Review Article

Fluorescence techniques in adrenal surgery

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Abstract: This chapter describes the use of fluorescence via indocyanine green (ICG) in minimally invasive adrenal surgery (laparoscopic and robotic). ICG is a non-toxic dye that can aid identification of vascular structures and parenchymal tissue planes in real time. The primary utility of ICG fluorescence in adrenal surgery is to help delineate the margins of resection, to guide a more precise operation. In particular, for patients with bilateral adrenal disease or a heredity associated with high risk of recurrence (e.g., VHL, MEN2a) this may facilitate subtotal adrenal resection (e.g., cortical sparing adrenalectomy), obviating the incidence of iatrogenic adrenal insufficiency and its numerous sequelae including lifelong hormone supplementation, osteoporosis and risk of Addisonian crisis.

Keywords: Adrenal surgery; fluorescence angiography; indocyanine green (ICG); near infrared imaging (NIR imaging); laparoscopy

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History

Fluorescence is a natural phenomenon known to humans for thousands of years. It was initially used in ophthalmology for retinal angiography (1) but as its utility was further understood, clinical application expanded to include various surgical procedures such as cholecystectomy (2,3), gastrointestinal anastomoses, renal auto-transplantation (4) and nodal dissections (5-10). More recently indocyanine green (ICG) has become available for minimally invasive surgery, with the development of more advanced laparoscopic and robotic platforms that can display ICG-enhanced images on the same screen (11). The utility of ICG is to provide additional visual information regarding tissue perfusion, critical vascular structures and planes of dissection (6,7,11-15).

ICG was first developed by Kodak Laboratories (Rochester, NY, USA) in 1955, for photography using near infrared (NIR) imaging technology. It was approved for medical use by the US FDA in 1959 (6,16) and the technology gradually crept into laparoscopic surgery offering real-time fluorescence angiography and assessment of vascular status of solid and hollow viscera (7,17,18).

The feasibility of ICG fluorescence for adrenal surgery was first described by Dip *et al.* in 2015 following a case series in pigs (19). They reported that adrenal fluorescence was distinct from the surrounding retroperitoneal tissue in all five animals and persisted for a mean of 4 hours.

The first clinical application of ICG in humans was made by Manny *et al.* in 2013 (20). In their case series of three patients undergoing robotic partial adrenalectomies, all of the adrenal tumours (phaeochromocytoma, lipoadenoma and follicular lymphoid hyperplasia) were hyperfluorescent. Subsequently, DeLong *et al.* reported the use of ICG in a series of five patients undergoing laparoscopic adrenal surgery and showed superior identification of adrenal vasculature and demarcation of the tumour from the retroperitoneum in all cases (11).

What is it?

ICG is an amphiphilic (water soluble), tricarbocyanine

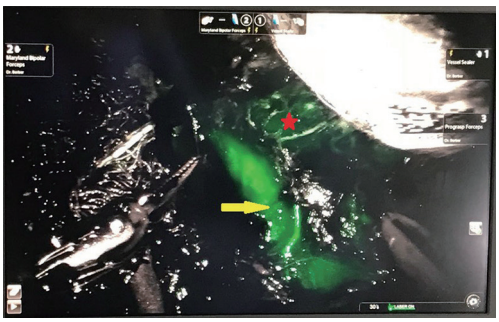

Figure 1 Photograph from robotic platform demonstrating a plane of dissection between the left renal vein (yellow arrow) and left adrenal tumour (red star) following ICG administration (original image).

organic dye (MW 751.4 Da) that exhibits fluorescence when excited by NIR light (wavelength ~800 nm).

Its use in biomedical applications is attributed to the variable concentration of ICG within different tissue types, which is related to their blood supply. Endocrine organs have an abundant blood supply and therefore are ideally suited to the use of ICG (5). In particular the adrenal glands have multiple feeding arteries and collecting veins. The mean organ blood flow of the adrenal gland is 1.87 mL/g/min, which is the third highest among the intra-abdominal organs after the spleen and renal cortex (21).

How does it work?

The mechanism of action of ICG fluorescence is incompletely understood. Upon intravenous administration, ICG becomes strongly bound to plasma proteins (especially lipoproteins) and is confined to the intravascular space (22). Its configuration is not altered by binding, resulting in a relative lack of toxicity. ICG enters the hepatic sinusoids, is uptaken by hepatocytes and ultimately excreted into bile via protein glutathione S-transferase (GST) (6).

When excited by NIR light, tissues are illuminated with light 750–800 nm corresponding to the excitation wavelength of ICG (22,23). Signal intensity is proportional to the relative blood flow to that organ (20). Furthermore, receptor mediated uptake of ICG by different tissues, depends on the differential expression of bilitranslocase, a carrier protein for ICG expressed in normal renal parenchyma (proximal and convoluted tubercles but not glomeruli) (24).

Observation of ICG fluorescence in real time provides different information based on the flow of the dye throughout the tissues. Similar to a phased CT contrast study, the arterial anatomy is first to be delineated. This is followed by the parenchyma and lastly the adrenal vein. Enhancement of the vascular anatomy is especially important when it is altered, as is the case with adrenal tumours (*Figure 1*).

Uses

Since Gagner *et al.* reported the first laparoscopic adrenalectomy in 1992, minimally invasive surgery has become the gold standard approach to remove both benign functional and non-functional tumours (25). Compared with conventional open surgery, minimal access surgery is associated with improved optics, decreased pain and wound complications and improved recovery time and cosmesis (26). On the other hand, it has eliminated tactile feedback traditionally used to determine the margin of resection.

The use of ICG in adrenal surgery is advantageous for two primary reasons. First, it provides contrast distinction between very vascular, hyperfluorescent adrenocortical tissue and less vascular, hypofluorescent retroperitoneal tissue, which helps with dissection (*Figure 2*). Secondly, it can guide cortical sparing adrenalectomy by demonstrating the borders between normal adrenal tissue and tumour when operating for phaeochromocytomas (medullary lesions). ICG also provides information in real time to the surgical team. It is quick to perform only adding minutes to the procedure. The real time feedback of ICG fluorescence helps to compensate for the lack of tactile feedback in minimally invasive surgery (27).

By contrast laparoscopic ultrasound which is a widely adopted intra-operative adjunct, requires interruption of dissection for scanning and might not be possible if there is not a good contact plane between the piezoelectric probe surface and the tissue.

In 2018 Kahramangil *et al.* characterized patterns of fluorescence exhibited by different adrenal pathological conditions in order to define the best clinical indications for the use of ICG (28). They reported that the adrenal, liver and retroperitoneal tissues all fluoresced after administration of ICG. Fluorescence of retroperitoneal tissue was transient. The liver and adrenal fluorescence persisted throughout the duration of the procedure and in particular, healthy adrenal cortical tissue was always hyperfluorescent (*Figure 3*). From 100 patients, 74% were hyperfluorescent and 26%

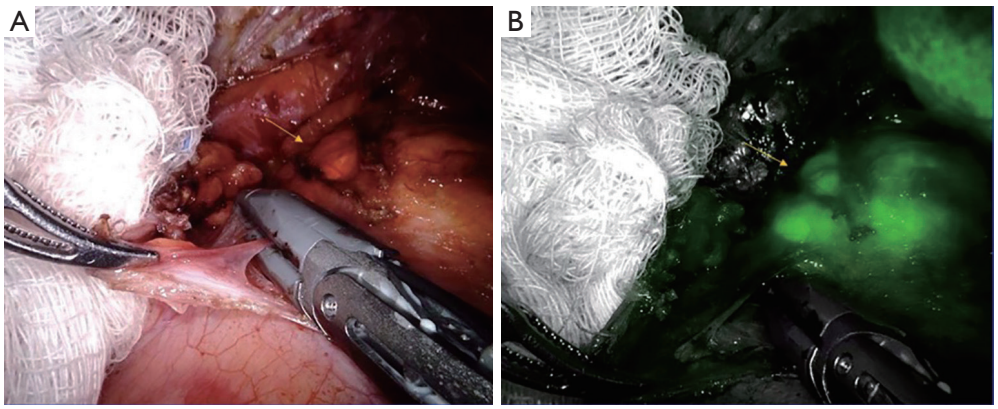

Figure 2 Photograph demonstrating the utility of ICG in delineating adrenal cortical tumours (yellow arrow) from the surrounding retroperitoneum, before ICG administration (A) and after ICG administration (B) (original image). ICG, indocyanine green.

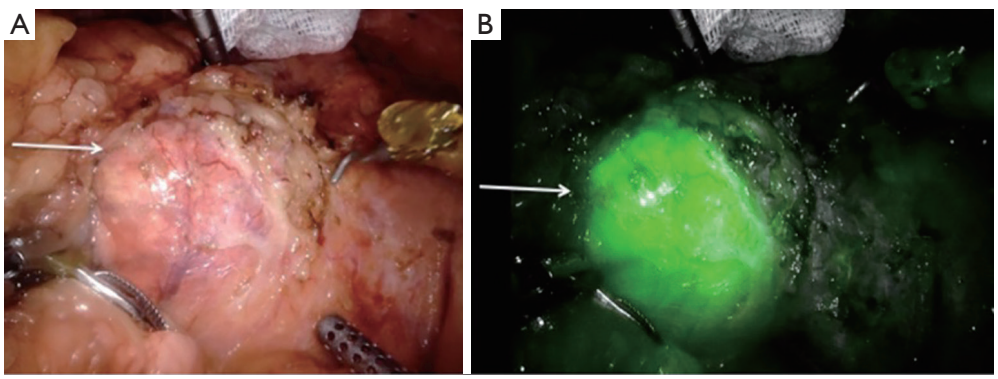

Figure 3 Photograph demonstrating hyper-fluorescence of adrenal cortical tumours (white arrow) before (A) and after ICG administration (B) (original image). ICG, indocyanine green.

were not. Exhibition of fluorescence was dependent on the histological origin (medullary *vs.* cortical). On multivariate analysis, adrenal cortical tissue origin was the only predictor of hyperfluorescence following ICG administration: 95%, 33% and 50% for tumours of adrenocortical, medullary and other tissue origins respectively. Of note, adrenal cortical cancer (ACC) manifested higher intensity of fluorescence than differentiated tumours. The weaker fluorescence from phaeochromocytomas compared with other adrenal tumours has been related to the lack of expression of bilitranslocase (20).

It should be anticipated that the utility of ICG in the resection of right sided tumours and or tumours of medullary origin will be inferior (27). The exception to this is cortical sparing resection of phaeochromocytomas where there is sufficient tissue distinction between the hyperfluorescent healthy adrenal cortex and the hypofluorescent medullary tumour.

Dosing/administration

Owing to its pharmacokinetics, the specifics of intraoperative ICG administration change with the organ system it is being used in. For adrenal surgery, our group prepares a solution by mixing 25 mg of ICG (Akron Inc., Lake Forrest, IL, USA) in 10 mL of distilled water, making a preparation with final concentration of 2.5 mg/mL (*Figure 4*). Doses less than 5 mg do not provide sufficient contrast discrimination between tissue types, whereas doses greater than 5 mg are associated with too much fluorescence and all the tissues are overexposed (29).

A single dose of this concentration (5 mg or 2 mL) is administered by the anesthetist, via a peripheral intravenous line. The timing is critical and nominated by the primary

Figure 4 Photograph of ICG vial and sterile (distilled) water required for constitution prior to intravenous administration (original image). ICG, indocyanine green.

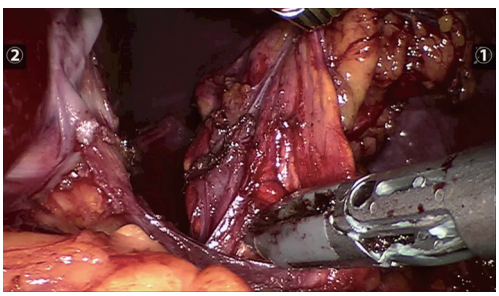

Figure 5 Photograph prior to ICG administration of left adrenal gland (original image). ICG, indocyanine green.

surgeon. ICG is most effective if it is administered after exposure of the retroperitoneum but before dissection of the adrenal gland. Typically, fluorescence of the adrenal gland and retroperitoneal tissues occurs with 30–60 s of ICG administration. Optimal contrast distinction between tissues is achieved at 5 minutes, when the retroperitoneal fat releases the ICG but the adrenocortical tissue still retains the molecule. Adrenal fluorescence can persist for up to 20 min (29,30).

Repeat doses of ICG can be administered to maintain contrast distinction if required.

The median lethal dose for ICG is relatively high (LD50 of 50–80 mg/kg) (6). In our experience most patients require an average of three doses (15 mg), irrespective of BMI and tumour size over the course of their adrenal resection (5,29).

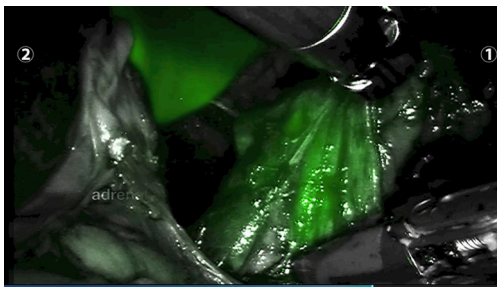

Figure 6 Photograph after ICG administration of left adrenal gland and hyper-fluorescent liver parenchyma in the background) (original image). ICG, indocyanine green.

ICG fluorescence systems are available for laparoscopic and conventional open surgery. There are multiple commercially available products. The ideal product fuses the laparoscopic or robotic images with the fluoresced images, avoiding the need to switch back and forth between platforms.

Limitations

Following administration, ICG circulates to the liver and is rapidly uptaken by hepatocytes. Hepatic fluorescence is bright and remains present for several hours, often the duration of the procedure. This can interfere with tissue plane discrimination for tumours on the right-hand side, as the hyperfluorescent liver obscures visualization of adjacent tissue (*Figures 5*,*6*). This is most problematic if the surgical approach is posterior because there is limited room for retraction of the liver in the smaller retroperitoneal space. A practical strategy to minimize this effect, is to zoom in on the adrenal gland to reduce the fraction of liver visualized in the NIR image. However, in general for right sided adrenal tumours, the lateral/anterior approach is preferable when using ICG.

Current ICG fluorescence systems provide qualitative data only. These need to be interpreted by the operating team and there may not be consensus. Ideally ICG and NIR imaging are used via a platform that integrates with the remote access set up as this enables the visual information to be visualized in real time.

Adverse reactions and contraindications

Contraindications against the use of ICG in adrenal surgery include iodine allergy, previous anaphylaxis to dye

injections, renal disease, liver disease and pregnancy (31). There have been no reported mortalities attributed to ICG.

Adverse reactions to ICG have primarily been reported to be allergic and vasovagal in nature. The rate of severe adverse reactions is 0.05% (7). In extremely rare instances (3 out of 240,000 cases in the largest reported case series), ICG has been associated with bronchospasm and cardiac arrest (32) but these were associated with administration of much higher doses (0.5 mg/kg) than is typically required (6).

Conclusions

ICG and NIR imaging are safe and useful adjuncts to remote access adrenal surgery. The intensity of fluorescence is related to differential perfusion of tissue types and expression of bilitranslocase. The pattern of fluorescence is dependent on histological origin of the tumour.

Utilization of fluorescence in adrenal surgery is particularly useful for patients requiring a subtotal resection to minimize the sequelae of adrenal insufficiency and in refractory cases where it is critical to resect all adrenal tissue. Future systems will hopefully enable quantitative interpretation.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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