Review Article

A reappraisal of vascular anatomy of the parathyroid gland based on fluorescence techniques

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Abstract: Identification of the parathyroid glands (PGs) during thyroid surgery may prevent their inadvertent surgical removal and prevent postoperative hypoparathyroidism. However, identification of the PGs does not guarantee their function, and their vascular supply needs to be preserved as well. The recent introduction of intraoperative indocyanine green (ICG) fluorescent angiography of the PGs during thyroid surgery allows for the appraisal of the vascular anatomy and evaluation of PG function. The use of this tool could lead to a significant reduction in the rate of postoperative hypoparathyroidism, as it allows surgeons to adapt their surgical technique for the preservation of the PGs. ICG fluorescent angiography is currently the only available real-time tool to assess the vascular blood supply of each individual PG intraoperatively and can thus assist surgeons in their decision-making. Herein, we review the relevant literature.

Keywords: Parathyroid gland (PG); indocyanine green fluorescence (ICG fluorescence); postoperative hypoparathyroidism

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Vascular anatomy of the parathyroid glands (PGs) and its importance in neck endocrine surgery

Knowing the anatomical position and vascular supply of the PGs is essential to avoid hypoparathyroidism after thyroid surgery (1,2). Temporary hypoparathyroidism with resulting hypocalcemia is the most common complication after total thyroidectomy and occurs in up to 30% of patients who undergo total thyroidectomy (3,4). Its incidence depends on the technical difficulty of the procedure and expertise of the surgeon. Permanent hypocalcemia, defined as hypocalcemia for more than 6 months after thyroidectomy, is reported in 1–10% of patients (5,6). Reducing the rate of hypoparathyroidism is essential for improving the quality of life, as postoperative hypocalcemia can result in prolonged hospitalization and multiple clinic visits, neuromuscular symptoms, the need for life-long calcium and vitamin D supplementation, and long-term complications, such as cerebral, vascular, ocular, and renal damage (7-11).

In a study of 100 cadaveric thyroid glands by Delattre *et al.* (12), 38.2% of the parathyroid feeding vessels were considered at risk for damage by dissection during standard thyroidectomy. Furthermore, all four PGs were at risk in 5% of the cadavers, with the superior glands at increased risk, as they usually presented with a shorter feeding vessel and were tightly positioned at the posterior side of the upper pole of the thyroid. Knowledge about the origin and course of arterial supply is thus of utmost importance. The authors found a single feeding vessel to the PGs in 80% of cases. In general, both the superior and inferior PGs received their blood supply from the inferior thyroid artery (ITA): the superior PGs received blood supply from the ITA in 77% of cases, from the superior thyroid artery (STA)

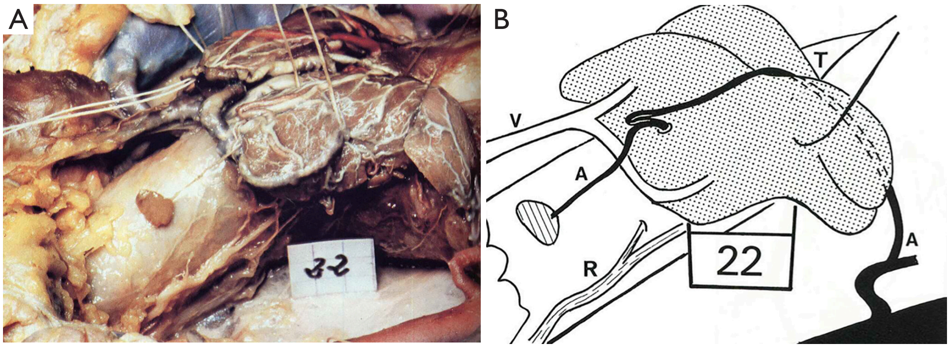

Figure 1 Cadaveric dissection of case with absence of inferior thyroid artery. (A) Absence of the inferior thyroid artery with the inferior parathyroid gland receiving its blood supply from a branch of the superior thyroid artery, which divides anterior to the thyroid gland (left side); (B) drawing corresponding to *Figure 1A*, showing the anterior position of this arterial branch. With permission from Delattre *et al.* (12). A, artery; T, thyroid; R, recurrent laryngeal nerve; V, vein.

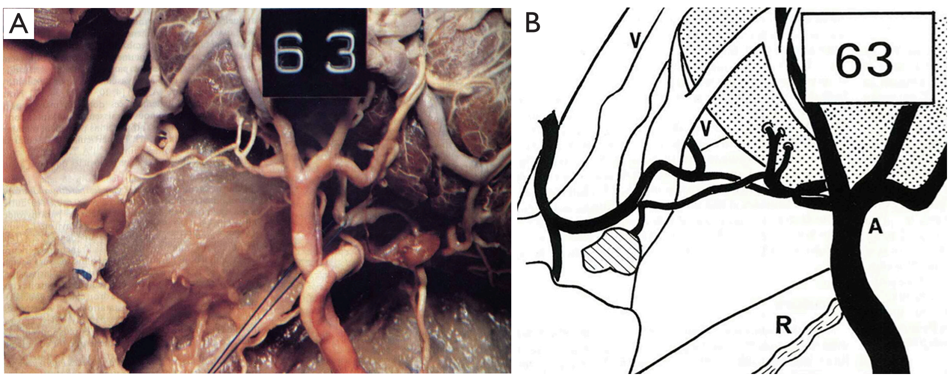

Figure 2 Cadaveric dissection of a case with a long vascular parathyroid gland pedicle. (A) An inferior parathyroid gland with a long pedicle (25 mm). This situation is at risk during lobectomy because of the presence of two very short branches (2 and 3 mm) attached and entering the thyroid (left side); (B) drawing corresponding to *Figure 2A*, showing at risk parathyroid blood supply despite a long pedicle. With permission from Delattre *et al.* (12). A, artery; R, recurrent laryngeal nerve; V, vein.

in 15%, and from anastomoses between the two arteries, running posteriorly to the thyroid in 8%. The inferior PGs were supplied by the ITA in 90.3% of cases, and by the STA in 5%. The authors found an absent ITA in 4.5% of cases; in such cases an anterior running vessel from the STA is particularly at risk during lobectomy (*Figure 1A,B*). These findings highlight the importance of considering the vascular supply as an interconnected network (loop of anastomoses) of vessels, possibly running close to the thyroid parenchyma and often with short branches connecting to or traversing the thyroid parenchyma. Such cases are at risk for devascularisation, even when a long feeding pedicle is present (*Figure 2A,B*).

Furthermore, Delattre *et al.* (12) reported that they were able to locate a greater number of PGs (at least all 4 PGs) during their last 40 cases of micro-dissection, suggesting that the experience of the surgeon might play an important role in PG localization and preservation. In addition, the authors concluded that the position of the parathyroid artery in relation to the thyroid parenchyma is the most important factor when considering the risk of devascularisation during lobectomy, rather than the length of the artery. Since these arteries are terminal vessels, systematic identification, precise surgical dissection, and micro-ligatures are key in reducing the frequency of iatrogenic hypoparathyroidism (12), a risk that was first described by Halsted *et al.* in 1907 (13). These results provide an anatomic explanation for the consistent 1–10% of definitive hypoparathyroidism reported in most registry-based or multicenter studies (5,14).

Hypocalcemia after total thyroidectomy might result from intraoperative damage to the PGs due to trauma, inadvertent removal, or devascularisation. The extent of damage to the PGs is difficult to predict intraoperatively. It is generally accepted that sufficient parathyroid hormone (PTH) can be produced by one half of a normal PG (6). To avoid postoperative hypocalcemia, parathyroid auto-transplantation can be performed; however, the results have been inconsistent, creating controversy (15-17). Therefore, capsular dissection techniques and preservation of the surrounding vasculature have been proposed and utilized, in an attempt to avoid inadvertent parathyroidectomy or the disruption of the parathyroid vasculature (18-20). Several studies have shown a reduction in transient and permanent hypoparathyroidism after adopting vascular-preservation techniques and classification systems that guide dissection, resection, and decisions regarding auto-transplantation (19,21).

Preservation of the PGs can be challenging, as normal postoperative parathyroid function is not guaranteed even when the PGs are thought to be well preserved during surgery. A study by Lang *et al.* (22) examined 103 patients who underwent total thyroidectomy with identification of all 4 PGs and a visual analysis of the PGs. The authors reported that having more than 3 discolored PGs was an independent risk factor for transient hypoparathyroidism. However, 12.5% of patients with 4 normally colored PGs, assumed to be fully functioning, presented with hypoparathyroidism. The authors concluded that PG discoloration is associated with transient hypoparathyroidism, and that normally colored PGs with assumed adequate blood supply do not necessarily imply a functional gland (22). The authors also highlighted the need for individual real-time intraoperative methods to assess PG viability.

Angiography with indocyanine green (ICG) can be used as adjunct technique to help identify the vascular blood supply of the PGs at risk for damage during thyroid gland dissection and to aid in the prediction of the functionality of the identified PGs.

Fluorescent techniques with ICG in neck surgery

Accurate prediction of post-thyroidectomy hypocalcemia might lead to a modification of surgical strategies. However, there is a need for reliable tools that can accurately predict whether a patient will develop hypocalcemia (5,23,24). The current techniques for evaluating parathyroid function are based on calcium (25,26) and PTH (6,27-31) measurements at various time points during or after thyroidectomy. Some studies have suggested that early (a few minutes to 12 hours after thyroid resection) PTH measurements reliably predict the absence of hypoparathyroidism, with a positive predictive value up to 97% (6,27,28). However, this finding has been challenged by other authors (32,33). Unlike ICG-angiography, which has immediate results, calcium and PTH level measurements are usually not able to guide intra-operative decision-making, as their results require a long time to develop. However, some authors have suggested using quick PTH measurements to demonstrate parathyroid insufficiency, providing results that can then help surgeons decide whether to auto-transplant a PG (29,34).

ICG is a water-soluble, 775 Da-sized molecule with a maximum absorption spectrum of 805 nm and re-emission at 835 nm when excited by a light/laser at a wavelength in the near-infrared (NIR) spectrum. Once injected, ICG becomes completely and permanently fixed to plasmatic proteins in the bloodstream, and circulates in the intravascular compartment only. It has a half-life of 3.4±0.7 minutes, and is taken up from the plasma almost exclusively by the hepatic parenchymal cells, before being secreted entirely into the bile. Iodine allergy is a contra-indication for ICG administration, as iodine is present in its molecular structure. The largest study performed to date found that allergic reactions occur in 1/80,000 patients who receive ICG (35).

Initially ICG was used in ophthalmology for the detection of macular degeneration (36). Subsequently, ICG angiography has been used to identify sentinel lymph nodes (37), determine the extent of oncologic resections (38), and study hepatic function (39). Recent studies have also demonstrated its usefulness in evaluating the vascular blood flow of intestinal anastomoses (40) and tissue flap reconstructions (41).

At our center, ICG for thyroid or parathyroid surgery is prepared according to the protocols used for abdominal surgery (38). Briefly, 25 mg ICG is mixed with 10 mL of sterile water (concentration, 2.5 mg/mL), and 3.5 mL is injected intravenously during the procedure by the anesthesia team. The injection can be repeated until a maximum dose of 5 mg/kg per day is reached. The catheter is then purged after each injection for rapid imaging gain.

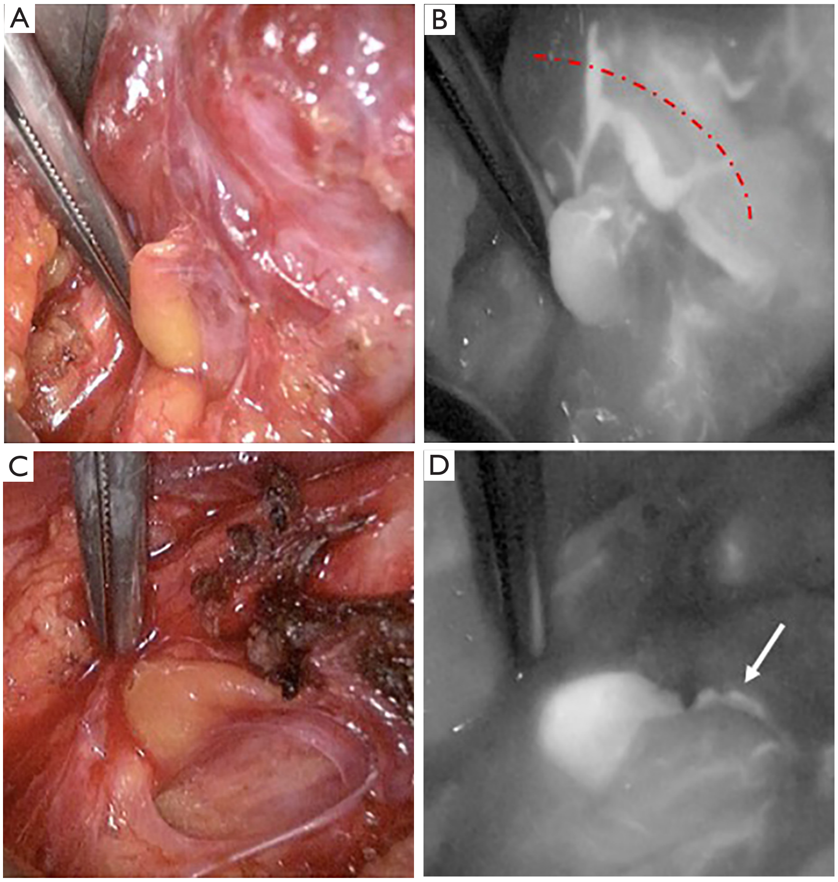

Figure 3 A 61-year-old female undergoing total thyroidectomy for multinodular goiter. (A) The inferior parathyroid gland on the left side (at the tip of the instrument), with thyroid lobe retracted for removal; (B) black and white near infra-red images after ICG injection of the same gland, showing the vascular blood supply loop with inferior and superior branches (white, well perfused). The planned surgical resection for the preservation of these loop anastomoses observed on ICG is marked with a red dotted line; (C) same inferior parathyroid gland after left thyroid lobe removal (PG at the tip of the instrument); (D) black and white near infra-red images of the same gland after the second ICG injection, demonstrating the preserved vascular blood supply (white arrow) and a well perfused PG (scored ICG =2). ICG, indocyanine green; PG, parathyroid glands.

After approximately 1–2 minutes, images are acquired using a laparoscopic NIR PinPoint® camera (Novadaq, Ontario, Canada).

One benefit of the use of ICG technology is that the anatomy of the feeding vessels to the PGs can be analyzed prior to performing a thyroid lobectomy, allowing the preservation of the vessel loops feeding the PGs (*Figures 3*,*4*). The video shows a case of thyroidectomy for malignant disease. After ICG angiography and the visualization of the feeding vessel loop attached to the thyroid, a precise capsular dissection technique was performed and a tiny thyroid remnant was left behind in order not to harm the vessel loop and thus preserve the PG.

We have systematically utilized standardized ICG angiography in hundreds of cases and are able to perform a vascular mapping of the PG feeding vessels. This has made us more clearly aware of the anatomy and locations of the PGs, as well as the presence of vascular loops, which are often very close to the thyroid parenchyma (*Figures 1*,*2*). Thus, we currently perform dissections for PG preservation in a very precise and arduous manner in terms of capsular dissection, occasionally leaving behind a small thyroid remnant to preserve the attached PG vessel loops. Whether this technique will further reduce postoperative hypoparathyroidism needs to be evaluated in future studies.

Figure 4 A 56-year-old female undergoing total thyroidectomy for papillary thyroid cancer, pT1b N1 (42). The video shows a left superior parathyroid gland (circle) being preserved, before and after left lobectomy. ICG images taken before lobectomy in the first part show the feeding vessel loop coming from the inferior thyroid artery. The second part after left lobectomy shows the left parathyroid gland (circle) after leaving a small thyroid remnant in order to preserve the vessel loop feeding the gland. ICG images show a well-vascularized left parathyroid gland next to the thyroid remnant. ICG, indocyanine green.
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Application of ICG in thyroid and parathyroid surgery for the evaluation of PG function

The PGs need to be identified early during the thyroidectomy dissection, and their vascular supply must be preserved to prevent postoperative hypocalcemia. The use of ICG for PG identification during thyroid surgery was first proposed in a study by Suh *et al.* (43) in 2014, in which the authors showed that the PGs could be visualized using ICG NIR imaging in dogs. In the same year, another group (44) managed to differentially visualize the thyroid and PGs using NIR imaging in pigs.

In our initial experience using ICG to evaluate intraoperative perfusion of the PGs for the prediction of parathyroid function after thyroidectomy (45), we demonstrated that the presence of one well-perfused PG or a well-perfused PG remnant was sufficient to avoid hypoparathyroidism (46). After total thyroidectomy, we found that at least one well-perfused gland was present on angiography in 30 of 36 patients; none of the 30 patients experienced postoperative hypoparathyroidism. On the other hand, transient postoperative hypoparathyroidism was noted in two of the six patients who did not have at least one well-perfused PG on angiography. In cases of discrepancy between the visual assessment and ICG angiography, an incision was made on the PG and glands that did not bleed were auto-transplanted (five cases).

In addition, we have shown the superiority of ICG angiography over visual assessment. In our preliminary study, 71 of 101 PGs were visually evaluated as well-vascularized, while only 51 were considered well-vascularized on ICG angiography (45). Thus, the perfusion status (and therefore the functional ability to produce PTH) was visually over-evaluated in 20 of 71 PGs (28.2%). Similar findings have been reported for 27 patients who underwent thyroidectomy (47). In this prospective study, a total of 84% visually identified PGs showed ICG uptake. PG perfusion was scored both visually and by ICG fluorescence. A discrepancy between visual and ICG scores was noted in 6% of cases. In addition, three patients had transient postoperative hypocalcemia, with only one patient being symptomatic. It should be noted that the utility of ICG is limited in patients with a present thyroid gland, as the parathyroid fluorescence is frequently obscured by the thyroid.

In 2017, Lang *et al.* (48) studied postoperative hypocalcemia after total thyroidectomy and its correlation with fluorescence intensity on ICG angiography, using the SPY® Fluorescent Imaging System (Novadaq Technologies, Inc.). The authors evaluated a total of 324 biopsy-confirmed PGs from 94 patients. The fluorescence intensity of each PG was expressed as the fluorescence intensity ratio between the PG and the anterior trachea, and the greatest fluorescence intensity (GFI) was assessed. The GFI value was found to be the best predictor of early postoperative hypocalcemia (0% chance of hypocalcemia for a GFI value >150% *vs.* 81.8% chance of hypocalcemia for a GFI value ≤150%). There were no cases of permanent hypocalcemia, regardless of GFI value (48).

One of the limitations of many studies analyzing ICG angiography during thyroidectomy is the fact that in most patients, not all 4 PGs are evaluated. Therefore, in those patients with less than 4 evaluated PGs, the perfusion and function of the non-visualized PGs remain unknown, obscuring a clear correlation between ICG perfusion (evaluated in 1, 2 or 3 PGs) and postoperative PTH levels (reflecting the function of all 4 PGs). We therefore analyzed patients undergoing subtotal parathyroidectomy (49) and reported our findings on ICG use in a prospective study of 13 patients undergoing subtotal parathyroidectomy for multiglandular disease (primary and secondary hyperparathyroidism) (46). Our goal was to determine whether postoperative single PG (or PG remnant) function was truly reflected by intraoperative ICG angiography. For this purpose, only cases with all four PGs visualized were included. The PG that was to be preserved was selected based on the degree of perfusion on ICG angiography. When the gland chosen by the surgeon visually showed poor perfusion on angiography, another gland was selected for preservation. On follow-up, normal levels of PTH were achieved in all patients, demonstrating that the well-perfused PG or remnant was functional.

In 2016, Zaidi *et al.* (50) published results of a prospective study involving 33 patients who underwent surgery for primary hyperparathyroidism. This study included both parathyroid adenoma excisions as well as subtotal parathyroidectomies (3.5-gland excision). Overall, 92.9% of the identified PGs visually demonstrated ICG uptake. In most cases, the presence of thyroid tissue limited the parathyroid fluorescence, as it has high vascular ICG uptake. The authors found ICG angiography to be useful in remnant PG function assessment in cases of subtotal parathyroidectomies and in patients who had a previous thyroidectomy.

Future directions, proposals and conclusions

The largely encouraging findings in the above studies, led us to design a prospective, randomized study to determine whether the systematic measurement of calcium and PTH levels, as well as the systematic supplementation of calcium and vitamin D therapy, can be omitted in patients with at least one well-perfused PG identified on ICG angiography after the thyroid gland has been removed. We hypothesized that patients with a well-perfused PG, as demonstrated via ICG angiography, would not develop postoperative hypoparathyroidism and therefore would not need post-operative calcium and/or PTH measurements nor calcium and vitamin D supplementation. The results of this study should be available soon.

There are several areas in this field that require further development. The technique could be further improved, especially regarding standardization, which would allow for universal applications and a more objective scoring system. In addition, cost-benefit analyses need to be performed. The material is costly; however, the cost can be shared by all departments (abdominal, gynecology, plastic and neck surgery), as in our institution. Fortunately, the materials can even be shared in high volume centers, as the ICG procedure itself takes less than 5 minutes.

In conclusion, we believe that the use of ICG angiography of the PGs during thyroid surgery can lead to a reduction in the rate of postoperative hypoparathyroidism. First, ICG angiography allows surgeons to adapt their technique for PG preservation depending on parathyroid perfusion and vascular anatomy. Second, ICG angiography allows surgeons to verify the perfusion of the PGs after thyroid resection, indicating whether a PG should be auto-transplanted. ICG angiography is currently the only available real-time tool able to intraoperatively predict the function of each individual PG, and can therefore assist surgeons in their decision-making regarding how to avoid post-thyroidectomy hypoparathyroidism.

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Footnote

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