaging technique for PG detection still lacks standardization and further studies are needed to establish its clinical utility.

Key Words:

Indocyanine green, fluorescence, parathyroid glands, thyroidectomy, parathyroidectomy, review.

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Introduction

Intraoperative identification of the parathyroid glands (PG) is a major concern either during parathyroidectomy (PTX) or when performing total thyroidectomy (TT) (1). Intraoperatively, the identification of PGs can be performed by two invasive alternatives: i) the frozen section method or ii) the “float or sink” technique. The frozen section analysis requires sacrificing a PG slice while the “float or sink” method is based on tissue density and thereafter a PG autotransplantation is needed (2).

The current identification method is usually based on visual inspection and palpation by the surgeon with careful preservation of the PG blood supply, depending greatly on the surgeon’s experience (1).

Although inspection and palpation are still the main tools, several other techniques have been proposed for PG visualization and perfusion, but most are of limited value or have become obsolete. Therefore, there is no proven or reliable non-invasive intraoperative method to identify PG and assess PG vascularization (3).

To overcome this, near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) imaging has been recently introduced and has been suggested as a useful tool for the identification and preservation of the PGs (4, 5). However, there are significant differences in study design, inclusions, definitions and management protocol between reported studies (6-8). Additionally, there is no consensus regarding the standardization of technical details, while a universal objective scoring system is missing, thus, the correlation between intraoperative findings and postoperative outcomes remains unclear (9).

Taking all this into account, we performed a pooled analysis of the available literature on this important yet controversial topic and review the utility of this clinically promising technique in PG detection and viability during total or near-total thyroidectomy (T-NT) or PTX.

Materials and Methods

Search strategy

This systematic review was conducted by searching the medical literature in MEDLINE and SCOPUS, guided by the PRISMA protocol (10, 11). The search was conducted in January 2019. All the retrieved article titles and abstracts were screened for relevant manuscripts. A full-text review of the selected relevant articles was made in order to detect the studies included in this systematic review. Relevant full-text review and/or systematic review manuscripts were used to retrieve articles of any publishing date from their reference list and include them in this systematic review.

Medical Subject Heading (MeSH) terms and text words were used based on the following search strategy:

- i) Group A terms: “indocyanine green” OR “ICG”,
- ii) Group B terms: “thyroid” OR “parathyroid”, Group C: “Intraoperative”,
- iii) Group’s A, B, and C terms were combined, so our search algorithm was (((((indocyanine green) OR ICG)) AND intraoperative)) AND ((thyroid) OR parathyroid), and
- iv) Additional limits were applied to restrict manuscripts to ones related to human subjects, reported in English, and dated back to 10 years at the most.

Inclusion - exclusion criteria. Of the articles retrieved through the above-described search strategy, only those that met the following criteria were included to this systematic review: i) studies on the use of intraoperative use of ICG for parathyroid visualization during thyroidectomies or parathyroidectomies but not studies on the intraoperative ICG fluorescence use for other surgeries, ii) original papers and not review papers, even though the reference lists of the latter were used to retrieve any relevant study, iii) articles reporting at least one clinical case but not animal studies, and iv) no articles with the same patients in different journals.

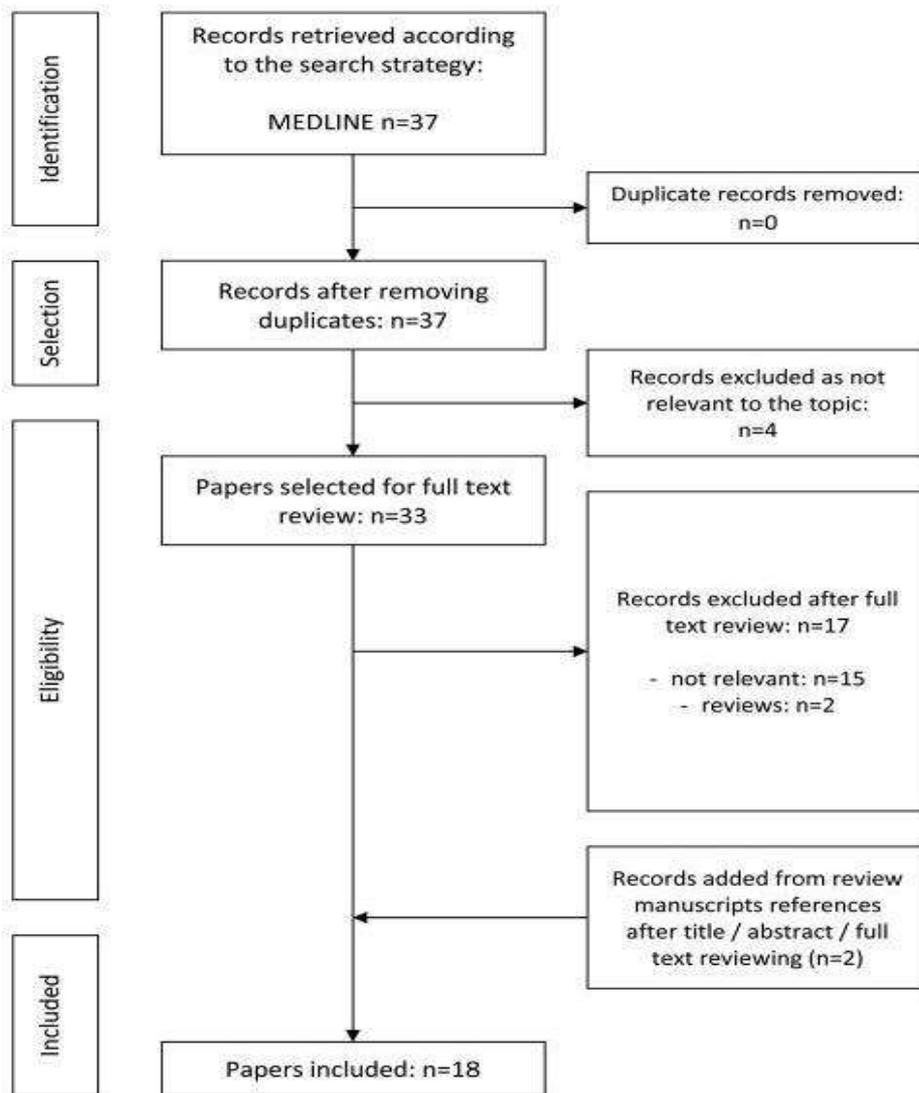


Figure 1. PRISMA search flow diagram.

Results

The search strategy with the limits applied yielded 37 articles. Of these articles, 4 were excluded according to the predefined criteria following title and abstract screening. Namely, one study was done in animals, two were not in the English language and the fourth article dealt with fluorescence ICG use in other surgical applications. There were, thus, 33 articles selected for a full-text review. Following the full - text review, 17 of them were also excluded as not relevant, two of them being review articles. The remaining 16 articles were included in the study. Additionally, two relevant articles were identified from the reference list of the reviewed articles and were added to the study. Finally, 18 articles were included in this systematic review. The flow diagram of the selection process is shown in Figure 1.

The characteristics of the included studies are presented in Tables I and II. As can be seen from Table I, the oldest report we found dates back to 2015. The 18 studies included a total of 672 patients who underwent ICG, namely 131 parathyroidectomies (PTX) and 541 total or

near- total thyroidectomies (T-NT). All studies aimed to examine the feasibility of the ICG technique to identify PGs. Most of the studies were observational as all the PTX articles were case reports (CR) or case studies (CS) while the T- NT articles comprised 8 CS, one CR, one retrospective cohort (RC) and just one randomized control trial (RCT). Regarding pathology, the vast majority of PTX were due to primary hyperparathyroidism (n=119), while the T-NT cases were a mixture of multinodular goiter, thyroid cancer, and Graves' disease. As can also be seen in Table I, the dose, as well as the frequency and the time of ICG administration varied greatly. When cited, the time elapsed following ICG administration and PG visualization expanded from 60 sec up to 292 sec, while the time that ICG was staying fluorescent into the PGs usually was around 20 min. Regarding perfusion estimation, just two studies were using quantitative measurement of ICG uptake, while the rest of them were using individually estimated qualitative scoring or visual estimation. Postoperative primary or derived parathormone (PTH) data were available in all 18 studies although focusing on different postoperative time slots. Mean operation time was available in half of the studies while intraoperative time devoted to ICG procedure was available in five of them. Both times varied greatly among the different studies (see Table I) (5,12 -28).

Discussion

Indocyanine green (ICG) is an inert, water-soluble organic dye that when delivered intravenously binds to plasma lipoproteins and confines to the vascular compartment until it is cleared exclusively through the hepatobiliary system due to the first -pass effect (29). It has a half-life of 3.4 ± 0.7 min, which allows repeated applications (9). These two properties make ICG ideal for angiography as it remains entirely in the blood circulation with a short lifetime. ICG has been widely used in fluorescence-guided surgery applications, such as for macular degeneration, fluorescence cholangiography, perfusion assessment of gastrointestinal anastomoses, real-time lymph node mapping, adrenalectomy, coronary artery bypass graft, and tissue flap reconstructions (3, 9).

ICG fluoresces at about 800 nm with a maximum absorption spectrum of 805 nm and reemission at 835 nm when excited by a light/laser at a wavelength in the NIR spectrum. The exact spectrum shape varies depending on the chemical environment, the temperature and the filters used (8, 9).

NIR ICG fluorescence imaging is a very promising method that can help surgeons to locate parathyroid glands in real- time during thyroid and parathyroid surgery. ICG has the advantage of accumulation in pathological PGs, which attributes to the higher fluorescence intensity compared to the surrounding tissues (9, 18, 30). However, ICG does not target specifically the parathyroid parenchyma. The exact mechanism of ICG uptake by the PGs the resulting fluorescent contrast compared to surrounding tissues is not known. It has been suggested that this may be related to their substantially increased blood flow compared to the flow in adjacent tissues (20). Additionally, it must be noted that bleeding can induce leakage of ICG into the operative field that may restrict fluorescent PGs visualization (1).

ICG substance contains 5% of sodium iodine for solubility and therefore any significant side effects and/or adverse events could be attributed to the iodide content. Thus, in a large study, the occurrence of anaphylactic or urticarial reactions was reported to be 0.00167% (4/240 000 cases); and in 34 years, 17 adverse reactions have been reported (31). It has also been published that intraoperative ICG administration can cause a "black thyroid"

phenomenon, like that seen following minocycline use (32). In none of the articles we reviewed did we notice any adverse reactions to ICG injection mentioned. However, it must be noted that in some studies patients that preoperatively reported iodine or drug allergy were excluded (15, 16).

The intraoperative identification of the parathyroid glands can be challenging even for experienced surgeons (1). Identification of PGs is of special importance in two types of endocrine surgery: i) when localizing PG adenomas in PTX and ii) when trying to avoid damaging the PGs during thyroid surgery in order to reduce postoperative hypoparathyroidism (1). Therefore, we have chosen to group those two types of articles separately (Tables I and II, respectively).

ICG enhanced fluorescence in parathyroidectomy. In 80-85% of the cases, primary hyperparathyroidism (HPT1) is caused by a single adenoma, in 5- 15% of cases by multiple PG hyperplasia and rarely by carcinoma (1). As there is no routine intraoperative tool to locate the variable locations of ectopic PG or to verify in real- time the successful PG resection, failure of the surgery can occur resulting in persistent hyperparathyroidism (9). Intraoperative and postoperative PTH levels can assist in estimating the function of the remnant PG, but this a time -consuming method and the results are obtained too late for the surgeon to adapt the surgical procedure (1).

From the reviewed studies regarding PTX, in most cases ICG NIR is used for identifying and localizing pathological PGs in HPT1 (14, 17, 20, 23), but also in redo-operation (12, 21) while two studies have included HPT2 cases (18, 23). *Sound et al.*, have reported three cases of video-assisted PTX due to PG adenomas (12). One was following thyroidectomy and two cases were following failed PTX. They were administered intravenous ICG at 8.75-10 mg/kg in 2 doses. The PGs were visible within 2 min following injection of the dose and the adenomas stayed fluorescent for about 20 min (12). *Zaidi et al.*, have reported the first prospective case study with intraoperative ICG fluorescent imaging of PGs involving 33 patients who underwent surgery for HPT1: i) a single adenoma in 20 patients, ii) double adenoma in seven patients, and iii) four glands hyperplasia in six patients (14). This study included both parathyroid adenoma excisions, as well as subtotal PTX (3. 5-gland excision). Out of all 112 PGs that were identified by the naked eye, 104 of them had ICG uptake (92.9%). Eight PGs did not demonstrate ICG uptake. None of these patients exhibited postoperative hypoparathyroidism. There were no adverse reactions to ICG injection (14). It is also worth to note that in 2017, *Mohsin et al.*, reported the successful resection of a PG adenoma, identified with the use of real- time ICG imaging, by performing a robotic transaxillary PTX with daVinci®Si™ in a patient with HPT1. The initial PTH baseline was 109.2 pg/ml and dropped to 39.1 pg/ml. The patient did not demonstrate postoperative hypoparathyroidism (17).

Most of the authors apply a double ICG injection protocol for both resection and remnant preservation of PG adenomas. Once the ipsilateral central neck is exposed and the thyroid lobe is retracted medially, the first injection dose is administered intravenously and usually uptake in the PGs is seen after 20-60 sec. The same dose is repeated for the contralateral side. ICG angiography can be used to assess perfusion before as well as following the resection (3).

Usually, PG imaging in hyperparathyroidism involves many modalities, such as CT, U/S and sestamibi (99mTc-MIBI). The sensitivities of the last two methods are around 69-75% and 49

- 70%, respectively, and their utility in locating normal PGs during a 4-gland exploration is even more limited (3) .

In our review, comparison data of ICG imaging with those modalities were available in three case series (CS) studies, all of which demonstrated the superiority of ICG imaging over any other imaging modality. Thus, in 33 HPT1 patients, *Zaidi et al.*, reported a 92.9% PG detection rate with ICG uptake vs. 29% with 99mTc-MIBI (14). Furthermore, Cui et al. have found that in 20 HPT2 patients the PG detection rate via ICG was 93.9% while this was 86% using CT, 82% with U/S and only 62% with 99mTc -MIBI (10) . Finally, another study with 60 HPT1 cases, ICG was positive in 94% patients, while CT in 22/25 (88%), U/S in 25/35 (71%), and 99mTc -MIBI in only 36/54 (67%). It is also worth noting that all negative CT, U/S and 99mTc-MIBI cases were positive in ICG imaging (20).

ICG NIR fluorescence imaging was used for intraoperative PG identification in 29 patients with secondary hyperparathyroidism (HPT2) divided into two groups: i) Group A (9 patients) with no ICG and ii) Group B (20 patients) with ICG imaging. Although a higher PG detection rate was observed in Group B (93.3% vs. 78.6%), there was no significant difference between the two groups either in PG detection or the therapeutic effect. However, in the ICG imaging group, lower operation time and rate of persistent hyperparathyroidism were observed compared to the group without ICG. The ICG fluorescence intensity of the PGs was greater compared to that of the thyroid gland, which in turn was consistently stronger compared to that of muscle, fat, and other surrounding tissues. A significantly higher ICG fluorescence was also observed in patients with preoperative PTH levels >1900 pg/ml ($p<0.05$) and in PTGs larger than 10 mm ($p<0.01$) (18).

ICG enhanced fluorescence in Thyroidectomy. Postoperative hypoparathyroidism and the resulting hypocalcemia are the most common complications following thyroidectomy. Therefore, in thyroidectomies, except PG localization, their vascularity and therefore their viability is also a desired outcome. Transient hypoparathyroidism occurs in around 19-38% of cases, while permanent hypoparathyroidism is estimated at around 0-3% (30). This is caused by inadvertent injury, ischemia, gland devascularization or incidental excision of PGs due to failure in identifying and preserving them (9). Postoperative hypoparathyroidism can cause prolonged hospitalization, neuromuscular symptoms, the need for life-long calcium and vitamin D supplementation, cerebral, vascular, ocular and renal damage (9). It is worth to note that a variety of hypocalcemia and hypoparathyroidism PTH levels has been published, adding confusion to the respective comparison of definitions among the different studies (30). In 2014, *Suh et al.* showed that PG could be visualized using ICG NIR imaging during thyroid surgery in dogs (33) and another group managed to differentially visualize the thyroid and PGs using NIR imaging in pigs (34).

From the reviewed studies regarding PG detection and viability following TT or N-TT, we identified eight case series (5, 13, 15, 16, 22, 24, 26, 28), a retrospective cohort (27), a randomized control trial (19) and a case report (25). Most of them were dealing with a mixture of thyroid pathologies: In 2016, *Zaidi et al.* reported a study where ICG was administered in 27 patients undergoing TT for multinodular goiter ($n=13$), thyroid cancer ($n=10$) and Graves' disease ($n=4$) . Eighty -five PGs were identified visually, 71 (84%) of them showed ICG uptake while 8 showed no ICG uptake. The false -negative rate was 6%. The ICG uptake was compared with the level of postoperative PTH. At postoperative day 1 PTH levels correlated with the number of PGs left & their fluorescence ($p=0.05$). Thyroid pathology & PG size did not show any correlation with ICG uptake (15). *Vidal Fortuny et al.* reported 36 patients that underwent ICG angiography during TT in 2016 (13) . One PG was identified in one patient, two PGs were identified in 11 patients, three PGs in 18 patients and four PTGs in 6 patients. In 6 patients ICG angiography did not demonstrate a well-vascularized PG and two of them demonstrated transient hypoparathyroidism. Postoperatively PTH levels were normal for all patients with at least one well-vascularized PG (13). *Yu et al.* have used robotic

bilateral axillo-breast approach (BABA) thyroidectomy for papillary thyroid carcinoma in 66 patients divided into two groups: i) Group A consisted of 44 patients without ICG imaging and ii) Group B comprised 22 patients (11 TTs and 11 lobectomies) with ICG NIR fluorescence. In total 32 PGs were successfully identified with ICG NIR fluorescence. Just one PG was not identified during surgery. BABA robotic thyroidectomy combined with Firefly improved the PG identification (16). *Lang et al.* have reported a case series article with 94 thyroidectomies of various etiology using ICG NIR (24). 324/340 PGs were detected using a quantitative (PG/trachea) ratio. The greatest ICG intensity (GFI) correlated with normal PTH. GFI value was the best predictor of early postoperative hypocalcemia (0% if GFI >150% vs. 81.8% chance if GFI ≤150%). Therefore, ICG uptake could be used as a prognostic factor of hypoparathyroidism incidence risk following TT (24). In 2018, *Vidal Fortuny et al.* reported a clinical trial for temporary postoperative hypoparathyroidism of 196 patients who underwent ICG angiography during thyroid surgery (19). 146 patients showed ICG uptake for at least one PG and 50 patients showed no ICG uptake. 499 PGs were removed in total, 387 of them were well perfused from ICG. Out of the 146 patients, none showed symptoms of hypoparathyroidism, whereas of the 50 patients, 11 of them presented hypoparathyroidism on postoperative days 1 and 10. The authors suggested that calcium and PTH levels may no longer need to be tested postoperatively in patients with at least one well-vascularized PG and they proposed ICG perfusion as a predictor of the absence of post-surgical hypoparathyroidism (19). *Jin et al.* used in 26 patients with various thyroid pathology an intraoperative navigation system with dedicated software to calculate ROI's Signal-to-Background Ratio detection of ICG. They found that 22 patients who had at least one PG with ICG score >2 had normal PTH levels postoperatively. In contrast, from four patients with PG ICG score <2, two of them developed transient hypoparathyroidism (26). In another study involving 26 patients of various thyroid pathologies, 30 surgeries were performed (28). By using white light 41/72 of PGs were detected while only 31/72 were detected using ICG NIR. It is worth to note that before resection, benign pathology patients had a higher target-to background ratio (measured by OsiriX Lite V8.5.2 imaging software) as compared to malignancy patients (28). However, it was not possible to derive any correlation of thyroid pathology with ICG uptake in the rest of the articles reviewed.

Finally, in a recent retrospective cohort study of various thyroid pathology and ICG angiography (ICGA), there were 86 patients with ICGA and 124 control cases. 281/344PGs were identified and two vascularized PGs on ICGA correlated with normal postoperative PTH levels that could potentially predict PG function (27). Recently, parathyroid autofluorescence (AF) has been introduced as yet another optical technology for identifying and assessing vascularized PGs (35). Parathyroid AF can be captured using a spectrometer (36) or a modified near-infrared imaging camera (17). It has been reported to consistently identify PGs across various disease states, and unlike ICG, no IV fluorescent dye injection is needed (18). Of note, parathyroid AF persists regardless of gland viability and can be detected even following surgical resection of the gland (4). On the other hand, its limitations include i) interference from background thyroid fluorescence hindering PG detection, ii) false-negative results where a visibly viable PG would not retain the dye, and iii) the lack of knowledge on the direct correlation between intraoperative ICG characteristics and postoperative hypocalcemia (16). Two of the reviewed studies compared AF imaging and ICG imaging to identify PG during TT (5, 12, 16). *Alesina et al.*, have presented a study where five patients underwent video-assisted neck surgery (5). One underwent PTX for HPT1 and four of them TT for multinodular goiter or Graves' disease. They used ICG imaging as well as parathyroid autofluorescence (AF). AF detected 11/16 PGs and ICG 12/16 PGs (5). Both techniques had a similar ability to detect PGs (22). The limitation of these studies is the small sample size and that operating room lights were turned off for AF measurements. Intraoperative ICG NIR fluorescence imaging angiography is a promising method for identifying and preserving PGs despite the variations observed across the different studies.

It is a simple, fast and reproducible method to verify perfusion of individual PGs. This procedure allows an objective selection of the remnant PGs by measuring ICG perfusion and verify that it is well perfused before resecting the other PGs in order to avoid hypoparathyroidism following thyroid surgery (18), as positive remnant PG angiography is correlated with postoperative gland function (37). However, further investigation with randomized control studies are needed to elucidate whether intraoperative ICG NIR angiography can further reduce postoperative hypoparathyroidism (9). There is some evidence that ICG angiography of normal PGs could predict their postoperative function (1). Furthermore, in hyperparathyroidism undergoing PG resection, ICG angiography permits to perform a mapping of the PG feeding vessels and therefore of the anatomy and location of the adenomas (13, 19, 23). As cited in the results section, there is a lack of standardization regarding the dose as well as the frequency and the timing of ICG administration, and all these parameters varied greatly in the reviewed articles. As outlined in Table I, many different devices are being used, while there are several technical factors in the various imaging systems that can affect the sensitivity levels of each device (30). Therefore, the big variation observed regarding the aforementioned parameters might be due to the various types of imaging equipment used (1). The advantage of ICG fluorescent angiographic technology in identifying PGs greatly depends on the method to localize and assess PG function in a non-invasive manner (38). It is also of interest to note that following injection, the time of its appearance in the PGs was longer in the two articles using robotic surgery (16, 18) while in the rest of the articles the PGs were visible from 15 sec - 2 min (5, 9, 13, 16, 19) and the adenomas stayed fluorescent for about 20 min (4, 12, 30). Therefore, an overall consensus on the optimal dosage and timing of ICG administration is still lacking (18) and further studies are required. Eleven of the reviewed articles have reported an estimation of the PG perfusion with ICG; a qualitative score was used in nine of them, with seven of them using a three-grade scoring (13, 19, 20, 23, 26-28) and another two a four-grade score system (14, 15). Quantitative fluorescence signal analysis was used in just two studies (18, 24). Furthermore, there was no real-time quantification and only post-processing was available. The lack of quantitative measurements of PG vascularization with the ICG NIR fluorescence was an important limitation prohibiting comparison of results and impacts on the reliability of the methodology between studies. Therefore, further investigation comparing the use of ICG NIR fluorescence imaging with intraoperative confirmation of PGs and real-time quantitative measurements should be conducted.

In conclusion, we reviewed the current status of ICG-enhanced fluorescence imaging and parathyroid preservation in both thyroid and parathyroid surgery. Although there still are questions regarding its usefulness, current data suggest that ICG imaging of the parathyroid glands during thyroid surgery can secure a reduction in postoperative hypoparathyroidism. Furthermore, it can intraoperatively predict the function of each individual PG and therefore if a well-vascularized PG with high ICG fluorescence intensity can be secured, calcium substitution and postoperative of hypoparathyroidism may become obsolete. However, an overall consensus on the optimal dosage and timing of ICG administration is still lacking and additional randomized clinical trials are necessary for further validating ICG angiography as an intraoperative tool in assessing real-time parathyroid preservation.

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Table I. Summary of publications.

Surgery	Authors	Type	Year	Number of patients	Pathology	ICG dose and time of injection	Time of appearance/Duration	Device	Other imaging
Parathyroidectomy	Chakedis <i>et al.</i> (21)	CR	2015	1	recurrent HPT	7.5 mg Before	20 s/10 min	PINPOINT®	CT: Yes
	Sound <i>et al.</i> (12)	CR	2015	3	Previous TT (1 case), previously failed PT (2 cases)	8.75- 10 mg in 2 doses	2 min/20 min	Novadaq	U/S: Yes 2/3 99mTc- MIBI: Yes 3/3
	Zaidi <i>et al.</i> (14)	CS	2016	33	30 HPT1, 3 Redo	5 mg	30- 60 s/ 20 min	PINPOINT®	U/S: Yes N/A 99mTc -MIBI: Yes 29%
	Vidal Fortuny <i>et al.</i> (23)	CS	2016	13	7 HPT1, 6 HPT2	7.14 mg Before	--/--	PINPOINT®	U/S: Yes N/A 99mTc - MIBI: Yes N/A
	Mohsin <i>et al.</i> (17)	CR	2017	1	HPT1	N/A	--/--	N/A	U/S: Yes 99mTc-MIBI: Yes
	Cui <i>et al.</i> (18)	CS	2017	29 (Group A: 9 pts w/o ICG, Group B: 20 pts with ICG)	HPT2	0.5 mg/kg	75±35 min/ 225 min	AISERY + J	CT: 86% U/S: 82% 99mTc-MIBI: 62%
	De Long <i>et al.</i> (20)	CS	2018	60	HPT1	7.5 mg	--/--	PINPOINT®	CT: 22/25 (88%) U/S: 25/35 (71%) 99mTc -MIBI: 36/54 (67%)
Thyroidectomy	Zaidi <i>et al.</i> (15)	CS	2016	27	Multinodular goiter (13) , thyroid cancer (10) and Graves' (4)	5 mg before & 5 mg after TT	1 min/20 min	PINPOINT®	U/S: Yes N/A
	Vidal Fortuny <i>et al.</i> (13)	CS	2016	36	Multinodular goiter, Graves', thyroid cancer	7.5- 12.5 mg (max 5 g/kg/d)	1-2 min/--	PINPOINT®	--
	Yu <i>et al.</i> (16)	CS	2017	Group A: 44 pts w/o ICG Group B: 22 pts with ICG	Papillary thyroid carcinoma	10 mg (max 30 mg/d) Before & after TT	203±89 s/ 20.8±6.0 min	Firefly	--
	Kahramangil & Berber (22)	CS	2017	22	Multinodular goiter (12), thyroid cancer (8) and Graves' (2)	5 mg Before	--/--	PINPOINT®	--
	Lang <i>et al.</i> (24)	CS	2017	94 (70 with 4PG identified)	Benign, Graves', cancer	2.5 mg after TT	15 s/--	SPY	--
	Alesina <i>et al.</i> (5)	CS	2018	5	1 HPT, 4 multinodular goiter or Graves	7.5 mg (3x2.5) During & after TT	30-70 s/--	5-mm 30° ICG endoscope & IMAGE1 S	The HPT case: positive U/S & 99mTc-MIBI. Combined AF & ICGA.
	Vidal Fortuny <i>et al.</i> (19)	RCT	2018	196	Multinodular goiter, Graves', Thyroid cancer	8.75 mg After TT	1-2 min/--	PINPOINT®	--
	Jin <i>et al.</i> (25)	CR	2018	3	Nodular goiter 1, Papillary Ca 2	5 mg	2 min/20 min	INS	CT: 2' U/S: 2
	Jin <i>et al.</i> (26)	CS	2018	26	Various	5 mg	2 min/20 min	INS	--
	van den Bos <i>et al.</i> (28)	CS	2018	26 (30 Surgeries)	Goiter: 5 Graves': 1 ?Ca: 17 Thyroid cancer: 7	7.5 mg ×2 Before & after	30 s/--	FIS + TBR	--
Rudin <i>et al.</i> (27)	RC	2019	ICGA: 86 Control: 124	Thyroid cancer, Multinodular goiter, Graves'	Up to 10 ml in 2 doses	--/--	PINPOINT®	--	

AISERY+J: AISERY Co. (Beijing, China) + Image J software; ?Ca: Suspected cancer; CR: case report; CS: case series; Firefly: Firefly system (Novadaq) integrated to the da Vinci®Si™; FIS: fluorescence imaging system (Karl Storz GmbH & CO., Tuttlingen, Germany); HPT: hyperparathyroidism; HPT1: primary hyperparathyroidism; HPT2: secondary hyperparathyroidism; ICGA: indocyanine green fluorescence angiography; IMAGE1 S: IMAGE1 S™ Camera Platform with OPAL™ technology (Karl Storz Endoskope, Tuttlingen, Germany); INS: intraoperative navigation system (Digi-MIH-I-001, Digital Precision Medicine Technology Co., Ltd, Beijing, China); N/A: data not available; NIR: near infrared light; PINPOINT®: PINPOINT® camera (Novadaq, Ontario, Canada); RC: retrospective cohort; RCT: randomized control trial; SPY: SPY imaging system (Novadaq, Ontario, Canada); TBR: target-to-background ratio measured by OsiriX Lite V8.5.2 Imaging software (Pixmeo, Geneva, Switzerland); 99mTc-MIBI: sestamibi scan; Various: malignant biopsy results/clinically worrying

lesion/compressive symptoms/recurrent cancer/recurrent cyst/thyroglossal duct cyst/thyrotoxicosis/cosmetic issues; w/o: without.

Table II. The final 18 papers included in this systematic review (results).

Surgery	Authors	Mean operation (ICG) time	Adenoma localized	No. of identified PGs	PG perfusion (Score)	Postoperative PTH data	Remarks
Parathyroidectomy	Chakedis <i>et al.</i> (21)	60 min. (10 min)	1	1	--	Yes PTH decreased to normal values	Further research is needed regarding ICG usefulness for HPT detection. Video-assisted technique with a laparoscope. Concomitant fluorescence of the thyroid gland limits ICG's usefulness. Impossible to correlate the quality of the perfusion with the postop PTH levels due to the small sample size. Compatible with daVinci®Si™, Realtime. Further studies are required to determine the optimal dosage of ICG & interval time between administration & imaging. All negative CT, U/S & 99mTc- MIBI cases were positive in ICG. Thyroid pathology & PG size did not show any correlation with ICG uptake. Vascularization of non PG tissue by ICGA, can lead to a false assumption that HYPOPT will not develop. BABA RoT combined with Firefly improved the PGs identification.
	Sound <i>et al.</i> (12)	N/A	3	3	--	PTH decreased for all patients 10 min after excision None HYPOPT	
	Zaidi <i>et al.</i> (14)	N/A	27	104 (92.9%)	Qualitative (0 to 3)	4 patients had low PTH on POD1	
	Vidal Fortuny <i>et al.</i> (23)	112.8±28.9 min (3.0±2.3)	--	52/52	Qualitative (0 to 2)	Yes	
	Mohsin <i>et al.</i> (17)	N/A	--	1	Visual estimation	No significant difference among the 2 groups	
	Cui <i>et al.</i> (18)	Group A: 156 min, Group B: 130 min	62	Group A: 33(78.57%) Group B: 77(93.3%)	Quantitative. Persistent HPT: Group A: 22.2%, Group B: 10%		
	De Long <i>et al.</i> (20)	56 min Range: 26-215 min	1	ICG positive for 94% patients	Qualitative (0 to 2)	Average PTH decrease of 124 pg/ml	
	Zaidi <i>et al.</i> (15)	N/A	N/A	71/85 positive. False negatives: 6%	Qualitative (0 to 3)	At POD1 PTH levels correlated with the number of PGs left & their fluorescence (<i>p</i> =0.05).	
Thyroidectomy	Vidal Fortuny <i>et al.</i> (13)	(6±2) min	N/A	91/99	Qualitative (0 to 2)	PTH normal for all patients with at least 1 well-vascularized PG	
	Yu <i>et al.</i> (16)	27.3±6.6 min	N/A	Group B: 32/33	ICG Fluorescence: PG seen 4 sec earlier than the thyroid gland	HYPOPT: Group A: 8/44 Transient, 1/44 Permanent & 7/44 incidental. Group B: 4/22 Transient, 1/22 Permanent & 0/22 incidental	
	Kahramangil & Berber (27)	N/A	N/A	60/63	Comparison with AF group	1 postoperative hypocalcemia	
							Both techniques have similarly high

Table II. *Continued*

Surgery	Authors	Mean operation (ICG) time	Adenoma localized	No. of identified PGs	PG perfusion (Score)	Postoperative PTH data	Remarks
	Lang <i>et al.</i> (28)	109.1±49.8 min (2.7±0.5)	N/A	324/340 (94 patients)	Quantitative (PG/trachea ratio)	Greatest ICG intensity (GFI) correlated with normal PTH. GFI value is the best predictor of early postop hypocalcemia (0% if GFI >150% vs. 81.8% chance if GFI ≤150%)	ICGA of <i>in situ</i> PG predicts postoperative HYPOPT risk after TT.
	Alesina <i>et al.</i> (5)	62 min	1	AF: 11/16 ICG: 12/16	Visual estimation	POD PTH normal	Superiority of combined AF/ICG vs. simple visualization to reduce the rate of post op HPOPT has not been demonstrated.
	Vidal Fortuny <i>et al.</i> (19)	N/A	N/A	387/499	Qualitative (0 to 2)	Yes, 11 pts w/on one well perfused PG had HYPOPT on POD1 and 6 on POD10-15	Calcium and/or PTH may no longer be necessary when at least one well perfused PG is seen by ICGA after TT.
	Jin <i>et al.</i> (25)	N/A	N/A	100%	Visual estimation	None HYPOPT	Successful preservation of PGs
	Jin <i>et al.</i> (26)	N/A	N/A	100%	Qualitative (0 to 2)	22 pts with at least 1 PG had ICG score >2, normal PTH. 4 pts with PG ICG score <2, transient HYPOPT in 2	Special software to control INS & to calculate ROI's Signal-to-Background Ratio.
	van den Bos <i>et al.</i> (28)	92±32 min (5.5±1.5)	N/A	White light: 41/72 ICG: 31/72	Qualitative (1 to 3)	N/A	Prior resection, benign pathology pts had higher TBR as compared to malignancy pts.
	Rudin <i>et al.</i> (3427)	N/A	N/A	281/344	Qualitative (0 to 2)	2 vascularized PGs on ICGA correlate with normal postop PTH levels & may predict PG function	Glands with no ICGA uptake were auto-transplanted (max 2 glands/pt). Autotransplantation: ICGA group (36%), Control group (12%)

AF: Autofluorescence; BABA RoT: bilateral axillo-breast robotic thyroidectomy; HPT: hyperparathyroidism; HYPOPT: hypoparathyroidism; ICGA: indocyanine green fluorescence angiography; N/A: data not available; PG: parathyroid gland; POD: postoperative day; PT: parathyroidectomy; PTH: parathormone; TBR: target-to-background ratio measured by OsiriX Lite V8.5.2 Imaging software (Pixmeo, Geneva, Switzerland); TL: thyroid

lobectomy; T-NT: total or near-total thyroidectomy; TT: total thyroidectomy; VPG: vascularized PG.

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