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Indocyanine Green Fluorescence Imaging in Parathyroid Surgery for Primary Hyperparathyroidism in Cases of Uncertain, Discordant, or Atypical Preoperative Localization: Narrative Review and Case Series

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Rezumat

Colorația cu verde de indocianină în chirurgia paratiroidiană pentru hiperparatiroidismul primar în cazurile cu localizare imagistică nesigură, discordantă sau atipică: review narativ al literaturii și serie de cazuri

Introducere: Hiperparatiroidismul primar (HPT primar) afectează aproximativ 0,9% din populația generală. Tratamentul definitiv este chirurgical, iar paratiroidectomia minim invazivă focalizată (MIP) este standardul actual, condiționat de o localizare preoperatorie corectă. Ratele de fals negativ ale scintigrafiei cu technețiu-99m sestamibi (MIBI) variază între 8% (adenoame >1000 mg) și peste 70% (adenoame <100 mg), iar localizările ectopice sau atipice sunt raportate la până la 22% dintre pacienții neexplorați chirurgical anterior. Eșecul localizării conduce la explorare extinsă, prelungirea timpului operator și creșterea riscului de leziune a nervului laringeu recurent (NLR). *Scop:* Sinteza narativă a evidenței recente (2017–2025) privind rolul colorației cu verde de indocianină (ICG) în chirurgia paratiroidiană și descrierea experienței proprii printr-o serie observațională de 5 paciente, bazată pe date clinice înregistrate prospectiv, cu scenarii clinice definite: discordanță imagistică, localizare atipică, prezentare biochimică extremă.
Material și metodă: Serie observațională, descriptivă, monocentrică, bazată pe date clinice înregistrate prospectiv, cuprinzând 5 paciente cu HPT primar selectate deliberat, operate de același chirurg între aprilie și august 2024 cu sistemul Karl Storz IMAGE1 S™ Rubina®. Doza ICG: 5 mg bolus IV (2,5 mg/mL). Au fost înregistrate timpul de apariție a fluorescenței, aspectul calitativ standardizat al fluorescenței glandei țintă și a glandelor normale, vindecarea biochimică precoce și complicațiile.
Rezultate: Vârstă 22–70 ani (mediană 55), hormon paratiroidian (PTH) bazal 100-192 pg/mL (medie 135,3), hipercalcemie în 4 din 5 cazuri (Ca 11,0–14,86 mg/dL; valoarea maximă a fost înregistrată în cursul internării endocrinologice premergătoare), 1 caz de HPT primar normocalcemic (Ca 9,7 mg/dL). Două cazuri cu discordanță MIBI-intraoperator, două cu localizări atipice solicitante tehnic, unul cu prezentare bio-

chimică severă la 22 de ani. ICG a identificat glanda hiperfuncțională responsabilă în toate cele 5 cazuri; debutul fluorescenței la 22-38 secunde; în fiecare caz glanda țintă a prezentat hiperfluorescență rapidă, intensă şi persistentă, net distinctă de captarea moderată şi tranzitorie a glandelor normale. Histopatologia a evidențiat adenom paratiroidian solitar în patru cazuri (300-1158 mg) şi țesut paratiroidian hipercelular cu hiperplazie discretă în cazul normocalcemic. Vindecarea biochimică precoce a fost obținută în toate cazurile; fără leziuni de NLR şi fără reacții adverse la ICG. Având în vedere selecția deliberată a cazurilor, rezultatele sunt raportate strict descriptiv şi nu pot fi interpretate ca estimări ale performanței diagnostice globale.
Concluzii: În experiența noastră, colorația ICG a oferit un ghidaj intraoperator util în trei scenarii clinice: discordanță cu imagistica preoperatorie, localizări atipice solicitante tehnic şi prezentări severe care necesită susținerea ipotezei bolii uniglandulare. Beneficiile raportate în studiile comparative (reducerea timpului operator, a extensiei explorării cervicale şi a riscului de leziune a NLR) nu au putut fi evaluate în această serie necontrolată şi rămân beneficii potențiale. Aceste observații au caracter generator de ipoteze şi susțin evaluarea ulterioară a ICG ca adjuvant al protocolului MIP.

Cuvinte cheie: hiperparatiroidism primar, verde de indocianină, paratiroidectomie focalizată, localizare adenom paratiroidian, discordanță MIBI, fluorescență în infraroşu apropiat

ABSTRACT

Background: Primary hyperparathyroidism (primary HPT) affects approximately 0.9% of the general population. The definitive treatment is surgical, and focused minimally invasive parathyroidectomy (MIP) is the current standard, conditional upon accurate preoperative localization. Technetium-99m sestamibi (MIBI) scintigraphy false-negative rates range from 8% (adenomas >1000 mg) to over 70% (adenomas <100 mg), and ectopic or atypical adenoma locations are reported in up to 22% of previously unexplored patients. Localization failure leads to extensive cervical exploration, prolonged operative time and an increased risk of recurrent laryngeal nerve (RLN) injury. *Aim:* To provide a narrative synthesis of the recent evidence (2017-2025) regarding the role of intraoperative indocyanine green (ICG) fluorescence imaging in parathyroid surgery and to describe our initial experience in an observational, single-centre series of 5 female patients, based on prospectively recorded clinical data, with defined clinical scenarios: imaging discordance, atypical localization, and extreme biochemical presentation.
Materials and methods: Observational, descriptive single-centre case series based on prospectively recorded clinical data, comprising 5 deliberately selected female patients with primary HPT, operated by the same surgeon between April and August 2024 using the Karl Storz IMAGE1 S™ Rubina® system. Standard ICG dose: 5 mg IV bolus (2.5 mg/mL). Outcomes assessed: time to onset of fluorescence, standardized qualitative fluorescence pattern of the target gland and of the normal parathyroid glands, early biochemical cure and complications.
Results: Patient ages 22-70 years (median 55), baseline parathyroid hormone (PTH) 100-192 pg/mL (mean 135.3), hypercalcaemia in 4 of 5 cases (Ca 11.0-14.86 mg/dL; the maximum value was recorded during the preceding endocrinology admission) and one case of normocalcaemic primary HPT (Ca 9.7 mg/dL). Two cases showed MIBI–intraoperative discordance, two presented technically demanding atypical localizations, and one was a 22-year-old patient with severe biochemical presentation. ICG identified the culprit hyperfunctioning gland in all 5 cases, with fluorescence onset at 22-38 seconds; in each case the target gland displayed rapid, intense and persistent hyperfluorescence, clearly distinguishable from the moderate, transient enhancement of normal glands. Histopathology showed a solitary parathyroid adenoma in four cases (300-1158 mg) and hypercellular parathyroid tissue with discrete hyperplasia in the normocalcaemic case. Early biochemical cure was achieved in all 5 cases; there were no RLN injuries and no ICG-related adverse reactions. Given the deliberate selection of cases, these results are reported strictly descriptively and should not be interpreted as estimates of overall diagnostic performance.
Conclusions: In our experience, ICG fluorescence imaging provided useful intraoperative guidance in three clinical scenarios: discordance with preoperative imaging, technically demanding atypical localizations, and severe presentations requiring support for the single-gland hypothesis. Reductions in operative time, extent of cervical exploration and RLN injury risk reported in comparative studies could not be assessed in this uncontrolled series and remain potential benefits. These hypothesis-generating observations support further evaluation of ICG as an adjunct within the MIP protocol.

Keywords: primary hyperparathyroidism, indocyanine green, focused parathyroidectomy, parathyroid adenoma localization, MIBI discordance, near-infrared fluorescence

Introduction

Primary hyperparathyroidism (primary HPT) is one of the most common surgically managed endocrinopathies, with a prevalence of approximately 0.9% in the general population and a marked female predominance (1,2). A solitary parathyroid adenoma accounts for 80-85% of cases; the remainder consists of multiglandular hyperplasia or double adenomas, while parathyroid carcinoma is a rare entity (under 1%) (1,3). The definitive treatment is surgical and, when a solitary adenoma is preoperatively localized, focused minimally invasive parathyroidectomy (MIP) currently represents the therapeutic standard, with biochemical cure rates of 95-98% (3,4). The success of MIP, however, depends critically on the accuracy of preoperative imaging localization.

The standard algorithm combines cervical ultrasonography with ^{99m}Tc-sestamibi (MIBI) scintigraphy with single-photon emission computed tomography/computed tomography (SPECT-CT) (3,4). Their cumulative sensitivities exceed 90% for a well-localized solitary adenoma, but performance declines markedly in several specific contexts. First, adenoma size has a direct impact on MIBI uptake: false-negative rates rise from approximately 8% for adenomas larger than 1000 mg to over 70% for adenomas under 100 mg (5). Second, concomitant thyroid pathology (multinodular goiter, Hashimoto thyroiditis with diffuse uptake, hypercaptating nodules) generates competing zones of fixation that mask the parathyroid signal (5,6). Third, ectopic or atypical localizations (thymic, retroesophageal, intrathyroidal, paracarotid) are systematically underrepresented in the reported sensitivity of conventional methods (7,8).

Cumulatively, parathyroid adenomas in ectopic positions occur in approximately 22% of unoperated patients and represent the most frequent cause of MIP failure (7,8). In practice, failed preoperative localization or marked discordance between ultrasound and MIBI leads to extensive bilateral cervical exploration, with significant prolongation of operative time, extensive manipulation of the paraesophageal and paracarotid recesses, dissection of the thyrothymic ligament, and a proportional increase in the risk of iatrogenic RLN injury, reported at 1-2% in standard cases but significantly higher in reoperations or difficult explorations (9).

Within this landscape, intravital indocyanine green (ICG) staining with near-infrared (NIR) imaging has evolved over the past decade from an experimental technique into an increasingly adopted intraoperative adjunct in cervical endocrine surgery, and its use is addressed in the 2023 consensus of the European Association for Endoscopic Surgery (EAES) on ICG fluorescence-guided surgery (10). ICG is a hydrophilic fluorescent dye, FDA-approved since 1959 and CE-marked, with an excellent safety profile; the rate of severe adverse reactions is below 0.01% (11). The mechanism for parathyroid adenoma identification is based on differential vascular perfusion: the adenoma, due to its increased cellular mass and hypertrophied vascular network, takes up ICG intensely and lights up rapidly on the NIR image (11,12).

The cumulative literature data of the past years are convergent. The meta-analysis by Kim et al. (Head Neck 2022, 21 studies) reports a pooled ICG sensitivity for parathyroid tissue identification of 93.8% (95% CI: 90.0-96.2%) (13). Specific to parathyroid surgery, Mizrakli et al. (Eur Arch Otorhinolaryngol 2025), in a prospective study with retrospective controls (76 patients, 19 ICG versus 57 controls), reported a significant reduction of net operative time from 79 to 59 minutes ($p = 0.002$) and a 100% adenoma identification rate in the ICG group (14). Modern NIR systems, including the Karl Storz IMAGE1 S™ Rubina® with the Overlay module, combine white-light vision with real-time NIR superimposition, preserving the anatomical orientation of the operative field (15).

The present article provides a narrative synthesis of the recent literature (2017-2025), together with a descriptive, observational single-centre series, based on prospectively recorded clinical data, of 5 female patients with primary HPT, deliberately selected for the spectrum of scenarios in which preoperative imaging fails or is misleading. The aim is to illustrate the potential added value of ICG in these specific settings, not to estimate its overall diagnostic performance.

Materials and Methods

Study Design and Case Selection

Observational, descriptive single-centre case series, based on prospectively recorded clinical data, conducted at the Department of Endocrine Surgery of the C.I. Parhon National Institute of Endocrinology, Bucharest, between April and August 2024. Five female patients with biochemically confirmed primary HPT, scheduled for parathyroidectomy by the same surgeon (D.R.B.) with consolidated experience in cervical endocrine surgery, were included. Cases were not enrolled consecutively but were selected to illustrate defined clinical scenarios (imaging discordance, atypical localization and extreme biochemical presentation) in which the added value of the method becomes directly demonstrable. Because enrolment

was non-consecutive and intentionally oriented towards cases in which the benefit of ICG was expected to be maximal, the series carries an inherent selection bias; consequently, no estimates of sensitivity, specificity or overall identification rates can be derived from it, and all results are reported strictly descriptively.

Inclusion criteria: biochemically confirmed primary HPT, complete preoperative imaging assessment (cervical ultrasonography + MIBI/SPECT-CT) and surgical indication according to the recommendations of the Fifth International Workshop (Bilezikian et al. 2022) (1).

Exclusion criteria: iodine allergy, age under 18 years, secondary or tertiary hyperparathyroidism and preoperatively known multiple endocrine neoplasia syndromes.

The study was conducted in accordance with the principles of the Declaration of Helsinki; all patients provided written informed consent preoperatively.

NIR Imaging System and ICG Protocol

The Karl Storz IMAGE1 S™ Rubina® system was used: POWER LED RUBINA TL 400 light source (excitation 780 nm), TC 201 and TC 304 camera control unit modules, Overlay module (simultaneous superimposition of the white-light image and real-time NIR image). The NIR gain setting was kept at the system default value throughout the entire series in order to ensure inter-session comparability. Verdye® (lyophilized ICG, Diagnostic Green GmbH, Aschheim, Germany) was used, reconstituted extemporaneously to 2.5 mg/mL. Standard dose: 5 mg ICG as a peripheral intravenous bolus, followed by a 10 mL flush of 0.9% NaCl. This dose is within the range most frequently reported for ICG-based parathyroid identification (16,17). In all five cases, ICG was administered as a single intravenous bolus at the start of the cervical exploration, upon initiation of the identification dissection of the compartment indicated by preoperative imaging; no patient received a second dose. The precise intraoperative moment of injection for each case is stated in Results.

Intraoperative Fluorescence Assessment and Outcomes

Fluorescence assessment was qualitative and standardized. Under constant acquisition conditions (default NIR gain, Overlay mode, camera held at working distance by the same operator), the intensity and kinetics of the fluorescent signal of the target lesion were compared in real time with those of the visible normal parathyroid glands and of the surrounding tissues. The expected adenoma pattern was rapid, intense and persistent enhancement, in contrast with the moderate, more transient enhancement of normal glands. The time from intravenous bolus administration to the first fluorescent signal (tf, seconds) and the total duration of ICG assessment were recorded. No dedicated software-based quantification of fluorescence intensity was performed; accordingly, no numeric signal-to-background ratios are reported. The primary outcome was correct identification of the culprit hyperfunctioning gland by ICG, confirmed by histopathology (adenoma or hypercellular parathyroid tissue) and by the postoperative biochemical response. Secondary outcomes were early biochemical cure, defined as normalization of serum parathyroid hormone (PTH) and total calcium in the early postoperative period (before discharge or at the first postoperative control), the rate of cervical complications (RLN injury, haematoma, infection) and ICG-related adverse reactions. Patients were scheduled for clinical and laryngoscopic re-evaluation at the 30-day surgical control; the availability and duration of subsequent biochemical follow-up depended on the territorial referral circuit and are detailed per patient in the Results.

Narrative Literature Review

For the review component, a structured, non-systematic (narrative) literature search was conducted in PubMed/MEDLINE and Web of Science for the period January 2017 - December 2025, using the terms: “indocyanine green”, “ICG fluorescence”, “parathyroid surgery”, “parathyroidectomy”, “primary hyperparathyroidism”, “MIBI scintigraphy”, “atypical parathyroid adenoma”, “near-infrared autofluorescence”. Priority was given to prospective studies, meta-analyses and consensus statements of professional societies. As this component was not designed as a systematic review, no PRISMA-type flow diagram or formal study-selection process was applied. The synthesis focused on three axes: performance of preoperative imaging, anatomical distribution of atypical adenomas, and the role of ICG and of related intraoperative fluorescence technologies in parathyroid surgery.

Results

Demographic and Biochemical Characteristics

The cohort included 5 patients, all female, aged between 22 and 70 years (median 55 years). Preoperative biochemical profile: baseline PTH range 100-192 pg/mL (mean 135.3 pg/mL, normal range 15-65 pg/mL), with one patient (case 3) diagnosed by the referring endocrinology service with the normocal-

caemic form of primary HPT (Ca 9.7 mg/dL, elevated PTH documented in the biological history prior to admission); the other 4 patients presented with hypercalcaemia (Ca 11.0-14.86 mg/dL, normal range 8.5-10.5 mg/dL). Preoperative 25-OH-vitamin D, where measured, was 32, 35 and 15.5 ng/mL (cases 1, 2 and 5, respectively), with deficiency present only in case 5. Main clinical manifestations: osteopenia/osteoporosis with renal lithiasis (case 1), asthenic-depressive syndrome with lithiasis (cases 2 and 3, the latter representing the normocalcaemic form), severe multisite osteoporosis on a background of major comorbidities, sarcoidosis and multiple sclerosis (case 4), and presentation in hypercalcaemic crisis at 22 years of age (case 5). Complete data are summarised in *Table 1.*

Imaging Discordance (cases 1 and 2)

Two cases presented discordance between MIBI/SPECT-CT and the actual anatomical situation. In case 1, MIBI indicated an adenoma in the right inferior pole; ICG was injected at the start of the cervical exploration, upon initiation of the dissection of this region. The rapid initial exploration of the right inferior compartment was negative; upon contralateral extension of the exposure, the adenoma in the left inferior pole was clearly revealed by its persistent, intense fluorescence, a lateralization opposite to the preoperative indication. No second ICG dose was required, as the residual fluorescent signal remained clearly discriminative at this stage of the procedure. In case 2, ICG was likewise injected at the start of the cervical exploration. MIBI suggested the right inferior pole; ICG enabled identification of the actual adenoma in the right superior pole, correct in lateralization but at an anatomical level different from the scintigraphic indication. In both situations, ICG corrected the direction of exploration in real time, avoiding unnecessary dissection of the imaging false-positive region.

Technically Demanding Atypical Localizations (cases 3 and 4)

Two further cases presented atypical localizations with direct added value of the method. In case 3, distinctive for its normocalcaemic primary HPT pattern (serum Ca 9.7 mg/dL, PTH 100 pg/mL documented prior to admission), the culprit gland was located paracarotid left superior, in the immediate vicinity of the RLN, a position requiring particularly fine dissection for nerve protection. ICG, injected at the initiation of the dissection of the indicated region, enabled accurate identification of the target gland without extensive mobilization of the region. In this patient, parathyroidectomy was combined, in the same operative session, with total thyroidectomy for a coexisting multinodular goiter; the parathyroid phase accounted for approximately 38 minutes of the 180-minute combined procedure. In case 4, the adenoma was located at the left superior level, deep retrothyroid, beneath the perivisceral fascia, a position which, in the absence of NIR guidance, would have required a much more extensive cervical exploration, with mobilization of the thyroid lobe and dissection of the paraesophageal recesses. ICG, injected at the initiation of the dissection of this region, enabled localization of the target directly through the transparency of the superficial tissues, guiding the deep incision.

Severe Biochemical Presentation at 22 Years (case 5)

Case 5 represented an extreme presentation in a 22-year-old patient: PTH 191.9 pg/mL (approximately 3 × the upper limit of normal), a peak total calcium of 14.86 mg/dL documented during the preceding endocrinology admission (12.0 mg/dL preoperatively, after medical stabilization) and phosphataemia 1.63 mg/dL, a picture compatible with hypercalcaemic crisis at presentation. MIBI correctly localized the

Table 1. Demographic, biochemical and imaging characteristics of the 5 patients with primary HPT

Case	Age (yr) / Sex	Serum Ca (mg/dL)	Baseline PTH (pg/mL)	Vit. D (ng/mL)	Main clinical manifestations	MIBI/SPECT-CT indication	Actual localization (ICG + surgical)
1	70 / F	11.3	105	32	Osteopenia, renal lithiasis, asthenia	Right inferior pole (false positive)	LEFT inferior pole, opposite lateralization
2	64 / F	11.3	115.5	35	Polydipsia, myalgia, depressive syndrome, renal lithiasis	Right inferior pole (false positive)	Right SUPERIOR pole, wrong anatomical level
3	55 / F	9.7	100*	—	Normocalcaemic HPT; asthenia, weight loss, renal lithiasis	Left superior pole, paracarotid	Confirmation paracarotid, RLN proximity
4	47 / F	11.0	164	—	Multisite osteoporosis, sarcoidosis, multiple sclerosis	Left superior pole, deep retrothyroid suggestion	Confirmation LEFT SUPERIOR, deep retrothyroid
5	22 / F	14.86†	191.9	15.5	Hypercalcaemic crisis, phosphataemia 1.63 mg/dL	LEFT inferior pole	Confirmation LEFT inferior pole

Age range 22-70 years, median 55 years. Baseline PTH range 100-192 pg/mL, mean 135.3 pg/mL (normal 15-65 pg/mL). Calcaemia: 4/5 cases with hypercalcaemia (total Ca 11.0-14.86 mg/dL); case 3 (*) presented normocalcaemic primary HPT (Ca 9.7 mg/dL), with preoperative PTH documented in the biological history prior to admission. † Case 5: peak total calcium documented during the preceding endocrinology admission; 12.0 mg/dL preoperatively, after medical stabilization. RLN = recurrent laryngeal nerve.

adenoma in the left inferior pole; ICG, injected at the initiation of the dissection of the indicated compartment, confirmed the localization with a particularly intense hyperfluorescence pattern. A clinically valuable additional observation: the absence of hyperfluorescence in the other parathyroid glands evaluated concomitantly provided a supportive, although not conclusive, visual argument against multiglandular disease, complementing the biochemical and imaging criteria on which the decision to proceed with focused parathyroidectomy was based.

Intraoperative Fluorescence Findings and Surgical Outcome

ICG enabled identification of the culprit hyperfunctioning gland in all 5 cases; the time from the intravenous bolus to the first fluorescent signal in the operative field (tf) ranged between 22 and 38 seconds (*Table 2*). In every case the target gland displayed rapid, intense and persistent hyperfluorescence, visually distinct from the normal parathyroid glands, which showed only moderate, more transient enhancement (*Figs. 1A, 1B* and *3A*). Ex vivo, immediately after resection, the excised specimens retained intense, homogeneous residual fluorescence, documented under identical acquisition conditions in Overlay and near-infrared monochrome modes (*Fig. 2A and 2B*); the macroscopic aspects are illustrated in *Figs.* 2C and 3B. Because the series was deliberately selected, the 5/5 identification result is reported strictly descriptively and does not constitute an estimate of diagnostic performance. Intraoperative PTH monitoring, available in four patients, confirmed complete excision according to the Miami criterion in all of them (case 1: 105 → 18 pg/mL, −82.9%; case 2:

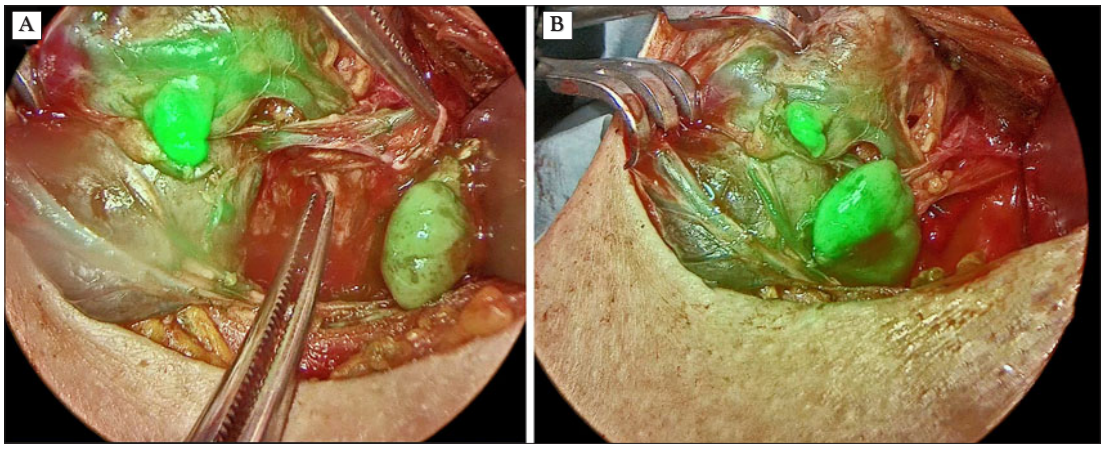


Figure 1. Progressive intraoperative exposure of a culprit gland (case 1), Overlay mode (real-time superimposition of the near-infrared ICG signal, green, on the white-light image); the same operative field at two successive moments during dissection. **(A)** Early dissection: a normal parathyroid gland (upper left) shows moderate, transient enhancement, while the left inferior culprit gland (lower centre-right) is only beginning to emerge from the surrounding tissue. **(B)** As dissection advances, the culprit gland is progressively revealed and displays increasingly intense, persistent hyperfluorescence, clearly distinguishable from the moderate enhancement of the normal gland; this is the practical visual difference on which real-time intraoperative discrimination is based.

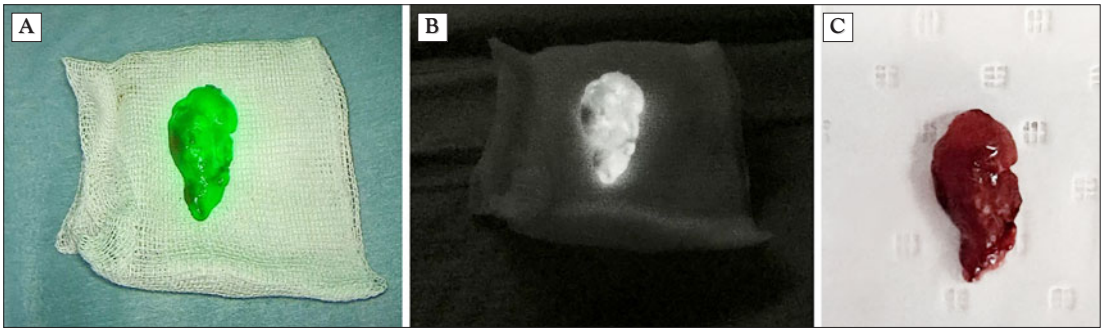


Figure 2. The excised specimen of a hyperfluorescent culprit gland (case 2), documented under three complementary modalities, immediately after resection, under identical acquisition conditions: **(A)** Overlay mode, showing intense, homogeneous residual ICG fluorescence that documents the hypervascular uptake pattern of the hyperfunctioning gland; **(B)** near-infrared monochrome mode, providing maximal signal-to-dark contrast; **(C)** macroscopic aspect under white light.

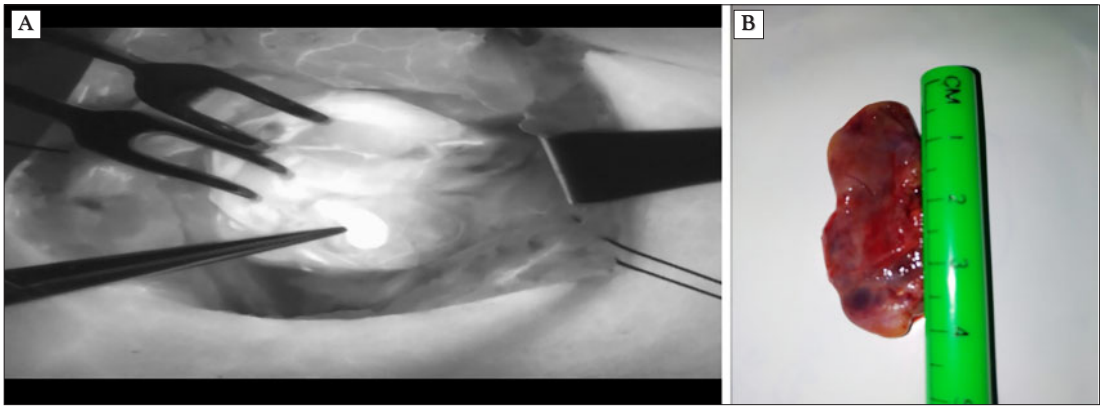


Figure 3. **(A)** In situ near-infrared monochrome view of the operative field (case 5): the intense fluorescent signal of the target gland stands out against the low background signal of the surrounding tissues. **(B)** Macroscopic aspect of a resected parathyroid adenoma (case 4), with centimetre scale.

115.5 → 20.28 pg/mL, −82.4%; case 4: 164 → 18.56 pg/mL, −88.7%; case 5: 191.9 → 21.74 pg/mL, −88.7%); intraoperative PTH was not available in case 3, in which biochemical cure was documented on postoperative day 4 (PTH 34.49 pg/mL, Ca 9.3 mg/dL). Early biochemical cure was thus confirmed in all 5 cases: serum PTH fell into the normal range in every patient, and total calcium at 24 hours ranged between 8.4 and 9.8 mg/dL across the series. Histopathology confirmed a solitary parathyroid adenoma in four cases, with weights of 667 mg (10 × 8 mm, case 1), 300 mg (case 2), 1158 mg (case 4) and 501 mg (case 5), all with chief-cell predominance and a rim of normal parathyroid tissue; in case 3, the excised left superior parathyroid showed hypercellular tissue with discrete hyperplasia and lipomatosis, without a classically encapsulated adenoma (see Discussion). Transient hungry bone syndrome occurred in three patients: symptomatic forms in cases 1 and 2 (paraesthesiae, Chvostek sign grade I; Clavien-Dindo II) and a purely biochemical form in case 5 (Clavien-Dindo I); all resolved under calcium and active vitamin D supplementation within 4-6 weeks and represent a remineralization phenomenon distinct from iatrogenic hypoparathyroidism. No RLN injuries were recorded (normal laryngoscopy at the 30-day control), nor persistent dysphonia, haematomas, wound infections or other cervical complications. No adverse reactions to ICG administration were recorded.

Longer-term biochemical follow-up was available in two patients. In case 1, the 2-month evaluation showed stable normocalcaemia (total Ca 9.2 mg/dL), replete vitamin D (42 ng/mL) and mildly elevated PTH (81 pg/mL), without recurrent hypercalcaemia, a pattern consistent with the remineralization phase following

Table 2. Intraoperative fluorescence findings and surgical outcome for the 5 patients.

Case	Clinical scenario	tf (sec)	Operative time (min)	ioPTH baseline → post-excision (pg/mL)	Histopathology (weight)	ICG-driven decision	Early biochemical cure	Complications
1	Opposite lateralization vs MIBI	22	40	105 → 18 (−82.9%)	Adenoma, 667 mg (10 × 8 mm)	Yes, lateralization correction	Yes	Transient hungry bone (symptomatic, resolved)
2	Anatomical level redirection	32	60	115.5 → 20.28 (−82.4%)	Adenoma, 300 mg	Yes, anatomical level correction	Yes	Transient hungry bone (symptomatic, resolved)
3	Fine paracarotid dissection; combined with total thyroidectomy	38	≈ 38 (parathyroid phase) / 180 (total)	Not performed	Hypercellular parathyroid, discrete hyperplasia and lipomatosis	Yes, RLN protection	Yes	None
4	Deep retrothyroid approach	35	70	164 → 18.56 (−88.7%)	Adenoma, 1158 mg	Yes, targeted deep incision	Yes	None
5	Hypercalcaemic crisis presentation	25	55	191.9 → 21.74 (−88.7%)	Adenoma, 501 mg	Yes, support for single-gland hypothesis	Yes	Transient hungry bone (biochemical, resolved)

tf = time from the intravenous bolus to the first fluorescent signal in the operative field; in case 1, the culprit left inferior gland itself became visible only upon contralateral extension of the exposure and was recognized by its persistent, intense residual fluorescence; ioPTH = intraoperative PTH, baseline → 10 minutes post-excision (Miami criterion: decrease >50%). In all five cases the target gland displayed rapid, intense and persistent hyperfluorescence, in contrast with the moderate, transient enhancement of the normal glands; fluorescence was assessed qualitatively, in real time, under standardized viewing conditions (see Methods), and no numeric signal-to-background ratios are reported. Early biochemical cure = normalization of PTH and total serum calcium in the early postoperative period. All interventions were focused parathyroidectomies through a minimal-access open Kocher incision; in case 3 the procedure was combined, in the same session, with total thyroidectomy for coexisting multinodular goiter. Hungry bone syndrome = transient remineralization hypocalcaemia, distinct from iatrogenic hypoparathyroidism, resolved in all cases by 6 weeks.

the transient hungry bone syndrome documented in this patient and with the normocalcaemic PTH elevation reported after a substantial proportion of curative parathyroidectomies (18). In case 3, sustained biochemical cure was confirmed at 12 months (PTH 48 pg/mL, Ca 9.5 mg/dL), the longest follow-up of the series. The remaining three patients, referred from other counties, resumed endocrine follow-up with their territorial specialists after the 30-day surgical control, and intermediate biochemical values were not systematically available to the surgical team.

Discussion

To the authors' knowledge, the present series appears to be among the first detailed descriptions in the Romanian literature of the use of ICG fluorescence imaging in parathyroid surgery for primary HPT. The limitation to 5 patients is deliberate: selection was made to illustrate specific clinical scenarios rather than to estimate global statistical sensitivity, for which recent meta-analyses on large patient numbers already provide robust data (13). Our observations confirm and nuance the recent literature in several distinct directions.

Limitations of Preoperative Imaging and the Role of ICG as an Intraoperative Correction Tool

The accuracy of MIBI/SPECT-CT depends on two main biological factors: cellular mass and metabolic activity of the adenoma, which determine ^{99m}Tc-MIBI uptake through mitochondrial proteins, and competition with neighbouring tissues for the scintigraphic signal (5,6). Small adenomas (<100 mg) have a reported MIBI sensitivity below 30% (5), and concomitant thyroid pathology generates competing zones of fixation (6). Atypical localizations (paracarotid, retrothyroid, intrathyroidal, mediastinal) are cumulatively reported in approximately 22% of unoperated patients (7) and represent the most frequent cause of MIP failure (*Table 3*). In this context, ICG functions as a real-time correction tool for the surgical direction: cases 1 and 2 of our series illustrate two distinct mechanisms of MIBI failure, opposite lateralization (case 1) and wrong anatomical level (case 2), both resolved through NIR guidance without unnecessary dissection of the imaging false-positive region.

Characteristic Adenoma Fluorescence Pattern

Parathyroid adenomas exhibit a characteristic fluorescent behaviour relative to normal parathyroid glands: rapid, intense and persistent hyperfluorescence. This pattern was observed consistently in our series and is concordant with the descriptions of DeLong et al. (12), Matson et al. (16) and Battistella et al. (19), which support the value of ICG over white-light identification in cases with uncertain localization. Some authors have additionally quantified the kinetics of adenoma fluorescence, such as time to peak signal (16); in the present series, fluorescence was deliberately assessed qualitatively, under standardized viewing conditions, because no software-based quantification of signal intensity was available. The biological mechanism resides in the increased cellular mass and the denser vascular network of the adenoma: a hyperfunctional, hypervascularized parenchyma takes up ICG more rapidly and in greater quantity than the surrounding tissues (11,12).

ICG in the Context of Other Intraoperative Identification Technologies

ICG angiography is not the only modern technology available for intraoperative parathyroid identification, and its role is best understood in relation to near-infrared autofluorescence (NIRAF). Parathyroid tissue possesses an intrinsic autofluorescence, described by McWade et al. (20), which can be exploited label-free either by camera-based systems or by probe-based devices such as PTeye™ (21). Randomized data support NIRAF in thyroid surgery: the multicentre PARAFLUO trial reported a reduction of postoperative hypocalcaemia with autofluorescence-based para-thyroid detection during total thyroidectomy

Table 3. Synthesis of the distribution of atypical parathyroid adenomas and the added value of ICG in each scenario.

Ectopic / atypical localization	Frequency (% of ectopic adenomas)	Imaging sensitivity	ICG added value
Thymic / anterior mediastinum	38%	MIBI high (>85%)	Confirmation at the thyrothymic ligament; sternotomy avoidance
Retroesophageal / paraesophageal	31%	MIBI medium-high	Selective dissection, RLN proximity
Intrathyroidal	18%	US more sensitive than MIBI	Identification through intraparenchymal hyperfluorescence pattern
Carotid / lateral cervical	rare (<10% of ectopic)	variable	Accurate localization; fine dissection near major vessels and RLN
Cumulative	≈ 22% in previously unoperated patients;	MIBI 89% / US 59% (ectopic glands)	Most frequent cause of MIP failure, maximal added value of ICG

The percentage distribution of ectopic localizations and the sensitivity of MIBI and US for ectopic glands are synthesized from Roy et al. (World J Surg 2013, n = 1,562 patients, 22% ectopic adenomas) (7); the prevalence of ectopia in reoperations and the cumulative sensitivity of conventional methods, from Parikh et al. (Endocr Pract 2018) (8). MIBI = ^{99m}Tc-MIBI scintigraphy with SPECT-CT; US = cervical ultrasonography; MIP = focused minimally invasive parathyroidectomy; RLN = recurrent laryngeal nerve.

(22), and a randomized controlled trial reported higher para-thyroid identification rates with NIRAF than with white light (23). In parathyroidectomy itself, probe-based NIRAF detection has been evaluated in a randomized single-centre trial by Kiernan et al. (24). The two technologies are complementary rather than competing (25): NIRAF is label-free, requires no injection and is well suited to locating parathyroid tissue, but it provides no information on perfusion and does not reliably distinguish hyperfunctioning from normal glands; ICG angiography requires an intravenous injection but offers real-time, perfusion-based contrast, which is precisely the property exploited both for identifying the hypervascularized adenoma and for assessing the perfusion of the remaining glands (26,27). In our practice, the choice of ICG was additionally motivated by the availability of an integrated NIR/Overlay endoscopic platform already in use for other fluorescence-guided procedures.

Primary HPT in the Young Patient: Particularities and Genetic Evaluation

The young age of the patient in case 5 (22 years), associated with severe biochemical presentation, represents an atypical context relative to the classical epidemiology of primary HPT, where the mean age at diagnosis is in the sixth decade. According to the recommendations of the Fifth International Workshop on the evaluation of primary HPT (1), any presentation under the age of 30 years requires additional evaluation to rule out familial and syndromic forms. In this regard, genetic evaluation for MEN1 mutations (multiple endocrine neoplasia type 1 syndrome) and CDC73/HRPT2 gene mutations (hyperparathyroidism-jaw tumour syndrome, associated with a risk of parathyroid carcinoma) is indicated. In our patient, genetic testing was recommended at discharge and scheduled as part of long-term endocrine follow-up. The histopathology of the resected specimen, a solitary 501 mg chief-cell parathyroid adenoma with a peripheral rim of normal glandular tissue with lipodystrophy, is compatible with both a sporadic presentation and a latent familial form, which does not modify the immediate management but justifies periodic biochemical surveillance and family counselling.

Three Clinical Scenarios with Maximal Added Value

Synthesizing the cohort data and the recent literature (13,14,16,19), we identify three clinical scenarios in which the use of ICG brings direct added value to the conduct of the operation: (1) marked discordance with preoperative imaging, in which ICG functions as a real-time correction tool for the surgical direction; (2) atypical or ectopic, technically demanding localizations (paracarotid, retrothyroid, intrathyroidal, retro-esophageal), in which ICG enables target-selective exposure without extensive mobilization of neighbouring structures; (3) cases without available preoperative localization or with uncertain imaging, where ICG can serve as a primary orientation tool; this third scenario is derived exclusively from the literature and is not represented in the present series, whose inclusion criteria required a complete preoperative imaging assessment. Battistella et al. described the progressive integration of ICG-guided navigation into a large single-centre experience of parathyroidectomy for primary HPT (19), and successful ICG-guided resection of ectopic adenomas, including within the carotid sheath, has been reported (28). In all these scenarios, ICG may help limit the extent of cervical exploration and the associated iatrogenic risk; reductions in operative time reported in comparative studies (14) could not be assessed in the present uncontrolled series and should therefore be regarded as potential, rather than demonstrated, benefits.

Normocalcaemic Primary HPT: Diagnostic Particularity and the Role of ICG

Case 3 represents a particular variant of primary HPT, the normocalcaemic form (serum Ca 9.7 mg/dL within normal limits, in the presence of an elevated PTH documented in the biological history prior to admission). This entity, recognized in the current classification (Bilezikian et al., Fifth International Workshop) (1), represents approximately 6-10% of primary HPT cases and entails additional diagnostic difficulties: preoperative imaging has lower sensitivity due to the small dimensions of the adenoma, and the classical hypercalcaemia criteria are not fulfilled. The diagnosis of normocalcaemic primary HPT additionally requires the exclusion of secondary causes of PTH elevation, including vitamin D deficiency, impaired renal function, reduced calcium intake, malabsorption and relevant medication (1). In our patient, the diagnosis was established by the referring endocrinology service in accordance with these criteria; the detailed laboratory work-up preceded the surgical admission, and the complete documentation for the exclusion of all secondary causes is not available in the surgical record analysed in this study, a limitation acknowledged below. Preoperative testing at surgical admission nonetheless showed normal renal function (creatinine 53 μmol/L), and the patient was not receiving thiazide diuretics, lithium or bisphosphonates. Notably, the histological examination of the

excised gland showed hypercellular parathyroid tissue with discrete hyperplasia and lipomatosis rather than a classically encapsulated adenoma. This finding is consistent with the known profile of normocalcaemic primary HPT, in which the culprit glands are smaller and the morphological changes subtler, contributing both to the lower sensitivity of preoperative imaging and to the recognized histological difficulty of distinguishing a small adenoma from asymmetric hyperplasia in a single excised gland. From the surgical perspective, the case illustrates a conceptually important point: ICG angiography marks the hypervascularized, hyperfunctioning gland irrespective of its final histological label. In this particular context, ICG enabled accurate localization of the paracarotid target in proximity to the RLN and showed a normal perfusion pattern of the other parathyroid glands, an argument against, although not a formal exclusion of, multiglandular disease. The sustained biochemical cure at the 12-month follow-up (PTH 48 pg/mL, Ca 9.5 mg/dL), the longest of the series, provides functional, a posteriori confirmation both of correct target selection and of the single-gland aetiology in this patient.

Study Limitations

The acknowledged limitations of this series are those inherent to a small, single-centre, descriptive study. First, the cohort is very small (n = 5), non-consecutive and intentionally selected for scenarios in which the benefit of ICG was expected to be maximal; this selection bias precludes any estimation of sensitivity, specificity or of a true identification rate, and the 5/5 result must be read strictly descriptively. Second, the absence of a control group does not allow quantification of the impact of ICG on operative time, extent of dissection or complication rates; comparative reference data are available from controlled designs such as that of Mizrakli et al. (14). Third, fluorescence was assessed by standardized visual evaluation only, without software-based quantitative analysis; numeric fluorescence ratios were therefore deliberately not reported. Fourth, postoperative biochemical follow-up was not uniform: the institute serves a national catchment area and patients referred from other counties resumed follow-up with their territorial endocrinologists, so that structured longer-term biochemical data were available in only two patients (2 months in case 1 and 12 months in case 3); similarly, part of the preoperative diagnostic work-up, notably the laboratory exclusion of secondary causes of PTH elevation in case 3, was performed in the referring services and could not be fully reproduced from the surgical records. Finally, the utility of ICG in a straightforward case, with a large adenoma and concordant imaging, is by definition less demonstrable; the present observations should therefore be regarded as hypothesis-generating.

Conclusions

In this deliberately selected series of 5 patients with primary hyperparathyroidism, intraoperative ICG fluorescence imaging appeared to be a useful and safe adjunct: it identified the culprit hyperfunctioning gland in all cases, including two with MIBI-intraoperative discordance and two with technically demanding atypical localizations, with no ICG-related adverse reactions and no cervical complications. The characteristic pattern of rapid, intense and persistent target-gland hyperfluorescence provided a practical visual landmark for dissection guidance. In agreement with the recent literature, the method appears most valuable in two clinical scenarios directly illustrated by this series, discordance with preoperative imaging and technically demanding atypical localizations; a third scenario, uncertain or absent preoperative localization, is suggested by the literature but was not represented in the present series and should be regarded as a literature-derived hypothesis. Benefits such as reduction of operative time, of the extent of cervical exploration and of RLN injury risk, suggested by comparative studies, could not be assessed in this uncontrolled series and remain to be confirmed. These hypothesis-generating observations support further prospective evaluation of ICG fluorescence imaging as an adjunct within the protocol of focused minimally invasive parathyroidectomy.

Conflicts of Interest

The authors declare no conflict of interest.

Ethical Considerations

The use of ICG fluorescence imaging was part of routine clinical practice, and all patients provided written informed consent preoperatively. The analysis and publication of the anonymized clinical data were conducted within the framework of the first author's doctoral research project, approved by the Ethics Committee of the Scientific Council of the C.I. Parhon National Institute of Endocrinology, Bucharest (approval no. 20, dated 30.04.2026). The study was conducted in accordance with the principles of the Declaration of Helsinki. Patient anonymity and data confidentiality were maintained throughout the study.

References

1. Bilezikian JP, Khan AA, Silverberg SJ, Bandeira F, Boutroy S, Cusano NE, et al. Evaluation and management of primary hyperparathyroidism: summary statement and guidelines from the Fifth International Workshop. J Bone Miner Res. 2022;37(11): 2293-2314.
2. Yeh MW, Ituarte PHG, Zhou HC, Nishimoto S, Liu IL, Harari A, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab. 2013;98(3):1122-1129.
3. Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, et al. The American Association of Endocrine Surgeons guidelines for definitive management of primary hyperparathyroidism. JAMA Surg. 2016;151(10):959-968.
4. Udelsman R, Lin Z, Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. Ann Surg. 2011; 253(3):585-591.
5. Hindié E, Zanotti-Fregonara P, Tabarin A, Rubello D, Morelec I, Wagner T, et al. The role of radionuclide imaging in the surgical management of primary hyperparathyroidism. J Nucl Med. 2015;56(5):737-744.
6. Mohebati A, Shaha AR. Imaging techniques in parathyroid surgery for primary hyperparathyroidism. Am J Otolaryngol. 2012;33(4):457-468.
7. Roy M, Mazeh H, Chen H, Sippel RS. Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients. World J Surg. 2013;37(1):102-106.
8. Parikh AM, Suliburk JW, Morón FE. Imaging localization and surgical approach in the management of ectopic parathyroid adenomas. Endocr Pract. 2018;24(6):589-598.
9. Bergenfelz A, Jansson S, Kristoffersson A, Mțrtensson H, Reihnér E, Wallin G, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. Langenbecks Arch Surg. 2008;393(5):667-673.
10. Cassinotti E, Al-Taher M, Antoniou SA, Arezzo A, Baldari L, Boni L, et al. European Association for Endoscopic Surgery (EAES) consensus on Indocyanine Green (ICG) fluorescence-guided surgery. Surg Endosc. 2023;37(3):1629-1648.
11. Reinhart MB, Huntington CR, Blair LJ, Heniford BT, Augenstein VA. Indocyanine green: historical context, current applications, and future considerations. Surg Innov. 2016; 23(2):166-175.
12. DeLong JC, Ward EP, Lwin TM, Brumund KT, Kelly KJ, Horgan S, et al. Indocyanine green fluorescence-guided parathyroidectomy for primary hyperparathyroidism. Surgery. 2018;163(2):388-392.
13. Kim DH, Kim SH, Jung J, Kim SW, Hwang SH. Indocyanine green fluorescence for parathyroid gland identification and function prediction: systematic review and meta-analysis. Head Neck. 2022;44(3):783-791.
14. Mizrakli Y, Hirschfeld Z, Pitaro J, Gavriel H, Muallem-Kalmovich L. Indocyanine green fluorescence in parathyroidectomy: enhancing efficiency through real-time adenoma identification. Eur Arch Otorhinolaryngol. 2025;282(12):6417-6423.
15. Karl Storz SE & Co. KG. IMAGE1 S™ Rubina® system: technical documentation. Tuttlingen: Karl Storz; 2022.
16. Matson J, Lwin TM, Bouvet M. Rapid intraoperative perfusion assessment of parathyroid adenomas with ICG using a wide-field portable hand-held fluorescence imaging system. Am J Surg. 2022;223(4):686-693.
17. Kahramangil B, Berber E. The use of near-infrared fluorescence imaging in endocrine surgical procedures. J Surg Oncol. 2017;115(7):848-855.
18. Oltmann SC, Maalouf NM, Holt S. Significance of elevated parathyroid hormone after parathyroidectomy for primary hyperparathyroidism. Endocr Pract. 2011;17(Suppl 1):57-62.
19. Battistella E, Pomba L, Toniato R, Burei M, Gregianin M, Watutantrige Fernando S, et al. Evolution of the diagnosis and treatment of primary hyperparathyroidism. J Clin Med. 2023;12(5):2057.
20. McWade MA, Paras C, White LM, Phay JE, Solórzano CC, Broome JT, et al. Label-free intraoperative parathyroid localization with near-infrared autofluorescence imaging. J Clin Endocrinol Metab. 2014;99(12):4574-4580.
21. Solórzano CC, Thomas G, Baregamian N, Mahadevan-Jansen A. Detecting the near infrared autofluorescence of the human parathyroid: hype or opportunity? Ann Surg. 2020;272(6):973-985.
22. Benmiloud F, Godiris-Petit G, Gras R, Gillot JC, Turrin N, Penaranda G, et al. Association of autofluorescence-based detection of the parathyroid glands during total thyroidectomy with postoperative hypocalcemia risk: results of the PARAFLUO multicenter randomized clinical trial. JAMA Surg. 2020;155(2):106-112.
23. Dip F, Falco J, Verna S, Prunello M, Loccisano M, Quadri P, et al. Randomized controlled trial comparing white light with near-infrared autofluorescence for parathyroid gland identification during total thyroidectomy. J Am Coll Surg. 2019; 228(5):744-751.
24. Kiernan CM, Thomas G, Patel A, Fan R, Ye F, Willmon PA, et al. Does the use of probe-based near-infrared autofluorescence parathyroid detection benefit parathyroidectomy? A randomized single-center clinical trial. Ann Surg. 2023;278(4):549-558.
25. Silver Karcioglu AL, Triponez F, Solórzano CC, Iwata AJ, Abdelhamid Ahmed AH, Almquist M, et al. Emerging imaging technologies for parathyroid gland identification and vascular assessment in thyroid surgery: a review from the American Head and Neck Society Endocrine Surgery Section. JAMA Otolaryngol Head Neck Surg. 2023;149(3): 253-260.
26. Vidal Fortuny J, Sadowski SM, Belfontali V, Guigard S, Poncet A, Ris F, et al. Randomized clinical trial of intraoperative parathyroid gland angiography with indocyanine green fluorescence predicting parathyroid function after thyroid surgery. Br J Surg. 2018;105(4):350-357.
27. Cui L, Gao Y, Yu H, Li M, Wang B, Zhou T, et al. Intraoperative parathyroid localization with near-infrared fluorescence imaging using indocyanine green during total parathyroidectomy for secondary hyperparathyroidism. Sci Rep. 2017;7(1):8193.
28. Rupp GE, Barba P, Goldhaber NH, Hu J, Bouvet M. Indocyanine green fluorescence guided resection of parathyroid adenoma of the carotid sheath: a case report and review of the literature. Gland Surg. 2023;12(4):548-554.