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Review and Meta-analysis

Cutting-Edge Innovations: ICG Fluoroscopy in Colorectal Cancer and Liver Tumors

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Indocyanine Green (ICG) fluorescence imaging has been revolutionizing the surgical management of colorectal cancer and liver metastases by providing a dynamic real-time visualization of tissue perfusion, lymphatic pathways, and tumor margins. This innovative technology has demonstrated significant benefits in colorectal surgeries by reducing anastomotic leakage rates, enhancing vascular assessment, and improving the safety of anastomoses, thereby decreasing postoperative morbidity. In liver surgery, ICG fluorescence enables precise identification of metastatic lesions, particularly small or deep-seated tumors, and aids in achieving R0 resections with better oncological outcomes. Moreover, its capacity to visualize the boundaries of tumors intraoperatively enhances surgical precision while minimizing unnecessary tissue resection. Despite these advantages, widespread adoption of ICG fluorescence imaging is hindered by the lack of standardized protocols and reliance on subjective interpretation of fluorescence signals. Future advancements, such as quantitative fluorescence analysis, integration with artificial intelligence, and robotic-assisted platforms, are expected to overcome these limitations and further enhance the utility of ICG in surgical oncology. As a minimally invasive, cost-effective, and versatile tool, fluorescence represents a paradigm shift in the approach to managing colorectal cancer and liver metastases, offering patients safer and more precise surgical interventions.

Introduction

Indocyanine Green (ICG) is a water-soluble dye that has gained prominence in the field of medical imaging, specifically in the context of fluorescence-guided surgery. Originally approved by the Unite States Food and Drug Administration in 1959 for monitoring cardiac and liver output [1], its applications have expanded significantly in the surgical domains of colorectal cancer and liver metastasis. The unique properties of ICG, including its near-infrared fluorescence, allow for enhanced visualization of tissues, blood flow, and lymphatic drainage. This capability makes it an invaluable tool for surgeons seeking to improve the precision and safety of resection techniques.

The mechanism of action is rooted in its ability to absorb and emit light in the near-infrared spectrum, which penetrates tissues more effectively than visible light. When injected intravenously, ICG binds to plasma proteins and circulates through the bloodstream, being rapidly taken up by functional hepatocytes and extracted unaltered via the biliary system. The fluorescence provided by indocyanine green, when excited by near-infrared (NIR) light, enhances the surgeon’s ability to make real-time decisions during procedures, in terms of tissue perfusion assessment. The integration of ICG into surgical practice has been transformative in the grounds of minimally invasive techniques. Surgeons can utilize it during laparoscopic procedures, allowing for a more accurate evaluation of the vascular supply of the digestive system. By improving surgical precision to recognize poorly perfused regions and selecting them for resection and performing anastomosis

in appropriate segments, this technology can potentially decrease postoperative complications and enhance recovery times.

Clinical studies have demonstrated the efficacy of ICG in various surgical settings, with particular attention to colorectal and hepatobiliary surgeries. They indicate that the use of ICG can lead to improved identification of critical structures, such as blood vessels and lymphatic channels, during surgery. Additionally, the ability to visualize the tumor in the liver and its boundaries may significantly reduce the rates of positive surgical margins, a common challenge for surgeons. As the body of evidence supporting ICG continues to grow, it is becoming increasingly clear that this innovative tool is poised to play a central role in the future of surgical oncology.

Historical context and development

The discovery of indocyanine green as a fluorescent dye is not recent, since it has its roots in the mid-20th century, originally developed by Kodak Research Laboratories, during World War II (1939 - 1945), for photography. It is basically a sterile amphiphilic, water soluble, molecule of tricarbocyanine, whose mass weights 774,99 g/mol [2], suitable for intravenous (IV) injection. Once in the bloodstream, approximately 98% of ICG binds to plasma proteins, primarily albumin, through interactions with hydrophobic regions of these proteins. This lipophilic interaction creates a stable, non-toxic interface that reduces the risk of dye disruption. ICG is taken up by hepatocytes via carrier-mediated processes and over 80% is excreted into bile within 18 hours, following first-order kinetics with closely matched uptake and clearance rates [1]. Initially, ICG is rapidly cleared from the bloodstream into bile with a half-life of 3–4 minutes. After this rapid phase, clearance slows, with residual dye potentially persisting in the blood for over an hour.

The first medical test happened in 1957 at the Mayo Clinic, in the USA, by Dr Irwin Fox [3], and in subsequent years ICG’s applications expanded to include measuring renal blood flow (1963), detecting cardiac murmurs (1965), and retinal angiography in ophthalmology (1970s). Technological limitations at that time prevented extensive development of ICG fluorescent angiography until the mid-1990s, and widespread acceptance of the technique was further delayed until the early 2000s when improved digital imaging resolution provided a satisfactory alternative to film-based photography [4]. The versatility of fluoroscopy is demonstrated in Figure 1, in which a few drops of indocyanine green were applied in the disk of a daisy flower, and then seen through fluorescence imaging.

Figure 1. Demonstration of Fluorescence in a Daisy Flower, whose stigma – the top of pistil, in the disk florets – was soaked with ICG (authors’ personal archive, picture taken during the European Society of Surgical Oncology Course on Fluorescence-guided Surgery, in Leiden, Netherlands, June 2024).

Today, ICG is getting more and more widely used to analyze tissue perfusion in various advanced medical procedures, including aneurysm surgery, gastrointestinal and hepatobiliary surgery, and lymphangiography, reflecting its versatility and importance in modern medicine. Its application in surgical oncology gained momentum as researchers explored its potential in tumor identification and sentinel lymph node localization. Surgeons began to adopt these techniques in clinical practice, driven by studies demonstrating that ICG-guided resections could significantly enhance the identification of anatomical areas that are mal perfused in the gastrointestinal system. This transition was further supported by the development of training programs and workshops aimed at equipping surgeons with the necessary skills to implement ICG fluorescence in their practice.

Mechanisms of action in medical imaging

According to Baldari et al. [2], fluorescence is the property of molecules, called fluorochromes, to emit radiation when excited by a source of energy, such as laser beams or near-infrared light, at

certain wavelengths. Once this energy is absorbed, there is a delocalization of electrons from a ground state to a higher level; on returning to initial state, the energy is emitted as photons. Those photons can be recognized as fluorescence of a specific wavelength. Figure 2, below, summarizes that scheme.

Figure 2. Demonstration of Fluorescence Principles, Extracted from Baldari et al. [2].

ICG becomes fluorescent once exposed to light in the NIR spectrum (wavelength ranging from 800nm to 1000nm), delivered by a special device. Detection of fluorescence is not able through the naked eye, because the range of the visible spectrum lays between 400nm and 700nm, therefore a specific scope is needed. The image received by the camera is transmitted to a video screen, enabling the surgical team to visualize the areas where the dye is accumulated in the organic tissue. The integration of ICG fluoroscopy into surgical practice is facilitated by the development of sophisticated imaging systems that utilize advanced near-infrared cameras. Those systems are designed to capture the fluorescent signals emitted by ICG, translating them into high-resolution images in the operation room (Figure 3).

Figure 3. (1) IV Injection of ICG; (2) Binding to Plasma Proteins; (3) circulating in the bloodstream excited by NIR light; (4) fluorescence detected by laparoscopy, before been transmitted to a monitor; adapted from Baldari et al. [2].

After being pushed intravenously, ICG rapidly links to proteins in the blood plasma, especially lipoproteins, having minimal leakage for the interstitium. There are no metabolites, and the excretion happens unaltered via the liver without conjugation in bile. The clearance speed depends on liver function and vascularization, but it is fast, around eight minutes. At the cellular level, the behavior of ICG is characterized by its rapid accumulation in tissues with high blood flow and its affinity for certain cellular structures. In liver metastasis, malignant tissues often exhibit altered vascularization and perfusion patterns compared to normal tissues. As ICG circulates, it preferentially accumulates in such abnormal vascular networks, allowing for clear differentiation between cancerous and healthy tissues. The phenomenon of enhanced permeability and retention, commonly observed in tumors, further amplifies the imaging contrast provided by ICG, thereby enabling surgeons to visualize tumor margins more effectively during liver resection.

The application of ICG in laparoscopic and robotic- assisted surgeries, exemplifies the innovative potential of this technology. The minimally invasive approach, combined with high-quality imaging, allows for precise navigation and minimizes trauma to surrounding tissues, allowing surgeons to assess optimal tissue perfusion in different organs, being the digestive system one of the most common uses. Also, the lymphatic drainage pathways and sentinel lymph nodes can be identified, which is a fundamental step for staging and treatment planning of some malignancies such as breast, melanoma and, most recently, uterine cancer.

The role of ICG fluoroscopy in colorectal surgery

Indocyanine green has emerged as an outstanding tool in surgical oncology, particularly in the context of surgical resection for colorectal cancer. This is beneficial in identifying relevant anatomical landmarks and assessing colonic tissue perfusion (also called visceral angiography), which are required for intestinal removal and successful reconstructions, preventing ischemic complications. Surgeons can identify poorly perfused areas that may require additional resection, during mesenteric division. This capability is more relevant in complex cases, including patients with pre-existing vascular compromise or those undergoing extensive procedures. The use of ICG for perfusion assessment has been shown to significantly reduce the incidence of postoperative

complications, improving patient outcomes. The application of ICG also extends to lymphatic mapping in colorectal cancer surgery. By injecting indocyanine green into the tumor or surrounding tissue, surgeons can visualize sentinel lymph nodes, facilitating a more accurate staging of the disease and guiding the extent of lymphadenectomy. Alius et al. [5] compared the results of 12 clinical studies regarding the role of ICG in identifying sentinel lymph nodes in colon cancer surgery. A total of 337 patients were enrolled, preoperatory classified into stages I or II, in which nodal metastases was excluded by computed tomography and magnetic resonance imaging. The results showed the detection rate of ICG up to 90%–95%, considering it useful in lymphography and locating sentinel lymph nodes in colorectal cancer. The identification of sentinel nodes can lead to a tailored approach to lymph node dissection, minimizing morbidity while ensuring comprehensive oncological treatment.

Optimal dose of ICG injection in colorectal surgery

Research has demonstrated that the effective dose of ICG can vary based on multiple factors, including specific surgical techniques employed, patient's body weight, and tumor burden. Generally, a range of 5 to 10 mg of ICG is applied in colorectal surgeries, but there are different protocols followed by distinct surgical groups. Baldari et al. [2] recommend a concentration dose of 0.2 mg/kg, to be diluted with 10ml of sterile water, pushed IV in boluses of 3 ml. This dosage has been found to provide sufficient fluorescence for effective intraoperative navigation, identifying vascular structures and assessing tissue perfusion. Lower doses may not yield adequate visibility, while higher doses could lead to unnecessary complications or prolonged imaging times. Figure 4, from a systematic review conducted by Christofi et al. [6], shows a variety of devices and dosages reported in 11 studies, stating that it lacks standardization in determining the optimum ICG dose.

Figure 4. Different sets of Fluorescence Imaging Devices and ICG Dosage among 11 Studies Compiled in a Meta-analysis by Christofi et al. [6]; BW, Body Weight.

The timing of ICG administration also plays a pivotal role in its effectiveness during surgery. Several studies have measured the fluorescence intensity of ICG and its behavior over time for optimal signaling during colorectal operations [7,8], showing similar distribution curves. After a latency period of 5 to 40 seconds, depending on the injected dose and concentration of ICG, fluorescence starts to glow in a slope, reaching a peak after 15 to 20 seconds. It decays slowly reaching 50% or initial intensity after 25 to 60 seconds (time to half of maximal fluorescence). The ratio of perfusion time corresponds to the reason between time to reach half of maximal fluorescence (T1/2MAX) and time to reach maximal fluorescence (TMAX), as it can be seen in Figure 5.

Figure 5. Pattern of Time-fluorescence Curve of ICG Angiography, Described by Ahn et al. [8], using a dose of 0.25 mg/kg diluted in 10ml of distilled water, injected slowly for 10 seconds; it shows the latency period (FMIN) until fluorescence glows, reaching the maximal fluorescence intensity (FMAX) at a time (TMAX), making the fluorescence rising slope (FMAX/TMAX), the time to half (T1/2MAX) of maximal fluorescence (F1/2MAX), and perfusion time ratio (TR = T1/2MAX / TMAX).

When a second injection of ICG is pushed IV after 1 to 3 minutes from the first bolus, the latency period overlaps with the ongoing decaying phase and a second peak of fluorescence occurs, however its maximal intensity tends to be around 10% lower than the first peak, as it can be seen by the area under the curve in Figure 6.

Figure 6. Change of Fluorescence Intensity During ICG Angiography at the Proximal Anastomotic Site in

Patients with a Second Peak of Fluorescence Intensity (AU, area under the curve), According to the Quantitative Evaluation Study of Anastomotic Perfusion During Colorectal Surgery, Performed by Kong et al. [9].

Does ICG improve results in colon resection and anastomosis?

Numerous studies have indicated that ICG can significantly improve the identification of perfusion patterns in bowel segments. By visualizing blood supply, surgeons can avoid areas with compromised perfusion, which are at higher risk for ischemia and subsequent necrosis. This technology can also aid the assessment of anastomotic sites, allowing for better decision-making regarding the location and type of anastomosis, ultimately leading to enhanced patient outcomes. Results have shown that the implementation of ICG fluorescence imaging can lead to lower rates of postoperative morbidity, related to anastomotic leaks and infections. These benefits are important in the context of colorectal cancer, where the goal is not only to achieve complete resection but also to minimize the impact of surgery on the patient's overall health and recovery. In the last decade the integration of ICG into the surgical workflow has been facilitated by advancements in imaging technologies and surgical instruments. The ease of use and immediate feedback provided by fluorescence imaging enable surgeons to make informed decisions on the fly, thereby enhancing their confidence during complex procedures. This innovation aligns with the trend towards minimally invasive approaches, where the reduction in surgical trauma is known to improve patient recovery. In despite of that, there is still debate around the contribution of ICG in reducing anastomotic complications.

Two recent large meta-analyses have found significant reduction in anastomotic leakage rates in studies comparing outcomes from ICG and non-ICG assisted procedures. Lin et al. [10] compared 3,137 patients across 11 studies showing that fluorescence not only reduced the rates of anastomotic leakage (OR, odds ratio = 0.31; 95% CI – confidence interval – 0.21 to 0.44; $p<0.0001$), but also postoperative complications (OR = 0.70; 95% CI 0.51 to 0.96; $p<0.025$), and reoperations (OR = 0.334; 95% CI 0.16 to 0.68; $p=0.003$) compared to surgery without ICG assessment. However not significantly affecting operation time or surgical site infection rates, those findings suggest ICG's potential in lowering anastomotic complications after colon and rectal cancer operations. Considering only rectal surgery, Xia et al. [11], in a meta-analysis of 22 studies involving 4,738 patients, demonstrated that using ICG significantly reduced overall anastomotic (RR, relative risk = 0.46) and type A (subclinical) leakage (RR = 0.25). ICG angiography did not significantly reduce clinically relevant leakages, classified as types B (RR = 0.70) and C (RR = 0.97).

The assessment of anastomotic perfusion at the time of rectosigmoid resection and stapled anastomosis has been prospectively investigated via NIR proctoscopy in a group of 133 patients undergoing cytoreductive surgeries for gynecologic malignancies in a six-years cohort (from January, 2013 to December, 2018), and paired for comparison with other 277 patients operated in the same period, who were not assessed by fluoroscopy [12]. The anastomotic leak rate in the NIR group was 1.5% (2/133) compared to 4.7% (13/277) in the non-NIR ($p=0.16$); also, diverting ostomy was performed significantly less in NIR patients (6.8% vs. 19.9%, $p<0.001$). Postoperative abscesses occurred in 6.0% of NIR patients versus 15.9% in the non-NIR cases ($p=0.004$). The NIR group also had fewer interventional procedures (9.0% vs. 19.9%, $p=0.006$) and 30-day readmissions (10.5% vs. 22%, $p=0.004$). Authors concluded that fluorescence proctoscopy is a promising tool in rectal anastomosis perfusion assessment to be added to cancer surgeries. While these findings support ICG's potential, multicenter randomized controlled trials with larger samples are needed to validate those benefits comprehensively.

Integrating ICG fluoroscopy in liver cancer surgery

One of the significant advantages of ICG fluoroscopy is its ability to delineate healthy liver tissue from liver cancer. Such mechanism is predicated by its unique property upon administration: the green dye bound to plasma proteins is predominantly taken up by hepatocytes via receptor-

mediated endocytosis, and extracted exclusively in the biliary system almost intact. Hepatic cancerous tissues present in hepatocellular carcinoma (HCC) often show impaired bile excretion due to disrupted pathways, leading to slower or incomplete clearance from these areas. For liver metastasis ICG is retained in noncancerous cells around (and compressed by) the metastatic lesion, which are also deficient in normal bile secretion. For both situations, fluorescence can be identified by NIR light in a very late period (typically 24 to 48 hours) after IV injection, making it a suitable technique in the operation room.

Such findings were initially described in the pioneering studies from Takeaki Ishizawa and his team from the University of Tokyo, Japan. After applying fluorescent imaging to develop intraoperative cholangiography in HCC patients, they observed that HCCs fluoresced strongly even before the intrabiliary injection of ICG for cholangiography. Because these patients had received an intravenous injection of ICG for a routine liver function test before surgery, they hypothesized that hepatocarcinomas fluoresced because they had retained the preoperatively injected dye as a result of biliary excretion disorders in the cancerous tissues. From those experiences, they developed novel imaging techniques that enabled highly sensitive identification of liver cancers using ICG [13]. At the same year, Gotoh et al. [14] published similar results in a group of ten HCC patients, being able to identify all cases through fluoroscopy and additionally new HCC nodules in four cases.

According to Dai et al. [1], at least two meta- analyses pointed out an association between ICG-guided laparoscopic hepatectomy, lower complications, and better outcomes when compared to non-ICG surgeries. Liu et al. [15] analyzed six studies, encompassing 417 patients, and demonstrated that fluorescence-imaging significantly reduced operative time [weighted mean differences (WMD) = -20.81 minutes, 95% CI, -28.02 to -13.59, p=0.000], intraoperative blood loss (WMD = -108.16 mL), and hospital stay (WMD = -1.23 days). It also decreased the incidence of postoperative complications (OR = 0.49; 95% CI, 0.26-0.91, p=0.025). However, no significant differences were observed in blood transfusion rates, hilar occlusion time, or surgical margin clearance between the two groups. These findings suggest that ICG enhances safety and efficiency of laparoscopic hepatectomy.

Use of ICG in localizing hepatic tumors and determining resection margins

As shown, timing plays a crucial role in ICG application for liver visualization. Baldari et al. [2] recommend an intravenous injection of 0.4 mg/kg of ICG solution 36 hours prior to surgery to enhance lesions identification, while other surgical teams use a dose of 0.25 mg/kg and 0.5 mg/kg, 24 hours before the procedure [16, 17]. All of them agree that the primary goal for ICG-enhanced fluorescence imaging on liver cancer surgery relies on localizing subcapsular lesion and helping surgeons to determine accurate resection margins, achieving R0 resection.

Ishizawa et al. [13] showed that indocyanine green is extremely sensitive in detecting liver tumors. In their remarkable study, ICG was injected IV to assess liver function prior to resection in 37 patients with HCC and 12 with liver metastasis of colorectal carcinoma. From those patients, 20 with HCC and 6 with metastasis underwent intraoperative ICG-fluorescent imaging of the liver surface and all surgical specimens (63 HCC and 28 metastatic nodules) were later analyzed using a NIR camera system. Specimens of HCCs appeared as uniformly fluorescing lesions, while metastases were delineated as rim-fluorescing aspect. Most importantly, fluorescent microscopy confirmed that fluorescence originated in the cytoplasm and pseudoglands of HCC and in the non-tumorous liver parenchyma surrounding metastases. During surgery, ICG identified 51% of the HCCs and 100% liver metastases. Their findings and description of fluorescence types helped surgeons understand the patterns of ICG visualization necessary to effectively identify liver tumors and perform accurate resections. As an example of liver tumor impregnation of indocyanine green, Figure 7 shows a specimen of hepatocarcinoma, in which ICG was applied prior to surgical

resection and fluorescence is still captured in the slide.

Figure 7. Segment of a Surgical Specimen of Hepatocarcinoma Fixed in Slide for Pathological Analysis (a) and Its View under Fluoroscopy – as NIR/ICG Monochromatic Mode (b), Intensity Map Mode (c), Overlay Mode (d) – and Regular white Light (e). Demonstrative picture taken during the European Society of Surgical Oncology Course on Fluorescence-guided Surgery, in Leiden, Netherlands, June 2024 (personal archive).

After this groundbreaking study, the feasibility of accurate surgical margins was assessed by Aoki et al. [18], who obtained 100% pathologically negative surgical margins in liver tumor resections in a series of 25 patients (12 colorectal individuals with 17 metastases) using laparoscopic fluorescence navigation. They were compared with 72 other patients (40 with colorectal metastasis) who underwent laparoscopic liver resection (81 nodules) without ICG fluorescence. In both groups, intraoperative ultrasonography using a flexible laparoscopic probe was used to assess the entire liver. ICG dosing was 0.5 mg/kg intravenously administered 2 to 14 days prior to surgery. Five lesions could only be found through ICG and not through normal laparoscopic imaging. Among the cases operated without ICG technology, four lesions were found to have a positive margin (R1 status, p=0.57). Statistical differences were not found either for other variables analyzed, such as complications, operative time, blood loss, and hospital stay. It was a small group analysis, however it showed the potential of ICG for improving the intraoperative liver examination and tumor location in determining the transection of liver parenchymal tissue with a tumor-free surgical margin.

A most recent study [19] evaluated the use of NIR fluorescence imaging with ICG to guide laparoscopic hepatectomy exclusively for colorectal metastases, aiming to determine its usefulness in securing free surgical margins. Fifty-nine patients (with a total of 94 tumors) were assessed at Sapporo Medical University Hospital, in Hokkaido (Japan), and received IV ICG 1-2 days before surgery for intraoperative fluorescence imaging. They successfully identified 59.6% of tumors (56 lesions) on the liver surface, achieving clear pathological margins (R0 resection) in 96.6% of patients (57/59). Pathological analysis revealed no tumor cells in areas of NIR fluorescence, with a median fluorescent margin distance of 1.074 mm. Those findings suggest, once again, that ICG fluorescence-guided hepatectomy enhances tumor identification and improves margin clearance, offering a reliable method to reduce positive resection margins in patients with colorectal liver metastases.

Can ICG change surgical decision?

In colorectal cancer surgeries, its primary application lies in assessing bowel perfusion, aiding in precise resections and secure anastomoses. This capability can significantly influence surgical strategy, encouraging a more extensive resection when necessary or a conservative approach when adequate perfusion can be visualized. Fluorescence may be also valuable in emergency surgeries, where assessing bowel viability is challenging. A group of surgeons from the Department of Surgery in Geneva University Hospitals and Medical School, prospectively evaluated 56 consecutive patients operated due to abdominal emergency indications, during 2014 and 2015, either through laparoscopy or laparotomy [20]. The primary endpoint was the modification of surgical strategy after ICG bowel assessment. The majority of cases were adhesions and internal hernias (32.1%), and occlusive intestinal tumors (21.5%). In 18 patients (32% or the cohort), the NIR angiography led to a change in surgical decision; from those, in 12 cases (67%) it was opted to a more conservative strategy, not performing resection, as initially thought. So far this is the only retrospective study available in PubMed focusing on surgical decision based on NIR-ICG intraoperative assessment.

The ARIES (ARtificial Intelligence in Emergency and trauma Surgery) project, promoted by the World Society of Emergency Surgery, aiming to investigate the knowledge, attitudes, and practices

of acute care surgeons, implemented a survey on fluorescence-guided surgery in the emergency setting [21]. Between March and April 2023, a questionnaire composed of 27 questions was sent to 200 emergency surgeons, with a response rate of 96% (192 questionnaires), from 31 countries. Respondents indicated that ICG fluorescence can support challenging surgical procedures, especially in cases of severe inflammation and bowel viability assessment. However, concerns were raised about the availability of fluorescence imaging in emergencies. Only 45.3% had access to fluorescence imaging for both elective and emergency surgeries, while 32.3% use it only for elective procedures. A mere 1% reported consistent changes in intraoperative decisions due to ICG. Expert consensus and increased accessibility are essential to integrate ICG fluorescence into routine surgical practice effectively.

Limitations of fluoroscopic technique

The first to be mentioned relies on its dependence on equipment and surgical experience with fluoroscopy. Suboptimal imaging can lead to misinterpretation of anatomical structures, which is critical in complex surgical resections. Variability in machine calibration, as well as differences in operator experience and proficiency, can result in inconsistent outcomes. Consequently, ongoing training and adherence to best practices are necessary to maximize the effectiveness of fluoroscopy in surgical settings. Another aspect to consider is the dye agent used in fluoroscopic imaging. While indocyanine green has shown promise in improving visualization during surgeries, its effectiveness can be influenced by factors such as tissue perfusion, timing and dosing of administration, since there is still no standardization in terms of ICG dosing for optimal fluorescence visualization.

In addition, most prior studies comparing outcomes for ICG in intestinal leakage were small-scale, single-center, and lacked comparable protocols for ICG angiography. Moreover, evaluations often relied on subjective surgeon judgment. It is important to notice that the liver assessment through fluoroscopy is not free from false positive images, since some benign lesions or regenerative nodules may also retain ICG, potentially leading to misidentification [13]. In order to improve its clinical application, the development of quantitative analysis for objective assessment of fluorescence might be considered the next step in research. Fortunately, in recent years, artificial intelligence is being integrated into minimally invasive surgery, with promising results in analyzing fluoroscopy and guiding surgeons into the most appropriated resection site.

Finally, although ICG-related side effects are rare, allergic reactions may occur, mainly when a patient has a personal history of contrast allergy. ICG solutions contain a trace amount of iodine, which is a component of solution used on computed tomographies. Therefore, it is necessary to review a patient’s allergy history before performing ICG angiography; it is also important to monitor for reactions during the surgical procedure [22].

Future directions in ICG fluoroscopy

Robotic surgery has emerged as a transformative approach in the realm of surgical oncology, including digestive cancer. The integration of robotic platforms into surgical practice capitalizes on advanced imaging technologies, such as indocyanine green fluorescence. Since 2010 NIR has been coupled into the daVinci® System platform, creating a synergic combination that not only facilitates enhanced surgical navigation but also aids in the early identification of several anatomical landmarks, ultimately improving the efficacy of intestinal resections [23].

One of the primary advantages of robotic surgery is its ability to provide surgeons with a three-dimensional view of the surgical field, combined with the dexterity of robotic instruments. This feature is beneficial in complex resections where traditional techniques may be limited by human ergonomics. The articulated arms of robotic systems can maneuver in tight spaces, reducing the

need for large incisions and minimizing tissue trauma. Consequently, patients often experience reduced postoperative pain, shorter recovery times, and lower rates of complications, which are important considerations in the management of complex cancers. The application of ICG fluorescence in robotic-assisted surgeries further enhances the precision of tumor resections, representing a significant advancement in the management of colorectal cancer. For medical professionals, staying abreast of these innovations is imperative for optimizing patient care and ensuring the successful implementation of cutting-edge surgical technologies.

Artificial Intelligence (AI) integration into the quantification of tissue perfusion during indocyanine green fluoroscopy can evolve to directly influence surgical decision regarding resections. AI algorithms have been developed to analyze ICG fluorescence data in real-time, providing surgeons with vital information about perfusion dynamics during operative procedures. These algorithms can identify variations in perfusion that may not be recognizable to the naked eye, allowing for a more nuanced understanding of the vascular supply to the digestive system. While some commercial NIR systems already incorporate basic fluorescence signal enhancement and estimation, integrating advanced AI methods could provide actionable predictions. This is effective during the dynamic inflow-outflow phase, which occurs within seconds to minutes after administering ICG or similar fluorophores. AI could optimize the interpretation of these signals, enabling more precise and timely decisions in surgical procedures [24].

Furthermore, machine learning technology can be applied to large datasets of ICG fluorescence images, enabling the development of predictive models that can forecast perfusion patterns based on individual patient characteristics. By training these models on diverse patient data, AI can assist in identifying those areas at higher risk for mal perfusion and guide surgeons on the tailored surgical resections. Currently, systems capable of performing AI assessment of tissue perfusion, such as the CLASSICA-OR, are being developed and have their prototypes validated [25].

In conclusion, in the current review, we have explored the transformative role of indocyanine green fluorescence in the surgical management of colorectal cancer and liver metastases. This innovative technology has demonstrated remarkable potential in digestive surgeries, by assessing bowel perfusion aiming to reduce anastomotic leakage rates and improving surgical safety. Additionally, we have highlighted its effectiveness in hepatic surgeries, where ICG enables precise localization of metastatic lesions and facilitates R0 resections. The versatility of fluoroscopy is also briefly discussed in lymphatic mapping. Despite its clear advantages, key challenges are emphasized, including the absence of standardized protocols, the reliance on subjective imaging interpretation, and limited access in certain healthcare settings. Future advancements in ICG use should focus on integrating artificial intelligence to quantify fluorescence signals, refining imaging techniques for broader applicability, and conducting multicenter randomized trials to establish robust evidence and international guidelines. With these developments, ICG fluorescence imaging is poised to solidify its role as a cornerstone in modern surgical oncology, improving precision, patient safety, and long-term outcomes in complex colorectal and hepatic procedures.

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