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Review Article

Indocyanine green fluorescence imaging: A novel adjunct to gastrointestinal surgery

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ABSTRACT

Indocyanine Green (ICG) has been applied in medicine since the late 50s for cardiac output measurement, to study the anatomy of Retinal vasculature, and liver functional reserve before major hepatectomy in cirrhotic livers. The dye can be injected into the human bloodstream with practically no adverse effects. ICG fluorescence imaging is advantageous in being compatible with the biochemical characteristics of living tissues. ICG has been used in medical science for the last several decades. However, its use in surgery has recently been explored and has found vast applications in the surgical field. In particular, its use in Gastrointestinal (GI) surgery including hepatobiliary surgery has started to define new trends and techniques to guide the modern surgeon in both simple and complex procedures. In this review we thus explore in light of recent literature the potential uses of ICG in GI surgery.

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1. Introduction

ICG has been used in medicine since the late 50s[1–3] to measure cardiac output,[4,5] to study the anatomy of the retinal vessels,[1] and to measure liver functional reserve before hepatic resection in cirrhotic livers.[6] The dye, ICG, can be injected into the bloodstream with practically no adverse effects.[7]

ICG has an excitation wavelength that produces maximum fluorescence at 800 nm, and the maximum fluorescence in the plasma of humans occurs at 840 nm.[8] It is known that ICG binds strongly to plasma proteins and in the absence of capillary protein leakage, it is exclusively distributed within the intravascular space. Excitation and fluorescence lights can deeply penetrate living tissues and results in fluorescence of ICG. ICG fluorescence imaging has the advantage of being compatible with the biochemical characteristics of living tissues.[9]

The fluorescence can be detected using specific scopes and cameras and then transmitted to a standard monitor allowing identification of anatomical structures where the dye is present (i.e., biliary ducts, vessels, lymph nodes, etc.[10]

ICG when given direct into tissues migrates in lymphatics and lymph nodes, providing an intraoperative map of tumor-specific draining area[11] and is emerging as the preferred modality for lymphatic mapping in colon and rectal cancer.

With so many potential clinical implications and utilities of ICG, our aim is to review the literature regarding ICG and its applicability in Gastrointestinal surgery so that same can applied to our patients at a high volume center and later validated in future studies

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2. Role of ICG In Intraoperative Anastomotic Perfusion Assessment

Anastomotic leak following esophageal resection continues to be a source of considerable morbidity and mortality.[12] At present, perfusion to the gastric conduit is subjectively assessed by clinical signs by way of color, temperature, and pulsation of vessels; however, these parameters do not reliably correspond to perfusion[13–15] and are not infallible. In the last decade, there has been growing interest in the use of indocyanine green (ICG) fluorescence angiography for intraoperative evaluation of gastrointestinal anastomoses

Anastomotic leaks following esophageal resections are a source of considerable morbidity and mortality and even in high-volume centers leak rates range from 5-40 %.[16–19] Anastomotic leaks often lead to an increased length of hospital stay with an increased need for further interventions like percutaneous drainage, IV antibiotics, and delayed oral feeding. Every attempt is made to make the anastomosis successful. Despite so many technical modifications it remains to haunt surgeons. Besides several factors, ischemia of the conduit is felt to be the single most determinant of anastomotic disruption owing to the tenuous blood supply at the tip of the conduit. Objective assessment of vascular supply at the anastomotic site has been sought after and ICG fluorescence angiography has been vouched as one potential methods for the same. It can objectively determine the perfusion at the proposed anastomotic site (Figure 1) and post anastomosis (Figure 2). ICG is given at 0.2-0.5 mg/kg and within seconds the fluorescence in tissues is observed. This can also be compared with other tissues and if needed revision of conduit tip to well perfused area can be done.

Meta analysis by Farah Ladak et.al[20] to compare ICG with intraoperative perfusion-improving interventions when needed to no ICG use. They included 17 studies in their final analysis. They found the pooled sensitivity and specificity of ICG for predicting postoperative leak were 0.78 (0.52-0.94; p=0.0889) and 0.74 (0.61-0.84; p=0.0116) respectively. The diagnostic odds ratio was 8.94 (1.24-64.21; p=0.1841). The absolute risk reduction with ICG was significant and was found to be 69 %. This is a promising finding and has the potential to obviate the significant morbidity and mortality associated with anastomotic leaks.

However, perfusion is not the sole factor in determining the anastomotic outcome. Other factors like tension, distal obstruction, and surgical technique are equally important in the good outcome of anastomosis. Perfusion assessment intraoperatively by an objective method like ICG fluorescence, when it matters the most as any possible revision or further resection can be done to improve the outcome and well-perfused bowel can be anastomosed. Anastomosing well-perfused ends will also decrease future chances of anastomotic strictures as strictures usually develop in compromised bowel segments. This is particularly important in Colonic replacement of esophagus in high corrosive strictures where anastomotic stricture rates are very high (30-40%) and require post operative anastomotic dilatations.

3. Role of ICG In Cancer Surgeries

Sentinel lymph node sampling has been utilized successfully for breast cancers and melanomas. Recently this concept has been extended to many more cancers with the aim of limiting lymphatic clearance to involved or more likely to be involved stations or avoiding clearance in case of negative sentinel lymph nodes and thus a more conservative surgery yet appropriate in the particular scenario is performed. Lymphadenectomy is a source of morbidity however oncologically necessary. Tapering Lymphadenectomy without affecting oncological outcomes is desired. ICG can help to locate sentinel lymph nodes and thus can be effective tool in oncological surgeries. Sentinel lymph node sampling has been recently extended to many GI surgeries including gastric and colonic cancer. Mitsuo Kusano et. Al[21] performed a study regarding sentinel node mapping by ICG fluorescence imaging for gastric and colonic cancer. Their series consisted of 22 patients with gastric cancer and 26 patients with colorectal cancer who had undergone standard surgical resection

They injected 0.5 % ICG solution into the subserosa of the gastric or colorectal wall at 4 sites (0.5 ml each) around the tumor. ICG fluorescence images were obtained using an infrared camera system. They didn't find any complications or adverse events associated with the ICG injection. Lymphatic vessels draining the main tumor were detected in all the patients. The lymph nodes draining ICG appeared as round spots of clear fluorescence and were considered to represent the sentinel lymph nodes. Lymph nodes were dissected from the specimen and examined for internal fluorescence. All fluorescent lymph nodes were considered as sentinel lymph nodes.

At least one sentinel lymph node was detected in 20 (90.9%) of patients with gastric cancer and 23 (88.5%) of the 26 patients with colorectal cancer. The mean number of sentinel lymph nodes was 3.6 +4.5 in patients with gastric cancer and 2.6 + 2.4 in patients with colorectal cancer. The accuracy and false-negative rates and positive and negative predictive values were 70.0% (14/20 patients) and 60.0% (6/10), and 100% (4/4) and 62.5% (10/16), respectively, in patients with gastric cancer, and 82.6% (19/23) and 66.7% (2/3), and 100% (2/2) and 81.0% (17/21), respectively, in patients with colorectal cancer.

The most important clinical implication of the SN concept in gastrointestinal cancer is the possibility of less invasive surgery in SN-negative cases. For minimally invasive treatments based on SN biopsy assessment of lymph node metastasis is crucial. However false negative results have been recognized to a certain extent in dye guided (ICG and Methylene Blue) as well as radio-

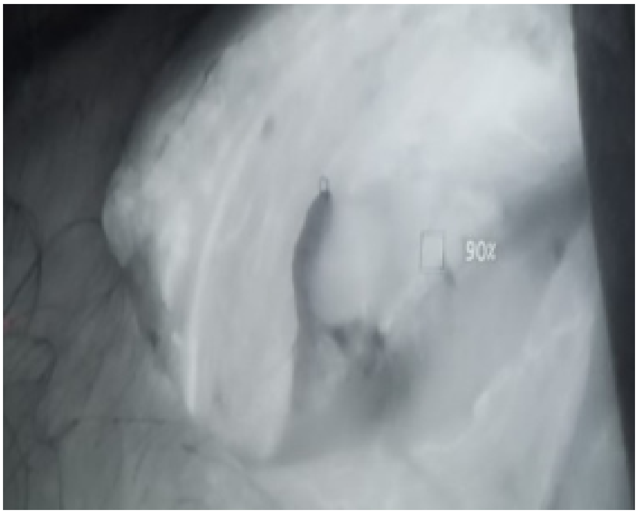


Figure 1: Black and White contrast mode showing 90% perfusion at conduit tip

Figure 2: post anastomosis perfusion 80%

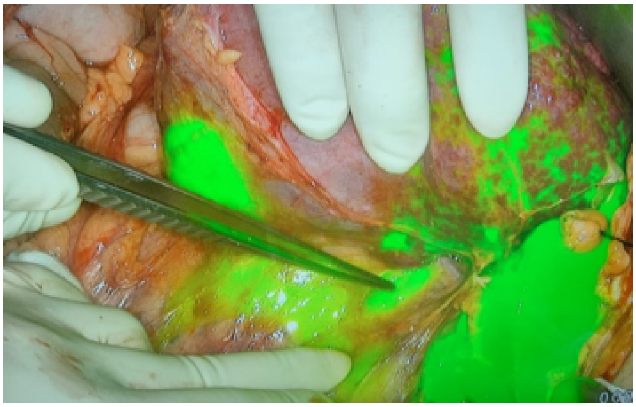
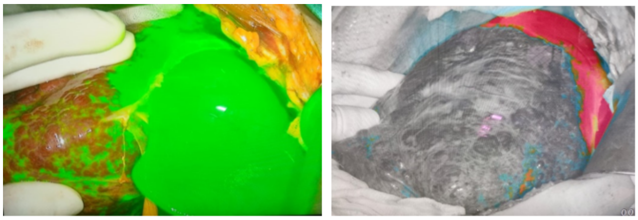


Figure 3: In a difficult calot ICG used to identify CBD



A B

Figure 4: (**A**) In liver Hemangioma liver fluorescence within minutes of ICG administration in Green light and (**B**) Color contrast mode

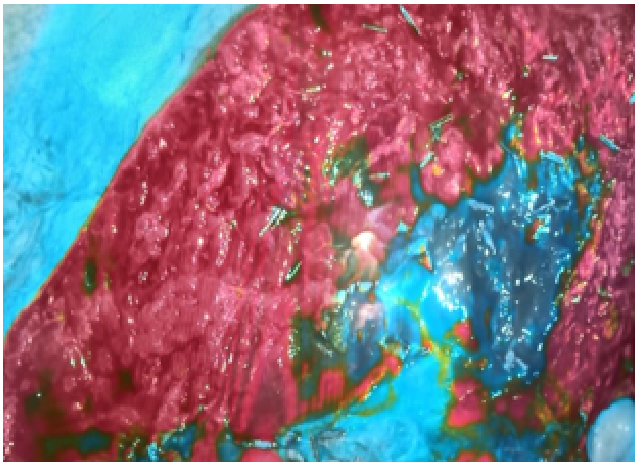


Figure 5: ICG fluorescence in contrast mode showing bile leak

guided (Technitium 99) methods. However, studies have also reported[22] that all additional metastasis including micrometastasis detected in non-SNs were located in the same lymphatic basin as the sentinel lymph nodes identified by dye guided method. ICG guided sentinel lymph node biopsy seem appropriate in cases with relatively early stage gastric cancer[23] and can change the management. Therefore it can be contented that sentinel lymph node-guided surgery using ICG has a potential role in gastric and colorectal cancers. However more robust studies with long-term follow-up regarding local recurrence and Disease free and overall survival are required to discern the potential role ICG can play in managing such cancers and guiding patient centric surgeries rather than a single blanket procedure. The major morbidity of these procedures is partly because of the extensive lymphadenectomy required oncological clearance. An abbreviated lymphadenectomy by sentinel lymph node sampling can decrease morbidity without compromising the adequacy of treatment

ICG fluorescence can detect small tumors like neuroendocrine tumors and help in localizing them. These tumors are usually multiple and small and are usually difficult to detect by naked eye, especially in laparoscopic setting where tactile feedback is lacking. Neuroendocrine tumors are also hypervascular and can rapidly take up ICG within seconds of administration when surrounding tissues are not yet flourescent. It can also help in ensuring adequate margins and inclusion of lesion in resected specimens.

4. Role of ICG in Laparoscopic Surgeries

Laparoscopic surgery is now used from cancers to complex surgeries and with improvements in imaging systems with the use of high definition and 3D imaging systems complex procedures are done laparoscopically. The lack of tactile feedback and two dimensional view predisposes laparoscopic procedures to certain inherent disadvantages. More recently ICG fluorescence imaging is emerging as a tool for intraoperative decision making.

Laparoscopic cholecystectomy has an inherent bile duct injury rate of 0.26 to 0.7% and conversion to open rate of 2.6-10 % where a critical view of safety can not be reached[24] Intraoperative cholangiogram is used to mitigate the same but has certain drawbacks and is not part of the standard operative procedure. Many studies have demonstrated that real-time fluorescent imaging, using indocyanine green (ICG) is a viable approach to real-time fluorescent identification of the bile ducts in uncomplicated cholelithiasis[25,26] and without the disadvantages of IOC

Luigi Boni et al[27] performed ICG-enhanced florescence-guided laparoscopic procedures in 108 patients. Patients included laparoscopic cholecystectomies to colorectal resections to living donor nephrectomies. They injected ICG and the high-definition stereoscopic camera projected high-resolution NIR (near infra Red) real-time images of blood flow in vessels and organs as well as highlighted biliary excretion. They found no intraoperative or injection-related adverse effects. Furthermore, the biliary/vascular anatomy was always clearly identified. The imaging system provided invaluable information to conduct a safe cholecystectomy and ensure adequate vascular supply for colectomy or to find lymph nodes. There were no bile duct injuries or anastomotic leaks in their cohort using ICG.

ICG-enhanced fluorescence may thus help to perform a sort of virtual cholangiography allowing the surgeon to identify the biliary anatomy. Most authors use 0.2-0.5 mg/kg body weight. More than 95% of ICG is captured by hepatocytes and excreted into bile within 15 mins of injection. Fluorescence of the liver and bile ducts can last up to 6 hours after IV injection of ICG. We used ICG in identification of CBD in a case of Giant Hemangioma in which Gall Bladder was compressed by hemangioma and CBD was not easily identifiable. Although the procedure was open but ICG guided dissection in the area of CBD as shown in Figure 3 below.

Intraoperative cholangiography is cumbersome and needs a C arm to carry it out. Surgeons do not routinely use this method except in case of doubtful anatomy and suspected intraoperative injury. ICG has the advantage of delineating both arterial and biliary anatomy and can be carried out without any separate equipment. Furthermore, the inherent rate of bile duct injuries in laparoscopic cholecystectomies can be further reduced by its routine application. The role of ICG in acute cholecystitis can not be over-emphasized where most bile duct injuries and conversion to open is more common. ICG can be a more reliable alternative to intraoperative cholangiography and may decrease the bile duct injury rate.

5. Role of ICG in Liver Surgeries

In the case of hepatocellular tumors, resection at present is guided by preoperative imaging. However this does not translate accurately in the operative field. Hepatic tumors can be identified by Near Infrared fluorescence imaging through the visualization of substances retained by the liver. ICG clears rapidly from the bloodstream and is secreted unmetabolized into bile and may accumulate in particular areas making them detectable through their acquired fluorescence.[28,29] When given 7 days before planned surgery, ICG can accumulate in liver tumors for lack of biliary excretion and can be detected intraoperatively. Furthermore, ICG can be used for Liver mapping, cholangiography, and partial liver graft evaluation

ICG has been used in the liver for the identification of small liver tumors and the detection of liver resection margin or hepatectomy line using fluorescence imaging. Ya-Min Zhang et al.[30] performed a study about the intraoperative identification of liver tumors using real-time ICG fluorescence imaging. Fluorescence of the normal liver developed within 1-2 minutes while in cirrhotic livers it was slow and not uniform when the dye was injected through the portal or right vein of the stomach. When ICG was given through the central venous catheter fluorescence of the normal liver developed in 5-10 minutes. After administration of the drug tumors appeared as a shadow with a photodynamic eye (PDE) as compared with normal liver tissues. However, there was no difference in the fluorescence pattern between benign and malignant tumors. Furthermore, the authors also found 12 small tumors in 8 patients in whom a preoperative imaging examination did not reveal these tumors. ICG fluorescence imaging with a PDE can also be used to determine the hepatectomy line in right or left hepatectomy after ligation of the portal pedicle. In some cases as the demarcation line doesn't appear even after ligation of portal pedicle, ICG Flourescence using PDE can rapidly demarcate the same. We used ICG in a liver hemangioma (Figure 4) and within minutes of administration (5-10 minutes), liver was fluorescent and hemangioma was clearly demarcated from it. This also helped us to remain close to hemangioma thus dissecting in proper plane preventing blood loss and bile leaks.

Direct fluorescence cholangiography with intrabiliary injection of ICG through the cystic duct stump after removal of hepatic parenchyma (tumor area) can also help in preventing bile leaks that are not visible to naked eye. Confirmation of bile leak point using ICG fluorescence imaging and repair by suturing thus reduces post-operative bile leakage in liver resections. ICG fluorescence cholangiography detects bile leakage that cannot be identified using a standard bile leak test. Intraoperative ICG fluorescence cholangiography has now replaced the role of radiological fluoroscopy with the benefit of avoiding unnecessary radiation exposure.[31] We used ICG fluorescence to detect bile leak in a case of CA GB where after segmentectomy a small bile leak was appreciated by ICG fluorescence and was sutured with prolene 3-0 suture as shown in the Figure 5 below using contrast mode of Imaging system that shows concentration of ICG as per different colors.

Small Liver tumors are currently identified intraoperatively using intra operative ultrasound (IOUS), however even IOUS can miss some lesions and is subjective. ICG can be used for identification and localization of these tumors as tumors usually retain ICG. It is especially useful and effective in superficial tumors and more importantly it can help in achieving negative margins. This technique can be used in neuroendocrine and colorectal liver metastasis when parenchymal preserving surgeries are contemplated.

ICG fluorescence can also be utilized in anatomical resections and demarcating the resection lines. For this purpose both positive and negative staining can be used for area of interest to be demarcated. Both techniques require the dissection of the portal pedicle of the segments to be resected. In negative staining ICG is given intravenous and clamping the pedicle of the resection area and thus doesn't take up ICG in contrast to rest of liver. However, in positive staining the portal pedicle needs direct puncture using IOUS and shows ICG fluorescence in contrast to rest of liver. Thus positive staining is technically more demanding. However, both methods have been utilized to resect liver segments.

ICG has been used in the liver as a functional assessment tool by determining the retention of ICG and thus selecting patients for surgery. The liver has always been a challenging organ to deal with surgically. Hepatectomies both anatomical and non anatomical pose specific challenges intraoperatively and postoperatively. Demarcation of resection area is not always clear with the conventional portal pedicle ligation. Wrong plane means a predisposition to bleeding and bile leaks. Furthermore, postoperative bile leaks are a source of morbidity and mortality.

6. Conclusion

ICG has been used in medical science for the last seven decades. However, its use in surgery has recently been explored and has found vast applications in the surgical field. In particular, its use in GI surgery including hepatobiliary surgery has started to define new trends and techniques to guide the modern surgeon in both simple and complex procedures. Aptly it has been termed as ICG navigation in surgery. Experimental studies are required to establish ICG as a standard adjunct in surgery.

7. Declarations

We did not receive support from any organization for the submitted work.

We have no competing interests to declare that are relevant to the content of this article.

8. Source of Funding

None.

9. Conflict of Interest

None.

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