

Indocyanine Green Fluorescence Angiography as a Navigational Adjunct in Focused Parathyroidectomy: Does It Contribute to Surgical Outcomes?

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Abstract

Introduction: Indocyanine green (ICG) fluorescence angiography enables real-time visualization of hypervascular parathyroid tissue and has shown promise as an intraoperative navigational tool. However, its specific additive value in focused parathyroidectomy—beyond preoperative localization and naked-eye exploration—remains unclear, particularly regarding surgical cure rates. **Materials and Methods:** This retrospective cohort study analyzed 35 consecutive patients with primary hyperparathyroidism undergoing focused parathyroidectomy at a single center between January 2024 and May 2025. Patients were stratified by intraoperative ICG use (ICG group, n=17) versus no ICG (non-ICG group, n=18). Preoperative localization (ultrasonography and sestamibi scintigraphy), naked-eye exploration (NEE), intraoperative PTH monitoring, surgical approach, and outcomes were compared. Cure was defined as normocalcemia and normal PTH levels at 6 months. **Results:** Baseline characteristics were comparable except for higher ultrasonography positivity and transoral approaches in the ICG group. Overall cure rate was 97.1% (94.1% ICG vs. 100% non-ICG, p=0.486). Among 17 ICG cases, 15 glands showed positive fluorescence. ICG identified the adenoma in one NEE-negative case despite concordant preoperative imaging, while one ICG-negative case resulted in persistent disease. No significant additive benefit of ICG on cure rates was observed across preoperative localization subgroups (all p>0.05). **Conclusion:** In focused parathyroidectomy with adequate preoperative localization, routine ICG fluorescence angiography does not significantly improve cure rates. However, it may serve as a valuable “rescue” tool for intraoperative navigation in selected cases where naked-eye identification is challenging, independent of preoperative imaging.

Keywords: Primary hyperparathyroidism, Focused parathyroidectomy, Indocyanine green, Near-infrared fluorescence, Intraoperative navigation

1. Introduction

Primary hyperparathyroidism (pHPT) is a prevalent endocrine disorder characterized by the autonomous secretion of parathyroid hormone (PTH) from one or more

parathyroid glands. It presents with a broad clinical spectrum, including hypercalcemia and its associated complications such as nephrolithiasis, osteoporosis, and cardiovascular morbidity.¹ In the vast majority of cases, the etiological cause is a single parathyroid adenoma, with a higher incidence observed in the female population.¹ Currently, surgery remains the only definitive and curative treatment for pHPT. Technological advancements in preoperative localization modalities—specifically high-resolution ultrasonography and technetium-99m sestamibi scintigraphy—have largely shifted the surgical paradigm from traditional bilateral neck exploration toward a "focused parathyroidectomy" approach.² Although this minimally invasive surgical strategy offers shorter operative times, lower morbidity rates, and superior cosmetic outcomes, its success is fundamentally contingent upon the precise intraoperative localization of the pathological gland.³

To optimize surgical success, various intraoperative adjuncts have been developed. Among these, intraoperative PTH (IOPTH) monitoring is considered the gold standard for confirming biochemical cure following excision.⁴ However, IOPTH does not provide the surgeon with real-time anatomical navigation; it serves only to validate the adequacy of the resection.⁴ Other adjuncts, such as radioguided surgery, frozen section histopathology, or methylene blue staining, involve logistical constraints including radiation exposure, the need for specialized equipment/personnel, increased costs, and time consumption.⁴

In recent years, indocyanine green (ICG)-enhanced near-infrared fluorescence (NIRF) imaging has emerged as a non-invasive, radiation-free technique that enables real-time visualization of the relatively hypervascularized structure of the parathyroid glands.⁵ The application of ICG in parathyroid surgery is primarily categorized into two domains: navigation for localizing the pathological gland and the assessment of remaining gland perfusion following thyroid surgery to predict the risk of postoperative hypoparathyroidism.^{3, 6} Nevertheless, data in the current literature are often based on limited patient series, and many studies fail to maintain a clear conceptual distinction between the intraoperative navigational function of ICG and the assessment of gland viability.^{7, 8} Particularly in focused parathyroidectomy, the specific contribution of ICG to the intraoperative identification of the pathological gland and its impact on the surgical decision-making process have not yet been sufficiently standardized.

The objective of this study is to retrospectively evaluate the effects of ICG fluorescence angiography, specifically for navigational purposes, on surgical success and anatomical identification in pHPT cases undergoing focused parathyroidectomy. Furthermore, the practical utility of ICG guidance in patients with challenging preoperative localization and the impact of integrating ICG with IOPTH results on clinical outcomes were investigated.

2. Materials and Methods

This retrospective cohort study included 35 consecutive patients with primary hyperparathyroidism who underwent focused parathyroidectomy at a single center between January 2024 and May 2025. Data from patients with biochemically confirmed primary hyperparathyroidism who underwent parathyroidectomy due to surgical indications (target organ involvement such as nephrolithiasis and osteoporosis, serum calcium levels greater than 1 mg/dl above the upper limit of the laboratory, glomerular filtration rate <60 ml/min, and high 24-hour urinary calcium) were retrospectively reviewed. Patients with secondary or tertiary hyperparathyroidism, multiple endocrine neoplasia syndromes, or concurrent thyroid pathology requiring total thyroidectomy were excluded. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee of Health Sciences University Antalya Training and Research Hospital (approval number: 22/33).

Patients were divided into two groups based on intraoperative use of ICG fluorescence angiography: the ICG group (n=17) and the non-ICG group (n=18). ICG (Verdye®, Diagnostic Green GmbH, Germany) was administered intravenously at a dose of 0.1 mg/kg immediately prior to exploration in selected cases at the surgeon's discretion, primarily during minimally invasive or transoral approaches. The use of ICG was prioritized in transoral endoscopic (TOEPVA) approaches, where haptic feedback is inherently limited and real-time visual navigation is critical for the surgeon to better comprehend the intraoperative anatomical configuration. Fluorescence imaging was performed using a near-infrared camera system (Olympus VISERA ELITE 2 laparoscopic imaging system). Parathyroid glands were classified as ICG-positive (hyperfluorescent) or ICG-negative (hypofluorescent or non-fluorescent) relative to surrounding thyroid tissue.

All procedures were performed by a single experienced endocrine surgeon. Focused parathyroidectomy was guided by preoperative imaging, with conversion to unilateral/bilateral neck exploration if necessary. Naked-eye exploration (NEE) was routinely performed to assess visual identification of the adenoma. Intraoperative parathyroid hormone monitoring (IOPTH) was utilized in all cases, with criteria for success defined as >50% drop from baseline at 10 minutes post-excision. Surgical approaches included selective open parathyroidectomy, transoral endoscopic parathyroidectomy vestibular approach (TOEPVA), bilateral neck exploration (BNE), or unilateral neck exploration (UNE).

Preoperative data collected included demographics, serum calcium, albumin, parathyroid hormone (PTH), vitamin D, creatinine, estimated glomerular filtration rate (GFR), 24-hour urinary calcium, history of nephrolithiasis, and osteoporosis. Postoperative outcomes included 4-hour and 6-month serum PTH and calcium levels, and surgical cure defined as normocalcemia and normal PTH at 6 months without persistent or recurrent hyperparathyroidism.

2.1. Statistical Analysis

Continuous variables were expressed as means and compared using Welch's t-test for unequal variances. Categorical variables were presented as frequencies and percentages and compared using chi-square test or Fisher's exact test as appropriate (Fisher's exact test preferred for small expected cell counts <5). Preoperative localization subgroups were defined as: both USG and scintigraphy positive (Both+), USG positive/scintigraphy negative, USG negative/scintigraphy positive, or both negative (Both-). The additive contribution of ICG to surgical success was evaluated within these subgroups using Fisher's exact test. Independent contribution was assessed via crosstabulation of NEE status (positive: visible to naked eye; negative: not visible) versus ICG uptake (positive, negative). A p-value <0.05 was considered statistically significant. All analyses were performed using the SPSS (Statistical Package for the Social Sciences Version 22.0; SPSS Inc., Chicago, IL, USA) software.

3. Results

A total of 35 patients (32 female, 3 male) with a mean age of 51.37 years were included. Baseline characteristics were largely comparable between ICG and non-ICG groups (Table 1).

Notable differences included higher preoperative albumin in the non-ICG group (46.87 vs. 44.45 g/L, $p=0.0267$) and more frequent positive ultrasonography in the ICG group (14/17 vs. 6/18, $p=0.0097$). Scintigraphy positivity tended to be higher in the ICG group, though not significant ($p=0.1173$). History of nephrolithiasis was more common in the ICG group (9/17 vs. 3/18, $p=0.0570$).

Table 1. Demographic, preoperative laboratory and imaging data.

		ICG (n)	Non-ICG (n)	Total (n)	P-Value
Mean Age (Years)		48.88	53.72	51.37	0.2879
Sex	Female	16	16	32	1.0000*
	Male	1	2	3	
Serum calcium (mg/dL)		11.91	11.88	11.89	0.8708
Serum Albumin (g/L)		44.45	46.87	45.69	0.0267
Parathyroid hormone (ng/L)		201.86	222.53	212.49	0.4960
Vitamin D (µg/L)		24.59	23.24	23.90	0.7499
Creatinine (mg/dL)		0.71	0.73	0.72	0.6553
Glomerular filtration rate (mL/min)		100.00	94.55	97.20	0.4425
24-hour urinary calcium (mg/d)		343.62	365.37	354.81	0.7204
Nephrolithiasis	Present	9	3	12	0.0570*
	Absent	8	15	23	
Osteoporosis	Present	11	7	18	0.2344*
	Absent	6	11	17	
Scintigraphy	Positive	16	13	29	0.1173*
	Negative	1	5	6	
Ultrasonography	Positive	14	6	20	0.0097*
	Negative	3	12	15	
Preoperative Localization	Right upper	2	1	3	0.9587*
	Right lower	9	7	16	0.6209*
	Left upper	0	5	5	0.0623*
	Left lower	5	8	13	0.5687*

ICG; Indocyanine green.

Operative and postoperative outcomes are summarized in Table 2.

Surgical approach differed significantly, with TOEPVA more frequently performed in the ICG group (8/17 vs. 2/18, $p=0.0325$). IOPTH values and early postoperative PTH/calcium levels showed no significant differences. At 6-month follow-up, surgical cure was achieved in 34 patients (97.1%), with one case of persistent hyperparathyroidism in the ICG group (ICG-negative uptake). Success rates were 94.1% (16/17) in the ICG group versus 100% (18/18) in the non-ICG group ($p=0.486$).

Table 2. Operative data and postoperative results.

		ICG (n,%)	Non-ICG (n,%)	Total (n,%)	P-Value
Type of Surgery (n)	Selective (Open)	8	13	21	0.0325
	TOEPVA	8	2	10	
	BNE	0	3	3	
	UNE	1	0	1	
IOPTH (ng/L)	Induction	212.91	245.28	229.56	0.3280
	Pre-excision	272.65	275.71	274.23	0.9575
	5th min	72.78	68.83	70.75	0.7353
	10th min	55.44	37.80	46.36	0.1671
4th Hour PTH (ng/L)		27.05	12.39	19.51	0.2050
4th Hour Calcium (mg/dL)		9.58	9.35	9.46	0.3717

		ICG (n,%)	Non-ICG (n,%)	Total (n,%)	P-Value
6th Month PTH (ng/L)		60.11	49.63	54.72	0.4163
6th Month Calcium (mg/dL)		9.47	9.39	9.43	0.6850
Outcomes (n)	Cure	16(94.1%)	18(100%)	34(97.1%)	0.486
	Persistent HPT	1(5.9%)	0(0%)	1(2.9%)	
	Recurrent HPT	0(0%)	0(0%)	0(0%)	

ICG; Indocyanine green, TOEPVA; TransOral Endoscopic Parathyroidectomy Vestibular Approach, BNE; Bilateral neck exploration, UNE; Unilateral neck exploration, IOPTH; Intraoperative parathyroid hormone monitoring, HPT; Hyperparathyroidism.

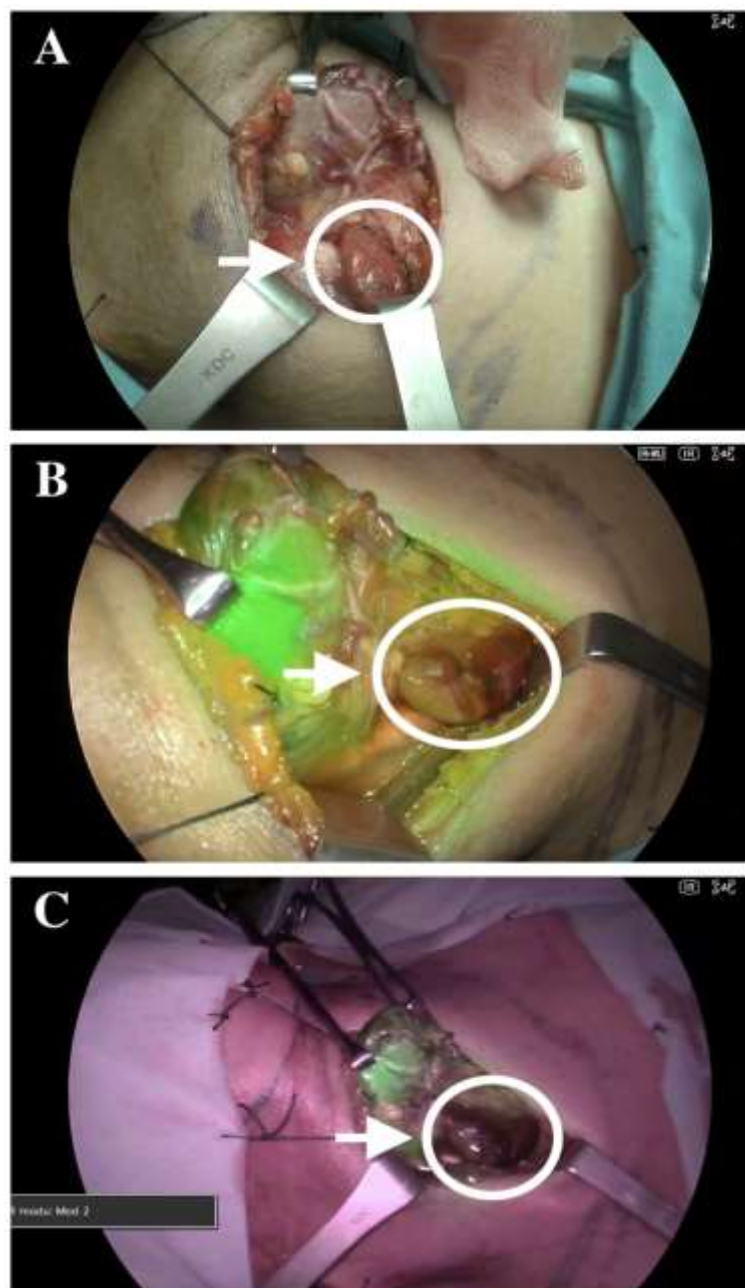


Figure 1. The image shows a parathyroid gland that is positive on naked-eye exploration but negative for indocyanine green fluorescence.

A; Naked-eye exploration of the left-lower parathyroid adenoma, B; Parathyroid gland not stained with indocyanine green, C; Near infrared camera view of the indocyanine green negative parathyroid gland.

The preoperative imaging-independent contribution of ICG is presented in Table 3.

Among 17 ICG-used cases, 15 showed positive uptake. NEE was positive in 15 cases overall (14 with ICG-positive, 1 with ICG-negative [Figure 1.]).

In two NEE-negative cases, one demonstrated positive ICG uptake (enabling identification [Figure 2.]), while the other was ICG-negative (associated with surgical failure).

Table 3. Distribution of ICG staining patterns independent of preoperative imaging.

NEE Status / ICG Status	ICG Positive (Fluorescence Present) (n)	ICG Negative (No fluorescence) (n)	Total (n)
NEE Positive (Visible to the Naked Eye)	14	1	15
NEE Negative (Invisible to the Naked Eye)	1	1	2
Total	15	2	17

ICG; Indocyanine green, NEE; Naked eye exploration

Stratified analysis by preoperative imaging status (Table 4) revealed 20 patients with concordant positive USG and scintigraphy, 9 with USG-negative/scintigraphy-positive, and 6 with both negative; no patients had USG-positive/scintigraphy-negative. Surgical success was 100% in all subgroups except both-negative (5/5 success in non-ICG vs. 0/1 in ICG-used, $p=0.167$). No significant additive benefit of ICG on success was observed in any subgroup (Fisher's exact test, all $p>0.05$ or not applicable due to absence of failure).

Table 4. Distribution of ICG staining patterns associated with preoperative imaging.

Preoperative Imaging	Total Patients (n)	ICG Not Used (n)	Success (n/%)	ICG Used (n)	Success (n/%)	Fisher's Exact Test p-value
USG+, Scint+	20	6	6/6 (%100)	14	14/14 (%100)	N/A (no failure)
USG+, Scint-	0	-	-	-	-	-
USG-, Scint+	9	7	7/7 (%100)	2	2/2 (%100)	N/A (no failure)
USG-, Scint-	6	5	5/5 (%100)	1	0/1 (%0)	0.167 (not significant)

ICG; Indocyanine green, USG; Ultrasonography, Scint; Scintigraphy

4. Discussion

The present study was conducted to evaluate the potential additive role of indocyanine green (ICG) fluorescence angiography as an intraoperative navigation tool in focused parathyroidectomy, particularly in relation to preoperative imaging modalities and naked-eye exploration. In our cohort, surgical success was achieved in 97.1% of cases, with no statistically significant difference in success rates between the ICG and non-ICG groups. These findings suggest that while ICG may not provide a routine statistically significant incremental benefit when preoperative localization is adequate, descriptive analysis highlights its potential utility in selected challenging cases.

A key observation supporting the preoperative imaging-independent contribution of ICG was the identification of the diseased parathyroid gland in cases where naked-eye exploration (NEE) proved insufficient. Notably, in one patient with concordant positive preoperative ultrasonography and scintigraphy, the adenoma remained undetected by NEE despite optimal localization; however, positive ICG uptake enabled precise identification and successful excision (Figure 2.).

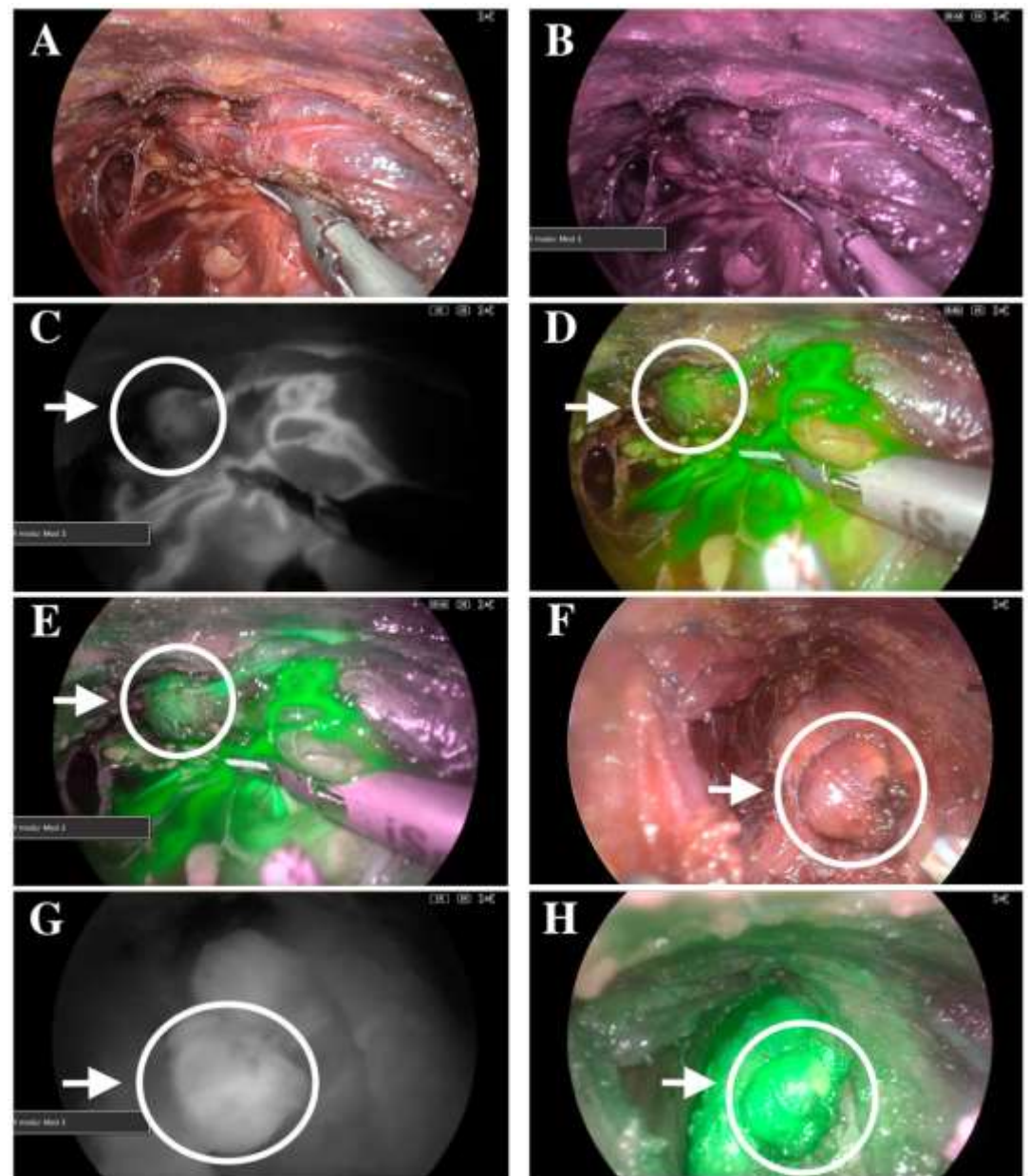


Figure 2. The image shows a parathyroid gland that is negative on naked-eye exploration but positive for indocyanine green fluorescence.

A; A negative image of the left parathyroid gland on naked-eye exploration, B; Near infrared camera view of the left thyroid lodge, C; Angiography image under near infrared camera after ICG administration, D; Left-lower parathyroid adenoma in indocyanine green mode, E; Image of left-lower parathyroid adenoma using a combination of indocyanine green and near-infrared camera modes. F; Naked-eye view of parathyroid adenoma after resection, G; Near infrared camera image of parathyroid adenoma after resection, H; Indocyanine green image of parathyroid adenoma after resection.

This "rescue" role of ICG fluorescence in overcoming the limitations of conventional visual exploration aligns with reports in the literature, where ICG has facilitated the detection of glands not visible to the naked eye during thyroid and parathyroid surgery.⁹ Furthermore, our study demonstrated that ICG was significantly more frequently utilized in endoscopic approaches, reflecting its synergistic potential in minimally invasive surgery. In endoscopic and robotic settings, the inherent limitations of haptic feedback and reduced depth perception can hinder the precise identification of anatomical structures. ICG fluorescence imaging mitigates these challenges by enabling real-time visualization of the

hypervascularized parathyroid gland, effectively distinguishing it from surrounding thyroid tissue. Moreover, although the ICG group exhibited a significantly higher rate of preoperative ultrasonography positivity compared to the non-ICG group (14/17 vs. 6/18), the comparable surgical success rates (94.1% vs. 100%) suggest that ICG's primary value lies in enhancing the safety and navigational precision of novel surgical techniques like TOEPVA, rather than solely increasing biochemical cure rates in already well-localized cases. While recent studies emphasize ICG's value in real-time identification and its capacity to enhance surgeon confidence, our series showed no overall statistical impact on surgical success.^{10, 11} This result is likely attributable to the high baseline success rate achieved with conventional techniques and the limited number of NEE-negative cases, underscoring the selective rather than universal benefit of ICG.

Regarding the contribution of ICG stratified by preoperative imaging status, our results indicated no significant additive effect on surgical success in subgroups with positive concordant imaging (both USG and scintigraphy positive) or single-modality positivity, with 100% success irrespective of ICG use. In the small subgroup with negative preoperative imaging (n=6), the single failure occurred in an ICG-negative uptake case, though statistical significance was not reached (p=0.167). These findings are consistent with meta-analyses reporting high parathyroid identification rates with ICG (94-100%) but limited incremental benefit when preoperative localization is robust.¹² Divergences from studies showing reduced postoperative hypoparathyroidism or improved outcomes with routine ICG¹³ may stem from differences in study populations (predominantly thyroidectomy cohorts versus focused parathyroidectomy) and outcome measures (parathyroid function preservation versus curative success in hyperparathyroidism). Furthermore, our low event rate for failure likely contributed to type II error, masking potential benefits in poorly localized cases.

Compared to other intraoperative adjuncts used for navigational purposes in parathyroidectomy, ICG fluorescence angiography offers distinct advantages in terms of safety and real-time visualization. Radioguided surgery using a gamma probe, which relies on preoperative technetium-99m sestamibi injection, provides reliable localization but involves radiation exposure for both patient and surgical team and requires additional logistical coordination.⁴ In contrast, ICG is radiation-free and enables immediate intraoperative angiography without preoperative radiotracer administration.⁵ Methylene blue staining, another historical adjunct, has been largely abandoned due to risks of neurotoxicity, anaphylaxis, and interference with pulse oximetry at higher doses; ICG demonstrates a superior safety profile with minimal adverse effects.¹⁴ While intraoperative parathyroid hormone (IOPH) monitoring remains the gold standard for biochemical confirmation of cure, it does not provide anatomical navigation and only validates excision post-resection.¹⁵ Thus, ICG complements rather than replaces IOPH, offering direct visual guidance that may be particularly valuable in minimally invasive or reoperative settings where tactile feedback is limited.

Despite its navigational benefits, the routine adoption of ICG fluorescence angiography is tempered by practical considerations, including equipment requirements and cost. Specialized near-infrared imaging systems are necessary, representing a significant upfront institutional investment, although the per-case cost of ICG dye itself is relatively low.¹⁶ Recent analyses suggest that ICG may be cost-effective in high-volume centers by potentially reducing operative time and conversion rates to bilateral exploration, particularly in cases with equivocal preoperative imaging.^{16, 17} However, limitations include occasional false-negative fluorescence in hypovascular adenomas—as observed in the single persistent hyperparathyroidism case in our series—and operator-dependent interpretation. Furthermore, ICG uptake relies on glandular vascularity, which may be reduced in fibrotic or previously operated necks. These factors reinforce the selective rather than

universal application of ICG, reserving its use for challenging cases where conventional naked-eye exploration and preoperative localization are insufficient.

This retrospective, single-center study is limited by its small sample size and low event rate for surgical failure, resulting in low statistical power and increased risk of type II error. The non-random use of ICG—more frequent in transoral endoscopic (TOEPVA) cases and patients with positive ultrasonography—introduces selection bias and baseline imbalances, limiting direct comparability between groups. Conducted by a single experienced surgeon, the findings may not generalize to less experienced operators or different institutional settings. Operator-dependent interpretation of fluorescence, occasional false-negative results (e.g., in hypovascular adenomas), and the absence of cost-effectiveness further constrain conclusions regarding routine versus selective ICG application. Despite these limitations, the study offers real-world insight into ICG's potential rescue role in challenging focused parathyroidectomies, particularly during minimally invasive approaches. Larger, prospective, multicenter trials are required to validate these observations and identify subgroups with the greatest benefit.

5. Conclusion

In conclusion, while ICG fluorescence angiography does not appear to provide a statistically significant routine additive benefit to surgical success in focused parathyroidectomy when preoperative imaging is adequate, it may serve as a valuable intraoperative adjunct in selected cases where naked-eye exploration is insufficient, independent of preoperative localization. These findings support the selective application of ICG as a navigative “rescue” tool to enhance precision in challenging parathyroid surgeries.

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Ethics approval: This study was approved by the Ethical Review committee of the University of Health Sciences, Antalya Training and Research Hospital (Approval No: 22/33).

Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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