



# Intraoperative indocyanine green angiography for predicting postoperative hypoparathyroidism

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## Abstract

**Background** Postoperative hypocalcemia is a common complication of thyroidectomy. This problem is most often associated with accidental devascularization or excision of the parathyroid glands (PG).

**Aim** Aim was to study near-infrared (NIR) fluorescent imaging with intraoperative PG indocyanine green (ICG) angiography to help identify and preserve PG during total thyroidectomy in order to avoid postoperative hypocalcemia.

**Material and methods** From 2017 to 2022, a total of 92 patients underwent total thyroidectomy at Odessa Regional Hospital. Indications for surgery were multinodular goiter ( $n=42$ ), thyroid cancer ( $n=43$ ), and Graves' disease ( $n=7$ ). By randomization all patients were divided into two groups: in the control group, 48 patients underwent standard total thyroidectomy, and in the main group, 44 patients underwent NIR-assisted total thyroidectomy with ICG angiography. Serum calcium and parathyroid hormone levels were compared between the two groups of patients in 1, 7–15 days after surgery and then 3, 6 months later.

**Results** In the control group, based on a visual assessment of the PG, autotransplantation of the PG was conducted in only five cases. In the second group, autotransplantation was performed in 16 patients. The transient postoperative hypocalcemia was observed in 8 patients of the control group (16, 70%) and in the 2 patients of ICG group (4, 50%) on 5–10 postoperative days. In the first group, 2 patients at 3 months after surgery had permanent hypocalcaemia.

**Conclusion** NIR fluorescent imaging with intraoperative PG ICG angiography is a safe and an easily repeatable method. This technique provides improved detecting and assessment of the perfusion of the PG. The need for autotransplantation of the PG can be determined more objectively using ICG imaging than simple visualization.

**Keywords** Total thyroidectomy · Parathyroid glands · ICG angiography · Hypoparathyroidism

The most common complications during thyroidectomy are hypocalcemia and recurrent nerve palsy. Recent studies report postoperative hypocalcemia rates of around 15% to 30% for transient hypocalcemia and 1% to 7% for definitive cases [1, 2]. Hypocalcemia primarily occurs due to unintentional damage to the parathyroid glands (PG) or their devascularization [2, 3]. Factors such as the small size and variable location of PGs significantly complicate their visualization, potentially leading to injury even with meticulous dissection by an experienced surgeon [2–6]. While most authors concur that one intact gland is adequate to maintain normal serum calcium and hormone levels in

the blood, preserving as many PG as possible can minimize the incidence of postoperative hypoparathyroidism [1–3]. Autotransplantation of devascularized PG has been shown to be an effective method of restoring their function. However, visual assessment of their blood supply is subjective and may not accurately reflect the actual situation.

Intraoperative identification of PGs is a critical concern during total thyroidectomy. The conventional identification method primarily relies on visual inspection and palpation by the surgeon, with careful preservation of the PG blood supply based on the surgeon's experience [5]. Recently, near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) angiography has emerged as one of the most popular methods for detecting PGs and assessing their vascularization [3–11]. Due to their higher vascularity compared to surrounding tissues, PGs exhibit strong fluorescence on ICG angiography [4].

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This study aimed to determine the potential benefits of routinely using intraoperative ICG angiography with NIR fluorescent imaging in total thyroidectomy. The primary objective was to examine the efficacy of NIR fluorescent imaging with intraoperative PG ICG angiography in identifying and preserving PG during total thyroidectomy, thereby reducing the risk of postoperative hypocalcemia.

## Materials and methods

From April 1, 2017 to January 1, 2022, a total of 92 patients underwent total thyroidectomy at Odessa Regional Hospital. The patients were randomly divided into two groups: the control group consisting of 48 patients who underwent standard total thyroidectomy, and the ICG group with 44 patients who underwent NIR-assisted total thyroidectomy with ICG angiography.

The indications for surgery included thyroid cancer, multinodular goiter, and Graves' disease. Parathyroid autofluorescence was detected using a NIR/ICG endoscopic system (Karl Storz, Tuttlingen, Germany). The system consisted of a high-end full high-definition camera system (H3-Z 3-Chip Full HD camera, Karl Storz) connected to a 10-mm 0-degree ICG laparoscope (Hopkins™ II, Karl Storz).

All patients received general anesthesia with endotracheal intubation. A 4 to 5 cm Kocher transverse collar incision was made 1 cm below the cricoid cartilage. The strap muscles were divided along the midline throughout their entire length until the thyroid gland was exposed. The sternohyoid muscles were separated from the underlying sternothyroid muscle through dissection until the internal jugular vein and nerves were identified. The inferior thyroid vessels were dissected and divided as close to the thyroid gland's surface as possible to minimize parathyroid devascularization or injury to the recurrent laryngeal nerves.

For the ICG group, ICG angiography was performed during surgery. The anesthesiologist administered a standard intravenous dose of 15 mg ICG. The PG absorbed the dye within 2 min and remained fluorescent for up to 15 min. The surgeon's assistant recorded the video in real time after ICG injection.

The parathyroid fluorescence intensity (FI) depended on the amount of ICG absorbed by the PG. The mechanism for parathyroid dye uptake is likely related to the abundant blood supply of endocrine organs. Consequently, the parathyroid FI reflects gland vascularization. In ICG angiography applications, different gray scale grades can indicate various levels of parathyroid function. PG were scored from 0 to 2 based on

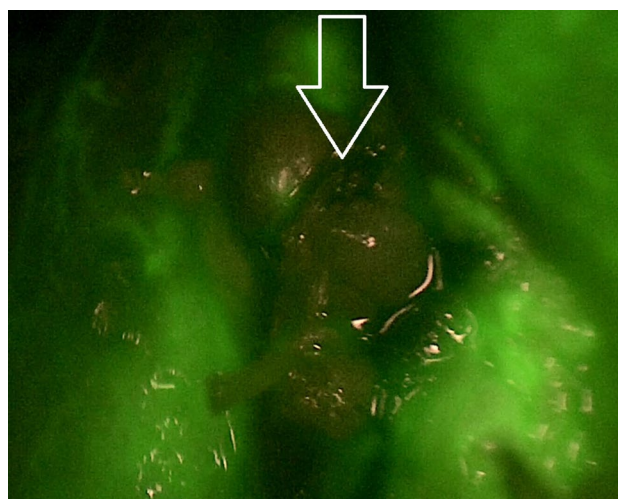


Fig. 1 Fluorescence imaging scores of the parathyroid (ICG score 0)

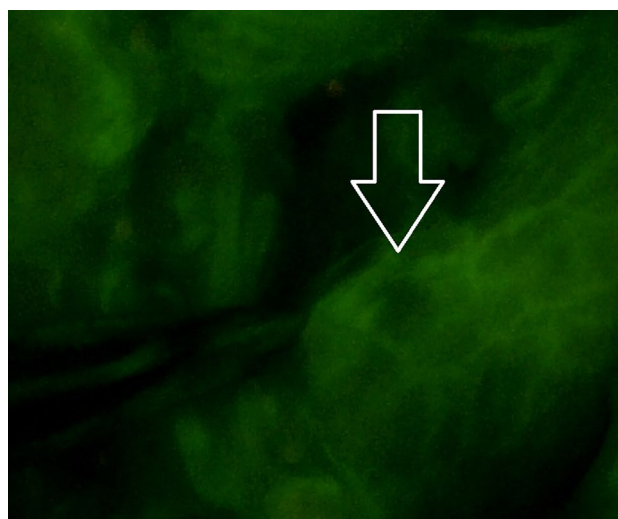
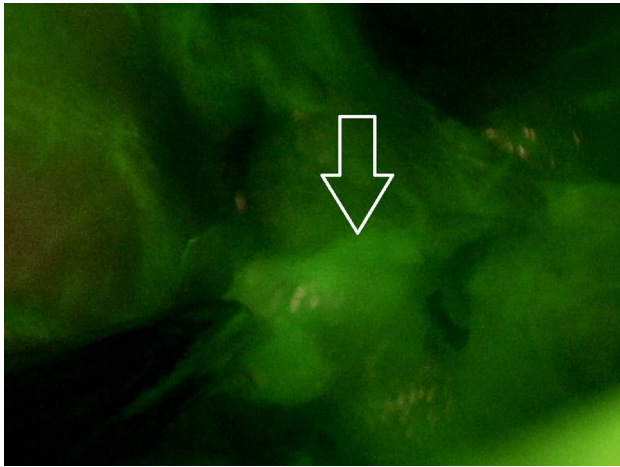


Fig. 2 Fluorescence imaging scores of the parathyroid (ICG score 1)

their FI after ICG angiography, with score 0 representing weak FI (Fig. 1), score 1 indicating moderate FI (Fig. 2), and score 2 signifying strong FI (Fig. 3). Surgeons performed parathyroid autotransplantation for glands that appeared well vascularized visually but were deemed devascularized in ICG angiography.

Serum calcium and parathyroid hormone (PTH) levels were compared between the two patient groups at 1, 3–10 days post surgery, and subsequently at 1, 3, and 6 months. Statistical analysis was performed using the  $\chi^2$  test for discrete variables, with  $p < 0.05$  considered statistically significant. Data for continuous variables are presented as mean (SD) values. The software Statistica version 5.0 was used for statistical analysis.



**Fig. 3** Fluorescence imaging scores of the parathyroid (ICG score 2)

## Results

The demographic profiles of patients were similar between the two groups. No significant differences were observed in comorbidities, including cardiac, pulmonary, vascular, or renal diseases (Table 1). In the control group, autotransplantation of the PG was performed in only five cases (three cases with one gland and two cases with two glands), based on visual assessment. In the ICG group, autotransplantation was conducted in 16 patients (9 cases with one gland, 6 cases with two glands, and 1 case with three glands). The

table showcases the specific number of parathyroid glands that were successfully identified using ICG (Table 2).

Hypocalcaemia (calcium level below 2.25 mmol/l) was observed in either group. The transient postoperative hypocalcaemia was observed in 8 patients of the control group (16.70%) and in 2 patients of ICG group (4.50%) on 5–10 postoperative days. There was no statistical difference in calcium or PTH levels between the groups on POD 30 (Table 3). But in the first group 2 patients at 3 months after surgery had hypoparathyroidism. Two patients in the control group experienced typical symptoms of hypocalcaemia but had PTH levels in the normal range on POD 30, without calcium supplementation. One had a calcium level of 2.05 mmol/l, PTH level of 3.7 pmol/l, and mild finger paraesthesia, which rapidly improved after oral calcium supplementation (dose 1 g). The other patient also experienced finger paraesthesia, with calcium and PTH values of 2.02 mmol/l and 5.2 pmol/l, respectively. The symptoms improved a few minutes after oral calcium supplementation (1 g). For patients in the control group, standard oral supplementation kept calcium levels within normal limits. In some cases, if necessary, we prescribed active vitamin D.

## Discussion

Over the past century, thyroid and parathyroid surgery have become increasingly safe, with significant advancements and improvements in surgical techniques and patient care [1–4].

**Table 1** Demographic and clinical features of patients

	Control group ( <i>n</i> =48)	ICG group ( <i>n</i> =44)
Age (years) <sup>a</sup>	44.6 ± 5.6	47.2 ± 6.4
Gender ratio (M:F)	15/33	12/32
ASA score	1.88 ± 0.23	1.87 ± 0.3
Indication for surgery		
Multinodular goiter	23	19
Thyroid cancer	22	21
Graves' disease	3	4
Duration of hospital stay (days) <sup>a</sup>	2.9 ± 0.6	2.7 ± 0.7

ASA American Society of Anesthesiologists, *F* female, *M* male

<sup>a</sup>Values are mean (SD)

**Table 2** Fluorescence imaging scores in 44 participants

	Left superior parathyroid	Left inferior parathyroid	Right superior parathyroid	Right inferior parathyroid
Total no. of identified parathyroids	42	40	42	39
Fluorescence imaging score 2	22	20	23	21
Fluorescence imaging score 1	10	12	10	12
Fluorescence imaging score 0	10	8	9	6

**Table 3** Postoperative results

	Control group (n = 48)	ICG group (n = 44)	Difference <sup>c</sup>	p value <sup>d</sup>
Calcium (mmol/l) <sup>a</sup>				
POD 1	2.18 (0.011)	2.3 (0.013)	(− 0.0570, 0.0192)	0.331
POD 30	2.28 (0.026)	2.3 (0.024)	(− 0.0436, 0.0027)	0.084
PTH (pmol/l) <sup>a</sup>				
POD 1	2.8 (1.281)	3 (1.267)	(− 0.4918, 0.0922)	0.176
POD 30	3.5 (1.291) <sup>b</sup>	4 (1.282)	(− 1.0648, 0.0640)	0.080

POD postoperative day

<sup>a</sup>Values are mean (SD)

<sup>b</sup>Calcium and parathyroid hormone (PTH) levels were significantly higher on POD 30 than POD 1 in the ICG and control groups (mean difference in calcium 0.0994 [95% CI 0.0661 to 0.1327] mmol/l,  $p < 0.05$ ; mean difference in PTH 0.6994 [0.2737 to 1.1250] pmol/l,  $p < 0.001$ )

<sup>c</sup>Values in parentheses are 95% confidence intervals

<sup>d</sup>Paired *t* test

The literature reports that transient hypoparathyroidism occurs with a frequency of 15 to 30%, and permanent hypoparathyroidism occurs with a frequency of 3–7% [3].

Despite these advances, hypoparathyroidism remains a concern, with 15–30% rates of post-thyroidectomy hypoparathyroidism reported in the literature [1, 2].

Permanent hypoparathyroidism leads to fatal consequences despite treatment: basal ganglia calcifications, renal calcification, carpopedal spasm, cardiac issues, and psychiatric problems [12].

Currently, there is no gold standard for detecting and preserving PG and their vascularization during thyroidectomy [7, 8]. The blood supply and localization of PG are crucial factors for preservation during surgery, but anatomical variability in this region is high, demanding great experience and flexibility from the surgeon [2, 9]. Some parathyroids receive their blood supply directly from the thyroid gland (8.2%), which makes preservation difficult [2, 9].

The location of the PG in relation to the thyroid gland has a huge amount of variation. In addition, there are various options for the blood supply to the PG. In some cases, they have a separate vessel. In some cases, they receive their blood supply from the thyroid gland or are generally located within the thyroid gland. Some authors distinguish up to five different types of blood supply to the PG. [13]. And in some of them it is impossible to maintain a normal blood supply during thyroidectomy.

There are several basic techniques aimed at preventing hypoparathyroidism.

The traditional technique is capsular dissection, which allows you to gradually identify all the PG with the release of the thyroid gland. [14]. However, it is not always possible to identify all PG. Identification of two or less PG dramatically increases the risk of developing hypoparathyroidism [15]. In addition, routine dissection may be accompanied by trauma to the nerve, blood vessels, and bleeding, which further complicates the identification of the PG and significantly prolongs the operation time [16].

The problem is so controversial that some surgeons suggest looking for PG only in a typical location. If they cannot be found there, then it is better to simply continue with the capsular dissection in order to avoid trauma to the glands located in atypical places [17, 18].

Most surgeons prefer a selective approach to autotransplantation. That is, autotransplantation is performed only for those PG that appear macroscopically ischemic or have been accidentally removed. However, macroscopic evaluation is very subjective and inconclusive. A discolored gland does not necessarily indicate that it is not viable. At the same time, the absence of discoloration is not a reliable sign of a good blood supply [19, 20].

Delbridge et al. suggested routine autotransplantation of at least one PG [21]. At the same time, the frequency of temporary hypocalcemia increases, and the frequency of permanent hypocalcemia decreases. However, selective autotransplantation remains the most widely practiced technique, although it is not perfect [22].

In our research, approximately two-thirds of unintentional parathyroid removals coincided with thyroid cancer cases and central neck dissections. Accidental PG excision has been linked to factors like a low volume of surgical procedures, the PG's intrathyroidal location, and central neck dissection operations [4, 5].

New optical-based techniques without radiation exposure have been developed to aid in the detection of PG (particularly autofluorescence) and confirmation of their vascularization (specifically ICG angiography) [23, 24]. The angiography imaging system has become essential for a wide range of surgeries [10, 23, 24]. One of the initial objectives of this study was to demonstrate that ICG angiography has emerged as a powerful tool for predicting parathyroid function immediately after thyroidectomy [25]. At the same time, fluorescence imaging systems are quickly becoming key instruments in thyroid and parathyroid surgeries [25]. Combining NIRAF with ICG can highlight not only anatomy but also vascularization and, consequently, gland function [4]. In fact, injecting ICG at the end of the procedure allows verification of PG vitality and can be considered a valid predictor of postoperative calcium levels, as demonstrated by several authors [4, 11]. In particular, Vidal Fortuny et al. emphasized that at least one well-vascularized PG at the end

of the surgical procedure is predictive of normal postoperative PTH levels [4].

Data from various studies suggest that ICG administration may have some complications [26]. Recent research has established those rare reactions, such as anaphylactic or urticarial reactions, may occur [27]. Over the past 34 years, only 17 adverse reactions have been reported, with no additional information available on ICG dye allergic reactions [27]. What is known about ICG dye allergic reactions is largely based on the fact that the ICG substance contains 5% sodium iodine for solubility, and patients allergic to ICG were all iodine-allergic and had renal insufficiency [27]. However, these reactions were reported to be 0.00167% and mainly occurred in patients with a history of allergy to iodides [27]. With an anesthesia team ready to treat allergic reactions, ICG angiography maintains a high degree of safety.

Regarding autotransplantation of PG, it is essential to determine which ischemic PGs require replantation. However, replantation does not guarantee that the gland will adapt to its new location and function normally. Therefore, the best use of the system to ensure safe blood flow to the PG is during dissection of the surrounding tissue [9]. ICG visualization is not only useful for the identification of PGs but also for a more reliable determination of gland viability. This study has demonstrated that intraoperative angiography with ICG is simple and reproducible. Although the laparoscopic imaging camera system is currently expensive, it produces high-quality images and can be used in other surgical procedures, making the equipment more cost-effective [28].

In analyzing the postoperative results from our study, we observed that calcium levels during the immediate postoperative phase (day 1) did not showcase any statistically significant differences, as initially anticipated. By day 30, while still not achieving statistical significance, we noticed a growing divergence in calcium and PTH levels.

However, of paramount importance to us was not solely the alteration in calcium levels but the noticeable decrease in the incidence of persistent hypoparathyroidism. Within the control group, persistent hypoparathyroidism was evident in 2 out of 48 cases at the 3-month mark, whereas in the main group, no instances were reported. While this difference was not statistically significant ( $p=0.225$ ), it hints at a trend that may become evident with a larger study cohort. Our hypothesis is that expanding the sample size could potentially yield statistically significant differences.

## Conclusion

NIR fluorescent imaging with intraoperative PG ICG angiography is a safe and an easily repeatable method. This technique provides improved detecting and assessment of the perfusion of the PG. The need for autotransplantation of the

PG can be determined more objectively using ICG imaging than simple visualization.

## Declarations

**Disclosures** Viktor V. Grubnyk, Volodymyr V. Grubnik, Yurii V. Grubnik, and Roman S. Parfentiev have no conflicts of interest or financial ties to disclose.

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