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On indocyanine green fluorescence and autofluorescence in thyroid and parathyroid surgery: A scoping systematic review ☆,☆☆,★

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ABSTRACT

Background: Autofluorescence (AF) and Indocyanine Green Fluorescence (ICG) were used for the first time for parathyroid gland identification in 2011 and 2015, respectively, during thyroidectomy and parathyroidectomy. Authors reported promising results. We aim to understand the impact on postoperative biochemical and clinical outcomes of these new techniques, as well as their influence on the intraoperative identification of parathyroid glands, the related technical challenges and their cost-effectiveness.

Materials and Methods: A systematic search of PubMed/MEDLINE was performed with the help of MeSH and following the PRISMA guidelines. Overall, 58 studies were included dating from 2008 to August 2020 in English, German, Spanish, and French. Due to the mainly observational nature of the papers on the topic, letters to the editor and responses to previous papers were included. Papers combining the use of both techniques in the same cohort were included.

Results: We analysed a total of 3 RCTs, 22 case series or reports, and 33 further observational studies. The use of AF/ICG increased the surgeon's confidence and demonstrated a better sensitivity for parathyroid gland identification in both thyroidectomies and parathyroidectomies compared to other techniques. Adverse events were uncommon.

Conclusion: After reviewing the literature, we acknowledge the feasibility of using ICG and AF as a powerful tool for the identification of parathyroid glands more effectively than with classic methods or the naked eye. These results are encouraging towards the use of such techniques intraoperatively. However, further research is needed to obtain high-quality evidence showing a possible reduction in postoperative hypocalcaemia rates and clinical symptoms that would justify the use of these techniques in routine surgical practice.

1. Introduction

According to the United Kingdom Registry of Endocrine and Thyroid Surgery (UKRETS), 30557 thyroidectomies and 13012 parathyroidectomies were performed between July 2010 and June 2015 [1]. These numbers are variable in other countries as the indications for surgery differ [2–6]. Postoperative hypocalcaemia is a relevant and frequent complication of both surgeries which can result from the removal of parathyroid glands (PG) or the interruption of their vascular supply [6]. Early hypocalcaemia is defined as corrected calcium <2.10 mmol l^{-1} or ionised calcium <1.2 mmol l^{-1} on the first postoperative day.

Patients with acute postoperative hypoparathyroidism might develop tetany, prolonged QT interval, fatigue, anxiety, heart failure, arrhythmias and hypotension, among others [7]. In the long-term, postoperative hypoparathyroidism can cause development of kidney stones, basal ganglia calcifications, cataracts, dental abnormalities, and ectodermal manifestations [7]. In some cases, these symptoms can improve after treatment with vitamin D and calcium, but this implies a need for long-term medication, clinic consultations and imaging investigations [7,8]. To sustain this burden, patients have created associations that intend to support and increase awareness towards the disease [9]. Moreover, the risk of reoperation after incomplete removal of PG

Abbreviations: AF, Autofluorescence; AUC, Area under the ROC Curve; BABA, Bilateral axillo-breast approach; FDA, Food and Drug Administration; HPT, Hyperparathyroidism; ICG, Indocyanine green; IOPTH, Intraoperative parathyroid hormone; MEN1, Multiple endocrine neoplasia type 1; PG, Parathyroid gland; POD, Postoperative day 0; PTH, Parathyroid hormone; RCT, Randomised clinical trial; UKRETS, United Kingdom Registry of Endocrine and Thyroid Surgery.

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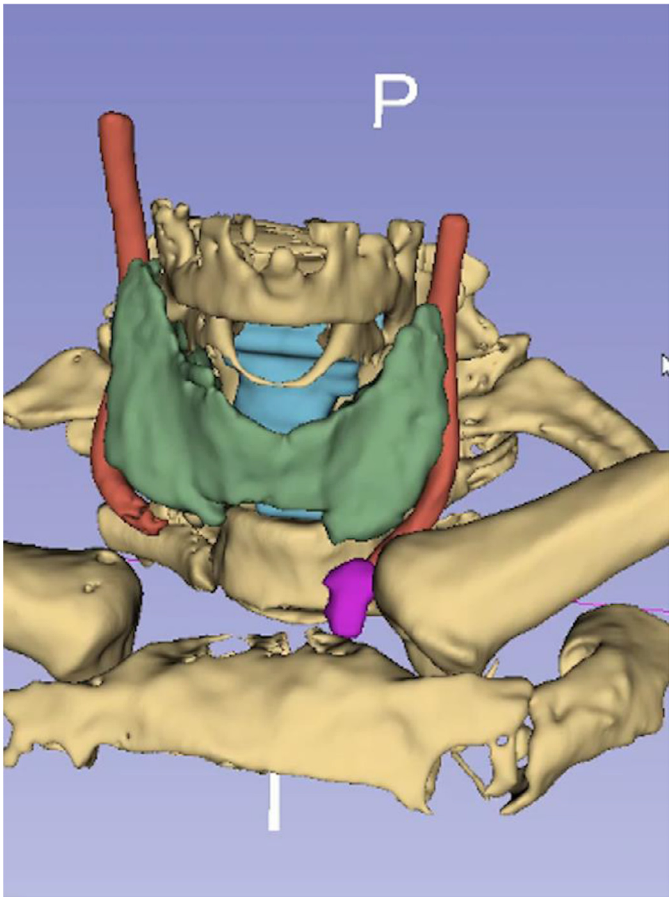

Fig. 1. Anatomical description of parathyroid location on 3D reconstructed imaging (unpublished).

during parathyroidectomies can reach up to 30% [10]. There is therefore an urgent need for a method that can efficiently identify the location of PG intraoperatively, assess their viability and discriminate pathologic from healthy tissue.

Different techniques to identify the location of PG intraoperatively have been developed in the past decades (Fig. 1). Methylene blue was first used intraoperatively in the 70s [11], but concerns regarding neurotoxicity were expressed [12]. 5-ALA can also be used for identification of the PG [13,14], but patients need to be protected from sunlight for 24–48h to prevent phototoxicity and photobleaching [15]. Intraoperative parathyroid hormone (IOPTH) monitoring was introduced in 1988 [16] and has been found to consistently outperform preoperative imaging such as ultrasound and nuclear scan MIBI in predicting cure [17,18]. Autofluorescence (AF) for PG identification—based on the fluorescence emitted by the PG when exposed to a near infrared, 750-800 nm wavelength—was published the first time in 2011 [19]. Since then, clinical devices have been approved by the FDA for its use intraoperatively [20]. Similarly, indocyanine green fluorescence imaging (ICG) is injected intravenously and binds to plasma lipoproteins. This dye can thereafter be excited by near infrared wavelengths, resulting in fluorescence and facilitating the PG identification [21,22]. Since 2015, ICG has been reported as an advantageous technique that can safely be used in medical practice [23]. Intraoperative localisation of PG with AF and ICG is illustrated in Fig. 2.

We aim to systematically evaluate (i) if the use of ICG and AF improves the patients' biochemical and clinical outcomes after surgery and (ii) how it influences the intraoperative identification of parathyroid glands. Furthermore, we aim to (iii) summarise the technical challenges reported when using these techniques, as well as (iv) the evidence on their cost-effectiveness.

2. Methods

This study is compliant with PRISMA 2020 [24] and AMSTAR 2 guidelines [25]. A systematic search of PubMed/MEDLINE has been performed with the help of MeSH: ((Thyroidectomy[Title/Abstract]) OR (Parathyroidectomy[Title/Abstract]) OR ((thyroid[MeSH Major Topic]) AND (surgery[MeSH Subheading])) OR ((parathyroid[MeSH Major Topic]) AND (surgery[MeSH Subheading]))) AND ((Near-infrared[Title/Abstract]) OR (Fluorescence[Title/Abstract]) OR (ICG[Title/Abstract]) OR (indocyanine[Title/Abstract])). The filter on publication date was set to January 2008 to August 2020. The language filter was set to allow for publications in English, German, Spanish, and French. Existing systematic reviews were excluded from the results. Data was extracted from text, tables, and figures by two authors independently and summarised in the form of a shared table. Data can be provided by the authors on request. When unclear, inclusion or exclusion of the paper was discussed between the authors and a joint decision was reached. Data included in the table was double-checked posteriorly by the two authors independently. This review has been registered and its unique identifier number (UIN) is reviewregistry1374 [26].

3. Results

The study selection process is depicted in the PRISMA flow diagram (Fig. 3). We have included a total of 58 primary studies: 3 RCT, 22 case series or reports, and 33 further observational studies.

4. Outcomes (biochemical, clinical, need for long-term treatment, length of stay, reoperation)

4.1. ICG

4.1.1. ICG for thyroidectomy

We have summarised the biochemical outcomes that were reported in most of the studies using ICG for thyroidectomy in Table 1. Generally, a correlation between ICG uptake and postoperative parathyroid hormone (PTH) levels was observed [21,27–34]. Yu and colleagues [35] found no significant differences in hypocalcaemia rate in the ICG compared to a control group but observed a significantly reduced rate of incidental parathyroidectomies. The same authors hypothesised that calcium and/or PTH measurements may no longer be necessary in patients with at least one well perfused parathyroid gland when using ICG angiography. This hypothesis was supported by Karampinis and colleagues [29] after concluding a prospective clinical trial aiming to reproduce such results. Furthermore, Vidal Fortuny and colleagues published the results of an RCT in 2018 assessing hypocalcaemia rates on POD 10–15 in patients with at least one well perfused PG on ICG [34]. They randomised patients to a control group (standard follow-up and systematic calcium and vitamin D supplementation) and an intervention group (no supplementation and no blood test on POD1) [34]. The intervention group was found to be statistically non-inferior to the control group [34]. In contrast, in 2019 in a single centre retrospective study including 210 patients, Rudin and colleagues [27] concluded that having one normal gland identified with ICG could not predict normal postoperative PTH values, but two well-functioning glands could predict such an outcome. In a reply to Rudin and colleagues [27], Triponez [36] highlighted the need to standardise the perfusion assessment of PG with ICG, e.g. by introducing numerical units, similar to Hounsfield units.

However, only a few studies reported outcomes of clinical hypocalcaemia [28,29,34,37]. Vidal Fortuny and colleagues observed clinical hypocalcaemia, but normal calcium levels, in 2 out of 73 non-calcium corrected patients who had at least one well perfused gland [34]. Karampinis and colleagues [29] included 27 patients in their study, and 4 of them did not have any well perfused glands: while two of the 4

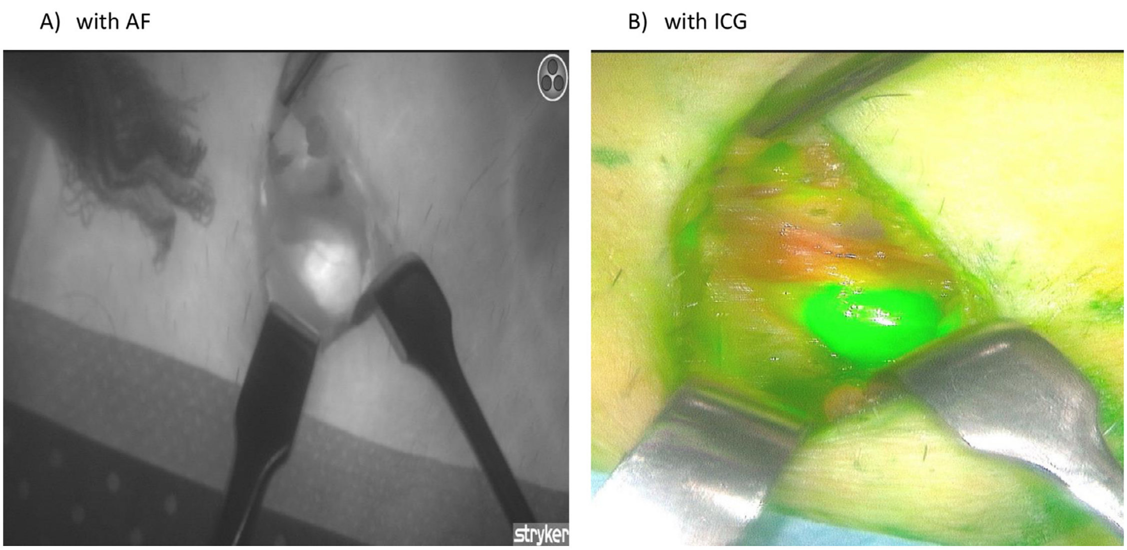

Fig. 2. Identification of intraoperative parathyroid gland location.

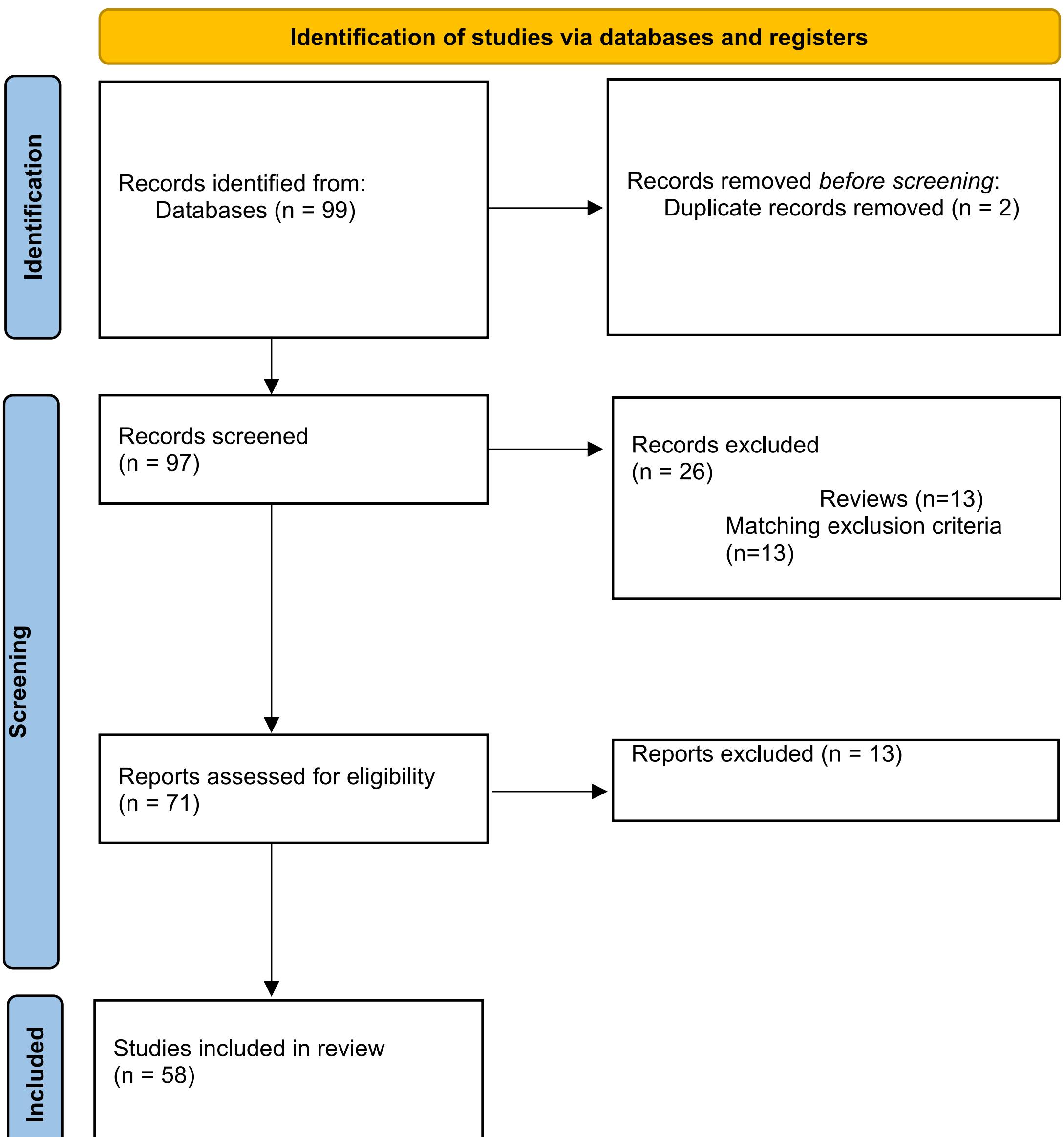

Fig. 3. PRISMA flow diagram for study selection [24].

Table 1
ICG for thyroidectomy. One RCT is highlighted in bold.

Study	Population (n)	Intervention	Study type	Definition of hypoparathyroidism	Definition of hypocalcaemia	Biochemical (hypocalcaemia, postoperative hypoparathyroidism) and clinical outcome
[21]	27	Total thyroidectomy	Prospective study	NA	Serum calcium value <8 mg/dl	3/27 (11%) hypocalcaemia. ICG uptake correlated with post-operative PTH levels. Mean POD1 PTH 9 pg/ml (where at least two PG exhibiting <30% fluorescence) vs 19.5 pg/ml (if <2 PG demonstrating <30% fluorescence) (p =0.05).
[27]	210	Total, near-total thyroidectomy +/- cervical lymph node dissection	Single-centre retrospective study	PTH <15 pg/mL	NA	Postoperative PTH levels not significantly different (32/86 in ICG group – 13 thereof had undetectable levels, and 45/124 in control group – 12 thereof had undetectable levels).
[28]	36	Total thyroidectomy	Case series	PTH <1.1 pmol/l	Adjusted calcium <2.00 mmol/l	30/36 patients had ≧ 1 parathyroid gland with an ICG score of 2, their postoperative PTH levels were in the normal range. 2/6 patients with an ICG score <2 had transient hypoparathyroidism. Clinical outcome: 0 cases of clinical hypocalcaemia.
[29]	27	Thyroidectomy	Prospective clinical trial	NA	<2 mmol/l	23/27 had ≧ 1 preserved PG with high fluorescence, none had hypoparathyroidism. The other 4/27 had PG with low intensity and received activated vitamin D3 prophylactically. Clinical outcome: 2/4 had symptomatic hypocalcaemia.
[30]	26	Total, completion thyroidectomy or hemithyroidectomy	Prospective clinical study	NA	Normal 1.1-1.3 mmol/L	All patients' calcium supplemented. Transitory hypocalcaemia on POD1 in 3 total thyroidectomy patients. Target-to-background ratio was lower than in patients with a normal calcium on POD1.
[31]	39	Total thyroidectomy	Clinical prospective trial (case series)	NA	Corrected serum calcium of <8 mg/dl	19% (n=6) had postoperative hypocalcaemia. 4-ICG discriminates well to predict for postoperative hypocalcaemia (AUC = 0.875 (0.710–0.965); p = 0.001). The optimal 4-ICG score cut-off value was 3 (sensitivity 83%, specificity 73%, positive predictive value 42% and negative predictive value 95%. PTH: 4-ICG score showed a moderate positive correlation with the postoperative absolute PTH levels (Spearman's rho = 0.572; p = 0.001).
[32]	70	Total thyroidectomy	Prospective clinical study	Normal range 1.2–5.7 pmol/L	Adjusted calcium <2.00 mmol/L within 24 hours	No patients with a greatest fluorescent light intensity >150% developed postoperative hypocalcaemia while 9 (81.8%) patients with a greatest fluorescent light intensity ≤150% did. Similarly, no patients with an average fluorescent light intensity >109% developed PH while 9 (30%) with an average fluorescent light intensity ≤109% did.
[33]	26	Total thyroidectomy	Case series	PTH < 1.1 pmol/l.	NA	No hypoparathyroidism in the 22 patients with ≧ 1 PG with an ICG score of 2. 2/4 patients with no PG with a score of 2 developed transient hypoparathyroidism.
[34]	146	Total thyroidectomy or completion thyroidectomy	**RCT**	PTH < 1.1 pmol/l	Corrected calcium <2.00 mmol/l	Included patients all had at least one well perfused gland and randomised to either standard follow-up and calcium and vitamin D supplementation or no supplementation and no blood test on POD1 (interventjon group). No hypocalcaemia and no hypothyroidism found in either group. The intervention group was statistically non-inferior to the control group. Clinical outcome: 2/73 non-supplemented patients had symptomatic hypocalcaemia.
[35]	66	Bilateral axillo-breast approach (BABA) robotic thyroidectomy.	Case-control study	Serum PTH <15 pg/mL and/or need oral calcium and vitamin D (tempo- rary) and need oral calcium > 1 year (permanent)	NA	The ICG and control groups had similar rates of transient hypoparathyroidism (36.4 vs. 40%,p = 0.842) and permanent hypoparathyroidism (9.1 vs. 5%, p = 0.657).
[37]	5	Video-assisted neck surgery	Case series	Serum calcium <2 mmol/l and/or PTH <10 pg/ml	Serum calcium <2 mmol/l	Not mentioned by the authors, but postop PTH and calcium (presumably POD2) were all in normal range. Clinical outcome: no symptomatic hypocalcaemia.
[63]	43	Total thyroidectomy	Prospective interventional pilot study	Normal range 12–88 pg/mL	serum adjusted calcium < 8.5 mg/dL	22 patients (51.2%) developed hypocalcaemia within 24 hours postoperatively, 5 patients (11.6%) developed a temporary hypoparathyroidism within 24 hours postoperatively. All patients recovered within 3 months of surgery.
[64]	3	Total thyroidectomy	Case report	Normal range PTH 1.60–6.90 pmol/L.	Normal serum calcium 2.11–2.52 mg/dL.	No hypoparathyroidism at postoperative day 1 and 2-week-follow-up.
[65]	60	Total thyroidectomy	Multi-centre prospective clinical trial	Temporary postoperative: PTH <14 pg/mL	<8.2 mg/dL	No association between intra-operative ICG staining score (expressed as the number of PG scoring <2 per patient) and 24-h post-operative PTH (r=0.011, p=0.933) or serum calcium concentrations (r=0.127, p=0.335).

Table 2
ICG for parathyroidectomy.

Study	Population (n)	Intervention	Study type	Normal PTH and calcium ranges	Biochemical (hypocalcaemia, postoperative hypoparathyroidism) and clinical outcome
[22]	1	Redo parathyroidectomy	Case report	NA	POD1 calcium decreased to 11 mg/dL, PTH level decreased to 10 pg/mL. One month postop: calcium 9.8 mg/dL, PTH 49 pg/mL. Clinical outcome: One month postop: improved symptoms, increased energy, no abdominal problems.
[40]	9	Subtotal parathyroidectomy	Case series	NA	PTH levels dropped to 76 ± 6.5 % from preoperative levels, all patients had normal calcium and PTH at follow-up.
[41]	1	Parathyroidectomy (robotic, transaxillary)	Case report	NA	Initial PTH baseline was 109.2 and dropped to 39.1 within 10 minutes of gland removal, which confirmed evidence of curative surgery. Clinical outcome: mobile vocal cords.
[42]	1	Subtotal parathyroidectomy	Case report	NA	POD 1, corrected calcium 1.93 mmol/L, PTH level 8 pmol/L. Intravenous calcium for 48 hours.
[43]	60	Parathyroidectomy	Retrospective series report	Cure defined as serum calcium of ≤10.6 mg/dL	All 60 patients had a decrease in their intraoperative PTH level of >50%. 19 had a documented cure at 6 months; 31 had a documented cure at 3 months.
[44]	29	Total parathyroidectomy	Controlled study	NA	No significant difference between the two groups preoperatively and postoperatively regarding serum calcium, phosphorus and PTH variations ($p > 0.05$). Clinical outcome: symptomatic relief rate 100%.
[45]	13	Subtotal parathyroidectomy	Case series	PTH normal levels 1.1–6.8 pmol/L Hypocalcaemia corrected calcium value < 2.0 mmol/L	POD1: 4 patients with low PTH (<1.1 pmol/L). POD 10: PTH Measurable, except in one patient (PTH 0.9 pmol/L, calcium 2.84 mmol/L, normalised at follow-up). Follow-up 4 months: all normal corrected calcium levels, no hypoparathyroidism.
[46]	33	Parathyroidectomy (6/33 subtotal)	Prospective case series	NA	All patients biochemically cured, no hypoparathyroidism.

patients developed symptomatic hypocalcaemia despite calcium and vitamin D supplementation, none of the participants with at least one well perfused gland did. The participants included in the other two studies did not display clinical hypocalcaemia [34,37]

As for the other outcomes of ICG usage for thyroidectomy surgeries, the average length of stay was not indicated in most studies, an exception being Alesina and colleagues [37], who mentioned that all patients were discharged on POD2. In seven studies [27,28,30,32,34,35,38] the need for long-term treatment, i.e., more than 6 months, was assessed, and no significant difference between ICG and control groups was found. In a reply letter to a study [31], Mattoo and Agarwal [39] highlighted the importance of long-term follow-up and the paucity of information on clinical outcomes and average timing of discharge.

4.1.2. ICG for parathyroidectomy

When assessing the usage of the same technique of visualisation during parathyroidectomies, there is a paucity of studies on ICG for parathyroidectomy and the clinical outcomes of such technique have not regularly been assessed (see Table 2). Authors of various studies have reported ICG as an auxiliary method in the identification of PG in a few case series with robotic transaxillary, redo and subtotal parathyroidectomy [22,40–42]. DeLong and colleagues [43] could identify PG with ICG which were not visible on sestamibi, and reported that all patients were cured within 3 months. Similarly, Cui and colleagues [44] concluded that ICG could help surgeons in identifying PG. Vidal Fortuny and colleagues [45] found that parathyroid gland perfusion and the postoperative parathyroid function correlate well. Similarly to the thyroidectomy studies, the need for long-term treatment was analysed only in a few parathyroidectomy studies [43,46]. DeLong and colleagues [43] and Zaidi and colleagues [46] observed no patient needing long-term treatment, even though in the former study 10 of 60 patients were not followed-up after 3 months.

4.2. AF

4.2.1. AF for thyroidectomy

We have summarised the effects of AF usage on biochemical and clinical outcomes of thyroidectomies in Table 3. It is worth noting that the first RCT evaluating the effect of AF on outcomes after total thyroidectomies was performed by Dip and colleagues [47] and published in 2019, comparing the effect of using AF to white light only in 170 patients. They found that calcium levels ≤7.5 mg/dL were one-tenth as common in the AF group and therefore concluded that the use of AF can decrease the rate of postoperative hypocalcaemia [47]. Similarly, Benmiloud and colleagues [48] published their multi-centre RCT in 2019 and analysed the rate of postoperative hypocalcaemia at POD1 and 2 as primary outcome. They observed a significantly lower hypocalcaemia rate in the AF group compared to the control group, but did not find a significant difference in permanent hypocalcaemia rate [48].

4.2.2. AF for parathyroidectomy

Only very few studies included only patients undergoing parathyroidectomy and analysed the effect of using AF on their outcomes; clinical outcomes and need for long-term treatment were generally not studied systematically (Table 4). There are more studies which included both patients undergoing either thyroidectomy or parathyroidectomies where the impact of AF on patients' outcomes is analysed (Table 5).

4.3. Studies using AF for both thyroidectomy and parathyroidectomy

Similarly to the studies mentioned above, the studies which included both patients undergoing thyroid and those undergoing parathyroid surgery did not have a main biochemical or clinical outcome and postoperative calcium and PTH levels were rarely reported. Table 5 summarises the biochemical outcomes of such studies. Unfortunately, in the included studies there was scarcity of information on long-term treatment needs and a lack of information on clinical outcome (e.g. symptomatic hypocalcaemia). Most of these studies focussed mainly on assessing the feasibility of AF and its utility in identifying and localising PG [49–61]. The results regarding the identification of PG are presented in next section of this review.

4.4. ICG vs AF

There is one study [62] directly comparing ICG to AF for the detection of PG: 22 patients per group underwent 39 total thyroidectomies

Table 3
AF for thyroidectomy. 2 RCTs are highlighted in bold.

Study	Population (*n*)	Intervention	Study type	Definition of hypoparathy-roidism	Definition of hypocalcaemia	Biochemical (hypocalcaemia, postoperative hypoparathyroidism) and clinical outcome
[47]	170	Total thyroidectomy (85 with white light and 85 NIRL)	**RCT**	NA	Hypocalcaemia serum calcium level <8.0 mg/dL, 'persistent' if at 6-month follow- up.	Hypocalcaemia 8.2% (n=7) in the NIRL group vs 16.5% (n=14) (non-significant). More severe hypocalcaemia, (serum calcium level <7.5 mg/dL): 1.2% in the NIRL group vs 11.8% in the control group (p = 0.005). Clinical outcome: symptomatic hypocalcaemia in 1 subject per group. Long-term: calcium replacement beyond hospitalisation in 1 subject per group, calcium normalised in all patients at 6-mo follow-up.
[48]	241	Total thyroidectomy +/- lymph node dissection 121 NIRAF group, 120 control group	**Multicentre RCT**	PTH POD1 normal when ≥15 pg/mL;	corrected calcium level < 8.0mg/dL (Payne formula)	Temporary hypocalcaemia: 9.1% (11/121) in the NIRAF group vs 21.7% (26/120) in control group (p = .007) Long-term: There was no significant difference in permanent hypocalcaemia rates (0% in the NIRAF group and 1.6% [2 of 120 patients] in the control group).
[66]	513	Total thyroidectomy	Before and after controlled study	NA	Corrected calcium level <8 mg/dL (with or without symptoms) at POD 1 or 2	Significantly lower transient hypocalcaemia in NIRL group (5.2% vs 20.9%; p < 0.001). Long-term: Permanent hypocalcaemia only in 2/153 patients in the NIR− group.
[67]	300	Total thyroidectomy with surgical loupe (100 NIFI, 200 controls)	Before and after study	NA	Serum calcium <8 mg/dL	Short and long-term: No statistically significant difference in transient (6.5% vs 5.0%) and permanent (0.5% vs 0%) hypocalcaemia in conventional vs NIFI group. Clinical outcome: There was one patient in each group who required an emergency room admission on POD2 due to symptomatic hypocalcaemia.
[68]	20	Partial and total thyroidectomy	Prospective clinical trial	NA	NA	4/20 experienced transient hypoparathyroidism, recovering no later than after 3 months.
[69]	20	Thyroidectomy	Case series	NA	NA	NA
[70]	4	Hemithyroidectomy	Preliminary clinical trial	NA	NA	NA
[72]	269	Total thyroidectomy (n = 140), hemithyroidectomy (n = 129). 106 NIRI and 163 controls.	Controlled trial (retro-spective controls)	PTH 1 < pmol/l or normal calcium and PTH but requiring calcium and vitamin D supplementation > 2 weeks	Serum corrected calcium < 2 mmol/l	POD1 hypocalcaemia in 10.5% (n = 9) of controls and 9.3% (n = 5) of NIRI group (p = 0.53) and hypoparathyroidism in 11.6% (n = 10) and 11.1% (n =6) (p = 0.38).
[83]	38	Total thyroidectomies (n = 17 patients), unilateral lobectomies (n = 21), no controls	Prospective clinical study	NA	NA	All patients maintained normal parathyroid gland function, except 1 patient, who required calcium supplementation for temporary hypocalcaemia.
[84]	8	Thyroidectomy	Pilot study	NA	NA	No patients experienced postoperative hypoparathyroidism.

and 5 thyroid lobectomies. The authors found similar rates of postoperative hypocalcaemia—defined as calcium <8mg/dL—in the AF (9%) and ICG group (5%), and no permanent hypocalcaemia.

5. Identification of parathyroid glands (other structures displaying ICG/AF, factors influencing the ICG/AF signal, distinction between pathological and healthy PG, viability, influence on surgeon's choice, number of parathyroid glands found in specimens)

5.1. ICG

5.1.1. ICG for thyroidectomy

In 2016, Zaidi and colleagues [21] reported that 84% of PG showed ICG fluorescence during thyroidectomy, suggesting that such anatomical structures could be identified prior to dissection, minimizing the risk of injury of blood supply. Other authors suggested that, as ICG intensity reflected perfusion [63], such technique could influence surgical practice [32]. Numeric scales were introduced to assess and record ICG fluorescence intensity. PG were classified after the injection of ICG as black (non-vascularised), grey or heterogeneous (partially vascularised) or white (well vascularised) [30,31,33,34,38,63–65]. A numeric value or a ratio comparing to the background [30,32,33,35,38] was given to these degrees of ICG fluorescence. In 2018, Jin and colleagues [33,38] aimed to apply ICG and observed a more accurate identification of devascularised PG with ICG angiography leading to more pertinent autotransplantations in a pilot study with 26 patients, in line with other studies [21,27,64]. In 2020, a multicentric prospective clinical trial was published gathering data on 60 patients: only 4/240 PG could not be identified with IGC (1.67%) [65]. Even in more specific settings, when assessing the viability of using ICG for bilateral axillo-breast approach (BABA) for thyroidectomy [35], all targeted glands were identified during surgery in 22 patients and the rate of incidental parathyroidectomies was lower than in the control group [35]. However, there are some factors which have an influence on the PG detection with ICG for thyroidectomy, such as misinterpretation of other well-vascularised anatomical

Table 4
AF for parathyroidectomy.

Study	Population (*n*)	Intervention	Study type	Normal PTH and calcium ranges	Biochemical outcome (hypocalcaemia, postoperative hypoparathyroidism) and clinical outcome
[73]	81	Ex vivo analysis of fluorescence decay in PG and other neck tissue (127 samples)	Prospective clinical study	NA	NA
[74]	39	Parathyroidectomy	Case series	PTH 15–65 pg/mL	Primary HPT: median preoperative serum PTH 132 pg/ml (85–4042 pg/ml), postoperative normalization in 27/29 (93%) patients with normal (n = 16) or subnormal values of PTH (n = 11). Cumulative PTH normalization rate 100%. Secondary HPT: 100% early biochemical cure.
[75]	5	Parathyroidectomy	Case series	PTH 11–65 pg/ml, calcium 8,5–10,4 mg/dl,	Intra-operative PTH assay showed surgical success (significant decrease compared with basal value) Long-term: no hyperparathyroidism at 6-month follow-up.
[76]	59	Parathyroidectomy (69 PG)	Prospective feasibility trial	NA	The criterium for concluding all surgeries was an appropriate fall of intraoperative PTH.
[77]	50	Bilateral neck exploration (+parathyroidectomies)	Prospective clinical study	Cure: normocalcaemia with normal PTH levels > 6 months follow-up.	37 patients were cured at 6-month bloodwork, whereas 13 patients had normalization of their serum calcium and PTH values on postoperative visits done at less than 6 months postoperatively.
[78]	71	Parathyroidectomy	Retrospective analysis	NA	NA
[79]	96	Parathyroidectomy (284 visualisable glands)	Case series	Normal upper limit PTH 6.4 pmol/l, calcium 2.6 mmol/l	NA

structures [28], misleading fluorescence [30], transient ischemia [27] or the position of the inferior thyroid artery [30].

When performing thyroidectomies, in several studies the use of ICG had a clear influence on the surgeon's actions intraoperatively [35,38,63]. Vidal Fortuny and colleagues [28] reported in 2016 a modification of the procedure in five patients whose angiography results showed a devascularised PG with a normal visual score. In 2018, the same group autotransplanted 23 PG based on the ICG results indicating absence of perfusion (out of 37 autotransplanted PG)[34]. Furthermore, van den Bos and colleagues [30] undertook a subjective assessment of the technique's usefulness. For 26 operated patients the surgeon rated ICG fluorescence to be useful in 57% of the cases, either because it reassured them about the location of the parathyroid glands or, in two cases, because the technique could identify glands that would have been otherwise missed.

5.1.2. ICG for parathyroidectomy

Correspondingly, in 2015, 2016 and 2017, three pilot studies presented the first satisfactory results for PG resection with ICG identification for primary hyperparathyroidism, secondary hyperparathyroidism and recurrent adenoma, respectively [22,41,42]. Similar numeric values were used when using ICG for PG identification in the case of parathyroidectomy [43,44,46]. In 2018, DeLong and colleagues [43] published a retrospective series report with patients who did not localise parathyroid adenomas on preoperative imaging studies. The authors concluded that ICG could be a useful adjunct to preoperative imaging in cases where the latter cannot localise the pathology [43]. Cui and colleagues reported a sensitivity of 91.9%—higher than that of preoperative US, sestamibi or CT—and a specificity of 80% for PG identification in patients undergoing parathyroidectomy for secondary hyperparathyroidism resistant to medical treatment [44].

Surgeons also benefitted in several studies from the usage of ICG for parathyroidectomies. In 2016, Vidal Fortuny and colleagues [40] concluded that ICG fluorescence is a useful method for the surgeon to double-check the perfusion of PG before completing the resection in parathyroidectomies. In 2017 a case-control study [44] reported that when undertaking parathyroidectomies in patients with secondary hyperparathyroidism, there was a substantially higher resection rate when ICG was used vs. without ICG use. They reported ICG to even be successful in identifying an ectopic PG in the thymus [44].

5.2. AF

5.2.1. AF for thyroidectomy

Similarly to ICG, AF is a non-invasive and useful technique for PG identification during thyroidectomy. Benmiloud and colleagues [66] designed a study which compared thyroidectomy outcomes in patients operated by junior doctors with AF, without AF and operations performed by senior surgeon without AF. PG identification rates were higher in the group using AF. Similar results were reported by Dip and colleagues [47] and Falco and colleagues [55]. In a randomised control trial on 245 patients [48], the rate of patients where all 4 PG could be identified was significantly higher in the AF group. Kim and colleagues in 2020 [67] reported a sensitivity between 90% and 100%, while Liu and colleagues [68] published an accuracy of 95% of PG identification and a positive predictive value of 95% when AF was used. It is worth noting that, according to some authors, the thyroid gland (and specifically if small nodules of colloid are present) can provide false positive images [66]. However, others have reported that the autofluorescence of the PG was significantly higher than that of the thyroid, fat and lymph nodes [55,68,69]. In fact, Kim and colleagues [70] reported the PG mean signal to be 332% stronger than that of the thyroid.

Several studies have demonstrated that AF has an influence on the surgeon's performance during thyroidectomies [48,66,71]. The advantage of the technique led to a lower number of patients needing autotransplantation and a significantly lower number of inadvertent parathyroid resections [47,66,69]. Importantly, in a case series with 23 patients [69], small sized PG were more frequently detected with AF whereas they were often missed visually. Conversely, in 2019 a study [72] comparing AF use to a control group showed no statistically significant differences in PG missed at operation and detected histologically in the two groups.

Table 5
AF for both thyroidectomy and parathyroidectomy.

Study	Population (n)	Intervention	Study type	Biochemical outcome (hypocalcaemia, postoperative hypoparathyroidism)
[19]	21	Thyroidectomy, parathyroidectomy	Pilot study	NA
[49]	117	Open thyroid or parathyroid surgery	Case series	NA
[50]	210	Total thyroidectomy (n = 95), thyroid lobectomy (n = 41) and parathyroidectomy (n = 74)	Multi-centre retrospective analysis of prospectively collected data	NA
[51]	20	Total thyroidectomy (n = 6), thyroid lobectomy (n = 3), completion thyroidectomy (n = 1), completion central neck dissection (n = 1), combined total thyroidectomy-parathyroidectomy (n = 1), and parathyroidectomy (n = 8)	Case series	NA
[52]	30	Parathyroidectomy and/or thyroidectomy (15 hyperparathyroidism (primary or secondary), 12 thyroid disease and 3 concurrent parathyroid-thyroid disease	Case series	NA
[53]	41	Thyroidectomy or parathyroidectomy. PTeye (n = 20), modified NIR imaging (n = 6) system and OTIS (n = 15)	Retrospective observational study	NA
[54]	30	Open or minimally invasive parathyroid (n = 21) or thyroid surgery (n = 9)	Serie report	NA
[55]	74	Thyroid and parathyroid surgery	Retrospective review of a prospectively maintained database	Long-term: No permanent hypocalcaemia. All patients with diagnosis of primary hyperparathyroidism (13/74) had a successful operation with normal postoperative serum calcium at six months follow-up.
[56]	28	Thyroid and parathyroid surgery. Primary hyperparathyroidism (n = 7), hyperthyroidism (n = 4), goitres (n = 3), thyroid cancer (n = 11), mixed pathologies (n = 3)	Case series	No postoperative hypocalcaemia.
[57]	35 in vivo, 28 ex vivo	Total and partial thyroid and parathyroid surgery	Feasibility study: Ex vivo study on resected operative specimens combined with a prospective in vivo study	NA
[58]	197	Thyroidectomy, parathyroidectomy Lab-built (n = 162), PTeye (n = 35); Lab-built vs PTeye: (n = 20 per group)	Blinded prospective trial	NA
[59]	17	Thyroidectomy, parathyroidectomy	Prospective clinical trial	NA
[60]	110	Thyroidectomy, parathyroidectomy	Pilot study	NA
[61]	310	Total thyroidectomy, thyroid lobectomy, and parathyroidectomy	Prospective clinical trial	NA
[80]	137	Thyroidectomy, parathyroidectomy (264 parathyroid glands)	Prospective clinical trial	NA
[81]	45	Thyroidectomy, parathyroidectomy	Prospective clinical trial	NA

5.2.2. *AF for parathyroidectomy*

AF has also been proved useful during parathyroidectomies for gland identification. After a study introduced ex vivo the concept of Dynamic Optical Contrast Imaging in 2017 [73], Wolf and colleagues [74] reported that 57 of 66 histologically-confirmed adenomatous and hyperplastic glands displayed autofluorescence. Despite previous contrasting results [75,76], a multivariate analysis [77] showed lower AF intensity of hyperfunctioning compared to normofunctioning PG. PG of patients with MEN1 syndrome displayed decreased AF signal when compared to other patients with primary hyperparathyroidism, perhaps as a result of differential expression of unknown receptors or proteins within parathyroid tissue [78]. Another study reported that hyperfunctioning parathyroid glands more often exhibited a heterogeneous pattern of autofluorescence that was different from normofunctioning parathyroid glands [77]. In some cases, the inferior PG could not be identified when hidden by blood vessels as the fluorescence was then of low intensity [71].

AF has also proven to influence the surgeon's decisions in parathyroidectomies. In 2019, a case series [75] of five patients reported the use of AF for parathyroidectomy as a useful tool for inexperienced surgeons who can benefit from confirmation of anatomical location of the parathyroid glands. Another study [76] confirmed this technique to significantly increase the confidence of the surgeon. However, other authors [74] underline that AF cannot substitute the surgeon's experience but is simply a tool to enhance technical expertise. Additionally, another study [79] with 96 patients concluded that 10% of glands do not emit enough AF for the surgeon to recognise.

5.2.3. *AF for thyroidectomy and parathyroidectomy*

Some authors reported their experience in the use of AF for both thyroidectomy and parathyroidectomy. Ladurner and colleagues [49] reported their 5-year experience on 117 patients. Parathyroid tissue was easily differentiated from lymph nodes and adipose tissue and its signal did not change when there were parathyroid adenomas [37,54]. Other studies confirmed that AF signal was higher in PG than in the thyroid (97% of the cases) and that muscle, fat, lymph nodes, thymus and trachea have very low fluorescence signal [19,51–54,56–61,80].

Studies taking into account thyroidectomies and parathyroidectomies have reported AF sensitivity for PG identification to range between 87.3 and 99% [50,51,53,57,58,81] and specificities of 80 to 95% [51,53,57]. The identification rates were 100% in two studies by the same author [60,81] and in 2016 Mc Wade and colleagues reported identification rates of 97% in patients undergoing thyroidectomy or parathyroidectomy [52,80]. In two other studies, 98% of the PG exhibited AF [53,61]. Those were higher than the detection rates for the naked eye, reported to be as high as 91% [53].

Since 2013, studies have reported AF to be a useful tool for surgeons to help with PG detection [51]. Cases were reported where the technique helped correcting the wrong identification with naked eye [58,81] as PG maintain their fluorescence regardless of their vascularisation [50,54,57–59,80], disease [56,58–60] or the presence of blood in the surgical field [58]. Cases have been reported where AF has helped the surgeon with the identification of glands that would otherwise have been missed [50,57] and facilitated autotransplantation in 5% of the cases [61], especially in the case of smaller PG more likely to be unrecognised on visual inspection [50]. Its use has also been reported as a potential educational tool for training surgeons [52].

5.3. ICG vs AF

As mentioned before, only a few studies have compared ICG and AF. Namely, in 2017, Kahramangil and colleagues [62] compared the techniques in patients undergoing total thyroidectomy or thyroid lobectomy and found similar PG detection rates. The main difference was timewise, as AF could detect PG before the naked eye more often than ICG due to less interference from background thyroid [62]. A different approach was adopted by Alesina and colleagues [37], who used AF followed by ICG if needed for PG identification in their study. The combination of both techniques has been found to be useful in this case series [37].

6. Technical challenges (need to turn off lights, duration of surgery, undesirable events) and cost-effectiveness

6.1. ICG for thyroidectomy and parathyroidectomy

Most studies specified that no ICG-related adverse events occurred in thyroidectomy [28–31,35,37,63–65] or parathyroidectomy [22,41,44–46]. In particular, no allergic reaction was observed [21,65]. Interestingly, a case of intraoperative “black thyroid” was observed with ICG use [82].

With regard to the timing of the surgeries and the usage of the technique, ICG performance generally takes about 6 minutes in both thyroid and parathyroid surgery [22,28–30,35,45], with fluorescence being observed about 1–2 minutes after injection and persisting for about 20 minutes [21,35,38,43]. Authors compared this to the longer time required for intraoperative PTH assessment, which takes at least 9 to 20 minutes [27,81] and therefore, in contrast to ICG, cannot provide real time assessments [27].

Interestingly, the cost of using ICG in thyroid surgery has been discussed by a few authors. The dye itself is “inexpensive” [27,38,42,43,45], costing around EUR 66.50–70 per 25mg vial [28,31]. The camera system is expensive—costing around USD 47,000 [31]—but can be used in other surgical procedures [28,31,45]. Lang and colleagues [32] estimated that one ICG fluorescence angiography costs around USD 253 including maintenance cost and consumables, amounting to about twice as much the cost of a PTH test at their institution. Some authors have highlighted that the high quality of the images and the possible reduction of hypocalcaemia rates could make it a cost-effective tool [28,31,32].

6.2. AF for thyroidectomy and parathyroidectomy

In contrast to most of the ICG systems, systems based on AF tend to require the theatre lights to be switched off. However, AF systems with fibre-probes can be used with theatre lights during thyroid [70] or parathyroid surgery [51,53,58].

The time needed to prepare the imaging system and map the PG prior to thyroidectomy is about 3 to 10 minutes [69,83,84]. Identifying the PG during thyroid surgery takes approximately 1–10 minutes in total [47,68,69,83,84]. Similarly, different effects on the total operating time have been reported, ranging from no significant effect [66,68,70,76,79] to an increase of a few minutes [48,72]. Similar times were reported by authors of studies on both parathyroid and thyroid surgery [49,50,52,60,76,79,81]. The time needed to identify PG with AF is shorter than the time—usually 20–30 minutes—needed for frozen section analysis [52,53].

No complications related to the imaging system were reported when AF was used [48,56,59,84]. DiMarco and colleagues [72] estimated that using the equipment of a commercially available AF system plus consumables for one year amounts to about GBP 35,000. It was pointed out by multiple authors that a widespread usage of the detection system even for other types of surgery would improve cost-effectiveness [49,52,53] and that the camera system depends on the needs of the medical centre.

7. Discussion

Overall, 3 randomised controlled trials (RCTs), 22 case series or reports , and 33 further observational studies were included in this scoping review. In general, in cases of thyroidectomy a correlation between ICG uptake and postoperative PTH levels was observed and, although only a few studies reported hypocalcaemia outcomes, its incidence was low when perfused glands were detected with ICG. For parathyroidectomies, PG perfusion with ICG and postoperative parathyroid function seem to correlate well. When AF is used, several observational studies report no differences in terms of outcomes after thyroidectomies. However, two RCTs from 2019 have concluded that the use of AF can decrease the risk of postoperative hypocalcaemia. Only feasibility studies or case series explore the role of AF in parathyroidectomies and show a good identification rate with its use. Only one study compared ICG and AF with similar results and nil cases of permanent hypocalcaemia.

The use of ICG or AF has an influence on the surgeon’s actions intraoperatively. In thyroidectomies this often leads to more pertinent autotransplantations and less incidental PG resections. In the case of parathyroidectomies confirmation of PG location can be obtained and a well perfused gland can be chosen for resection, increasing the surgeon’s confidence. Overall, no ICG nor AF related adverse events occurred in thyroidectomy or parathyroidectomy studies. The main difference between the techniques is the timing of detection.

One of the limitations of our study is that “autofluorescence” is not a MeSH term. Another limitation is that the cohorts where not big enough to allow subgroup analysis. The applications of ICG and AF could differ among subgroups of patients and their efficacy in PG identification could vary, as the characteristics of disease progression and response to surgery might differ between subgroups [85]. Many studies rely on the surgeon’s experience to determine whether imaging was successful in identifying the parathyroid when it is left in place and not confirmed histologically. Also, the definition of hypocalcaemia differs in the included papers, as it has been reported in the literature [86]. We did not include grey literature and acknowledge the possibly of publication bias in this review.

Although many papers present results on the use of AF and ICG for thyroidectomies and parathyroidectomies, the studies are usually observational and analyse small sample sizes with no control groups. Only 3 RCTs are included in this review. Little information has been published on the impact of the use of these techniques on reducing hypocalcaemia, and often clinical and biochemical outcomes are missing in the selected studies.

8. Conclusion

We acknowledge the feasibility of the use of ICG and AF with low risk of side effects and as a useful tool to identify PG more effectively than with classic methods or the naked eye. These results are encouraging towards the use of ICG and AF intraoperatively. However, further research with standardisation of study design systematically assessing short- and long-term biochemical and clinical outcomes is needed to obtain high quality evidence showing a clear reduction in postoperative hypocalcaemia rates that would justify the use of ICG or AF in routine surgical practice.

Declarations of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Annalisa Hauck: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Aina Pons:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Tarek Abdel-Aziz:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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