



Review

Indocyanine green enhanced surgery; principle, clinical applications and future research directions

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Abstract

Over the past decade a new emergent technology has become very popular in all fields of surgery using Indocyanine green and near infrared fluorescent optical systems. This revolutionary approach overlaps conventional and near infrared images to produce highly informative intraoperative images on the anatomy and physiology of various tissues.

Near infrared fluorescence is employed for perioperative angiography in vascular mapping, assessment of anastomoses, location of sentinel lymph nodes and delineation of biliary tree anatomy, highlighting tumours and metastatic deposits, improving surgical techniques and for many other uses.

A lot of researchers have reported better surgical outcomes and technique innovations facilitated by this novel technology which although in its early stages, it lights up great interest worldwide.

This article reviews the principle of the method, the properties of the fluorescent dye, the main clinical applications and discusses future research directions.

Keywords : indocyanine green, surgery, near infrared fluorescence

Highlights

- ✓ Clinical applications of Indocyanine Green in surgery encompass all surgical subspecialties and target functional and anatomical assessment with a view of improving intraoperative timing, surgical techniques and overall outcomes.
- ✓ Future research directions for Near Infrared Fluorescence in surgery consider labeling of Indocyanine Green molecules for cancer diagnosis and therapy

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Introduction

Novel technologies with potential to revolutionize the surgical field have been proposed over the past decades with various results. Near infrared fluorescence (NIRF) guided surgery using Indocyanine Green (ICG) is a promising emerging technique which enhances the surgical optical perspective beyond conventional viewing by overlapping in real time standard and NIR acquired images (1, 2). All surgical subspecialties have reported new uses for ICG and beneficial outcomes by employing NIRF technology. Recent data suggest that supplementary characterization of blood supply and lymph nodes in colorectal surgery improves the outcomes (3-5). This is possible by complete excision of affected lymph nodes, better intraoperative views of anatomical structures, vascular mapping and prevention of anastomotic leaks (6, 7). This article reviews the basic properties of the fluorophore, the fundamentals of the imaging systems and numerous clinical uses for NIRF assisted surgery. It puts emphasis on how these clinical applications could change various surgical techniques and envisages future research directions. When first synthesized in 1959 ICG was used in photography and then clinically translated to ophthalmology and neurosurgery (8-9). For decades its uses have been limited to topical applications and laboratory research. It was only because of the advances in optical technologies that we started to view ICG as a revolutionary chromophore. This coupled with its safe clinical profile has led to an exponential spread of the NIRF enhanced surgery. The first optical devices developed less than 15 years ago had large dimensions and modest specifications. In less than 10 years they have miniaturized, increased their technical characteristics and conquered all surgical subspecialties. Today we are looking into researching ICG labeled antigens with high affinity for tumoral markers in order to identify cancerous tissues, holographic goggles projecting ICG based augmented reality and highly potent chemical substances derived from ICG (10).

Discussion

- Basics of NIR fluorescence imaging and ICG properties

Fluorescence is defined in simple terms as the emission of light from a substance which has already absorbed light or any other form of radiation. ICG is therefore a fluorescent molecule because it can re-emit light following light excitation. Since the emitted light has a lower energy than that of the absorbed radiation, its wavelength is longer. This characteristic defines all

fluorophores, but what makes ICG unique among all other clinically safe fluorescent dyes is its emission light wavelength around 830nm (11). Although this band is in the invisible spectrum it allows differentiation of the ICG emitted light from the autofluorescence generated by blood and endogenous proteins which emit at lower wavelengths; this wavelength is also advantageous because infrared light above 900nm is absorbed by water. For these reasons Methylene Blue which has a peak emission spectrum around 700nm is much more challenging to use and less specific (1). Fluorescent NIR light is able to penetrate tissues to up to 1 cm (11-13) revealing details inaccessible to the naked eye, but in the invisible spectrum. Thanks to modern optical systems conventional imaging and NIR data can be overlapped to create augmented reality images that can provide supplementary anatomical and functional data.

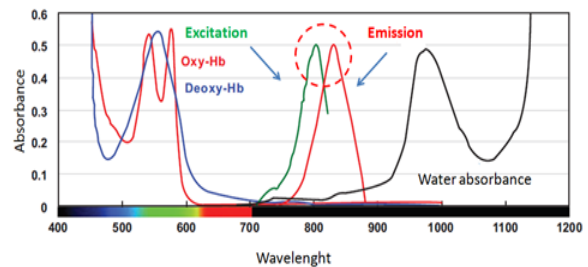


Figure 1. ICG excitation and emission spectra

Indocyanine green is an anionic tricyanin molecule with fluorescent properties when exposed to excitation lights between 750-800nm. It emits at around 830nm and has very low toxicity. ICG binds to plasma protein almost momentarily and has a relatively short half-life into the bloodstream (3-5 min). It is quickly extracted by the liver and concentrated unchanged into the bile for excretion. Since it is excreted almost entirely into the bile, ICG makes a perfect dye for visualization of biliary ducts under fatty tissues impenetrable to conventional light (14-16). Although with low toxicity and few side effects ICG is a sodium iodide compound and should not be used in patients with iodine allergy, or those suffering from certain thyroid conditions (17). ICG is unstable in aqueous solutions and needs to be used within 6 hours from reconstitution adding to the cost of using NIRF technology.

- Clinical applications

Surgeons pursuing better outcomes for their patients have imagined and used multiple uses for NIRF assisted surgery. Although initially ICG was used for clinical trials only, experimental surgery and new surgical techniques have been published by various authors (18).

- Colorectal surgery

The field of surgical techniques is constantly changing under the pressure of providing faster, safer and cheaper surgery. Colo-rectal surgeons are pursuing to improve the outcomes by lowering complications and by increasing survival rates for malignant conditions. Anastomotic leaks are reported with a frequency of up to 6-8 % depending on the site, types of anastomoses and general status of the patient (19-21). In order to reduce these numbers some authors have used ICG injected intravenously to assess the microvasculature of the bowel before fashioning anastomoses. ICG rapidly disperses into the blood stream and binds to plasma proteins. Its half live of 3 to 5 minutes allows sufficient time for assessment of perfusion at the bowel ends. Although the vast majority of the surgeons reported very good results, a recent systematic review concluded after analysing 790 papers that the lack of randomized controlled trials renders this technique promising but not backed up by strong evidence (22).

Ismael published in 2015 the first reported use of ICG in identification of the plane of resection in total mesorectal excision (TME). A small amount of ICG injected intramurally provided a pool of dye which leaked into the lymphatics progressively during the operation allowing for continuous assessment of resection limits and ensuring complete excision of the mesorectum (CME) (18).

Another closely related use of ICG in dissection techniques was reported by Kewada in 2018 in transperineal abdominopelvic resections (APRs). It consists of injection of fluorescent dye into the rectal mucosa to help delineate the posterior rectum and to identify the endopelvic fascia. Tattooing the endopelvic fascia could prevent nerve damage and contribute to lowering the morbidity associated with rectal surgery (23).

Assessment of bowel perfusion has a role in intraoperative evaluation of the ischemic bowel and in strangulated hernias. A recent concern regarding diffusion of the dye from the arterial phase into the venous circulation raised the possibility of misinterpretation of vascularization in borderline situations making intraoperative decision-making challenging. This phenomenon was observed especially when the bowel was assessed outside the optimal time frame (24).

Perhaps one of the most spectacular uses of NIRF technology consists of lymph node identification and correct designation of the apex lymph node. This allows for correct ligation of the vessels and compliance with

the most rigid oncological principles. The identification of the sentinel lymph node (SLN) is translated from breast surgery and consists of injecting ICG in albumin 30% allowing for slower absorption into the lymphatic system (25).

Although permanent tattooing is most usually employed at the time of index colonoscopy for tumour localization, ICG could be used with this purpose as well provided that tattooing is periprocedural. All of the above clinical applications have been proposed over the past decade and contributed to reshaping the approach of benign and malignant colorectal conditions. Authors who refashioned anastomoses and avoided leaks, those who performed more accurate lymphadenectomies and those who proposed new dissection techniques or mapping protocols have contributed immensely to the development of NIRF in surgical practice and reported improved outcomes. Despite these encouraging data some metaanalyses have failed to demonstrate unequivocal superiority of fluorescent assisted surgery over conventional techniques suggesting the need for larger and statistically powerful clinical studies.

- Hepatobiliary surgery

One of the most common uses of ICG enhanced surgery is hepatobiliary surgery. Although liver resections and metastasectomies are performed in selected specialized centers, cholecystectomies are performed routinely worldwide. ICG is used to visualize the anatomy of the bile ducts through fatty tissues of various thickness which cover the common bile duct (CBD). The incidence of CBD injuries associated with laparoscopic cholecystectomies is three times higher than with the use of open techniques (26). Similarly, early cholecystectomy is considered to be more dangerous than interval cholecystectomy hence the strong recommendations in some parts of Europe to avoid surgery in the index admission. We demonstrated in a small study that early laparoscopic surgery assisted with NIRF is safe and the paradigm about late cholecystectomies might suffer revision should a larger study confirms the findings (27).

The use of ICG in surgery is still a grey area since there are no definite guidelines regarding the amounts of ICG to be administered. ICG is a very safe contrast agent. Doses for intraoperative assessment have been established empirically by using different amounts of ICG in various centers utilizing NIRF technology. Like with all fluorescent dyes quenching is a major disadvantage, meaning that at high concentrations of ICG the fluorescent effect stops following a linear increase and diminishes, fluorescence being absorbed by

the fluorophore itself (28). From this point of view some authors have titrated from small concentrations to large concentrations, others have decided to administer ICG at 3 hours preoperatively, others with 24 hours before surgery. These different approaches have produced various results and established different methods. For instance, it has been empirically discovered that injection of ICG into the blood stream will help identifying liver metastases after 10-14 days because tumoral tissues will capture fluorophore molecules and will wash them out slower than normal tissues (29).

NIRF assisted surgery could be used to identify anomalies within the biliary tree and guide surgeons intraoperatively. In a recent article Coubeau affirms that biliary tract complications `remain the Achilles heel in transplant surgery` and emphasizes how vascularization of the CBD is crucial for a successful transplant. The authors presented a novel ICG based technique for assessing the donor bile duct blood supply more accurately.



Figure 2. Conventional laparoscopic view of the cystic pedicle

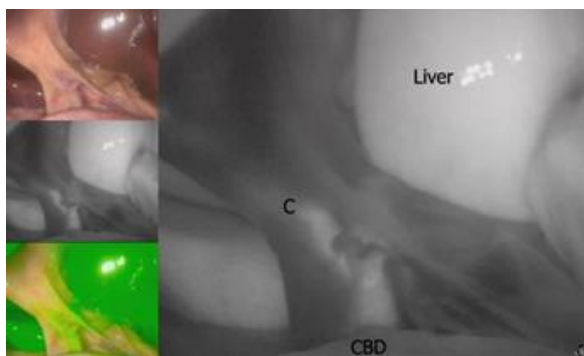


Figure 3. NIRF image showing cystic duct and CBD in augmented reality

- Plastic and breast surgery

ICGs main uses in plastic and breast surgery revolve around two main concepts: characterization of local blood supply and lymphatic assessment. Being able to observe the location and to evaluate the vascular bed of flaps and skin paddles has reduced morbidity and the need for reintervention in a lot of studies (30, 31).

Holm was the first to use this technique in 2002 on 20 flaps reporting a strong correlation between NIRF filling defects and healing issues. We have used this technique to assess the skin flaps in mastectomies in order to prevent postmastectomy skin necrosis with variable results, but in dedicated oncoplastic centers a decrease in hypo-perfusion related complications have been reported (32, 33). The use of ICG in lymphatic mapping, SLN biopsy and lymph vessel assessment has gained a lot of popularity because of good results. The specificity of fluorescent dyes in SLN identification rose up to 95%, thus avoiding the need for unnecessary axillary node dissection (33, 34).

An interesting application was described by Sakuray who performed reverse lymphatic mapping using ICG in order to perform better dissection and to predict patients at high risk for developing postoperative lymphoedema (35, 36). Experimental data showed that in vitro ICG displays enhanced fluorescent properties if combined with plasma albumin, but in vivo Hutterman found no difference between subdermal injection of ICG alone and ICG premixed with serum albumin in identification of SLN (35). There are still controversies and contradictory results in relation to the optimum doses of ICG needed for various procedures and up to date consensus has not been reached. This is because the technique is young, and fluorescence is governed by concentration dependent quenching, the chemical environment varies, and optical systems have different performances.

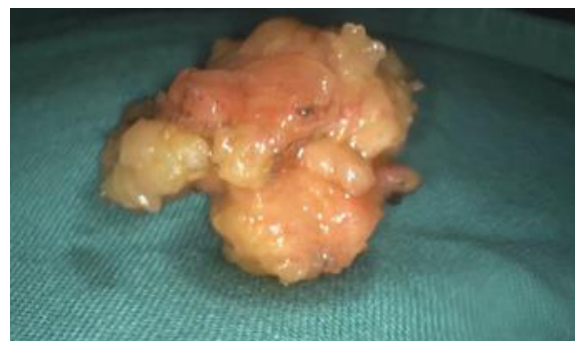


Figure 4. Conventional image of SLN

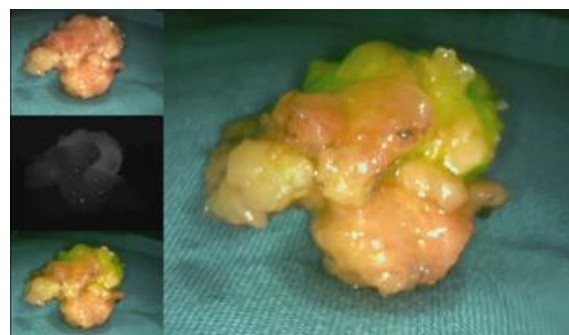


Figure 5. NIRF of SLN in augmented reality

- Endocrine surgery and miscellaneous indications

Real time intraoperative angiography of the parathyroid and adrenal glands has been recently reported. Currently intraoperative evaluation of the parathyroid glands is performed by visual inspection and postoperatively by measuring the level of parathyroid hormone. This has inferior specificity to intraoperative angiography and is easier to perform than laser Doppler flowmetry and oxygen spectroscopy (37, 38). The same technique is used in adrenal surgery to facilitate dissection of the gland from the surrounding tissues. Since ICG is relatively cheap and clinically safe, surgeons have envisaged numerous applications such as: identification of aberrant hepatic ducts, diagnosis of arterial occlusive disease, assessment of extravasation injuries associated with central lines and oncological catheters, treatment of varicose veins, identification of metastatic deposits, evaluation of gastric sleeves to predict leaks, etc. (39-42).

Conclusions; future research directions

Having reviewed the main uses of ICG in surgery one can imagine the potential of this technology and the importance of continuous research in this field. By reducing the hospital stay, the amount and the severity of complications related to surgery ICG NIRF could become affordable for smaller hospitals. Besides avoiding physical and emotional trauma in patients with postoperative complications the cost of using sophisticated technology for prevention of morbidity could be lower than the cost of treating the complications. The simple principle of ICG fluorescence has been reproduced with many artisanal devices designed and built by doctors and researchers all over the world (43). Relying on feedback from different in vivo studies we have begun to understand that different optical systems and differences in chemical composition, pH and temperature contribute to differences in reported excitation and emission spectra for ICG. From this point of view the fluorophore and the environment where it exhibits its fluorescence should be regarded as a dynamic complex (44-46).

In this direction studies related to the stability of ICG in aqueous solution, interactions with plasma proteins, changes in spectral activity and dose related efficiency have shown equivocal results. This area of research should be exploited in order to achieve a chemical compound with higher stability after reconstitution and with better fluorescent properties. Imaging systems have evolved constantly and research in this field must enhance the sensitivity of the detection

methods even further. The penetration of NIRF systems goes up to maximum depths of 10-15mm with a lot of clinical researchers reporting poor results in cohorts of patients with high BMIs. Colorectal surgery has made good progress in reducing postoperative complications using NIRF and although consistent data are lacking survival rates might be improved by more accurate dissection and identification of lymph nodes and vascular mapping. Some researchers wanted to go even further and proposed encapsulation and nanoparticle-ICG complexes in order to ensure slow release doses of ICG for tumour accumulation. ICG labelled with antibodies for targeting tumoral cells were studied in vivo on murine subjects. All the aforementioned research directions have reported modest results because binding ICG to other molecules alters its fluorescent properties (47-49).

Some tumours exhibit peculiar behavior in relation to ICG and extract small doses of fluorophore from the blood stream. Since ICG has a very short half-life it is rapidly washed out and the only remaining ICG molecules are those extracted and incorporated into the tumoral cells. This behavior might be used at staging laparoscopy to detect metastatic deposits. If used with high definition optical endoscopes ICG has a big potential in chromoendoscopy for assessment of Barrett's esophagus or inflammatory bowel diseases. We believe that NIRF will play an important role in the surgical field shortly and research in this domain should be encouraged. This article summarized the main clinical applications of ICG in surgery, introduced the NIRF technology and mentioned some future research directions.

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