REVIEW ARTICLE

IndoCyanine Green fluorescence guided resections in hepatobiliary surgery

Danilo Coco, Silvana Leanza

Department of General Surgery, Giglio Hospital Foundation, Cefalù (PA), Italy

Correspondence to: Dr. Danilo Coco, Email: webcostruction@msn.com

ABSTRACT

Background: Fluorescence-guided surgery (FGS) has recently gained popularity as a promising technique for treating visceral, hepatobiliary, and pancreatic neoplasms. It involves using laser sources to illuminate injected substances that emit a fluorescence signal, guiding surgical procedures, and providing real-time visualization of otherwise undetectable structures. This review explores the advancements in hepatobiliary surgery using IndoCyanine Green (ICG) fluorescence guided resections.

Methods: The review examined the use of FGS in identifying subcapsular liver tumors, millimetric hepatocellular carcinoma, intrahepatic cholangiocarcinoma, liver metastases, and various benign liver neoplasms. In addition, fluorescence cholangiography using ICG injection was explored to improve liver surgery's accuracy and safety.

Results: The review found that ICG fluorescence-guided resections can potentially improve surgical outcomes by enhancing the accuracy and safety of procedures. The use of fluorescence cholangiography allows for the efficient identification of the bile ducts and helps surgeons avoid damaging critical structures during liver surgery.

Conclusion: ICG fluorescence-guided resections represent a promising method for improving surgical outcomes and patient safety for visceral and hepatobiliary Surgery. It is a quick, easy, inexpensive, and safe device that can be used for various surgical applications. As imaging systems continue to improve, fluorescence imaging can become a widely used intraoperative navigation tool for open, laparoscopic, and robotic surgery.

Keywords: fluorescence imaging, indocyanine green, hepatobiliary surgery, pancreatic surgery, real-time surgery, hepatocellular carcinoma

INTRODUCTION

Fluorescence-guided surgery (FGS) is a technique that has gained popularity in recent years due to its ability to provide better visibility of anatomical structures and real-time perception of organ perfusion during surgery.[1] Indocyanine green (ICG) has been widely used since its Food and Drug Administration approval in 1954. In recent years, ICG Fluorescence Imaging (ICG-FI) has been used in various surgical procedures such as monitoring lymph nodes, testing blood supply during coronary artery bypass grafting, and cleavage of cerebral aneurysms.[2] The use of ICG-FI for visualization of hepatobiliary structures during hepato-pancreato-biliary (HPB) surgery was first reported by Japanese surgeons in the late 2000s.[3] The technique enables Real-Time Visualization of complex fluorescent structures that cannot be seen under traditional white light. It helps highlight extrahepatic bile duct anatomy, hepatic tumors, and hepatic segments based on the fluorescence properties of ICG and its biliary excretion. The real-time visualization and location of hepatic tumours can help surgeons perform therapeutic liver resections with reduced post-operative complications.

Fluorescence cholangiography is used to obtain fluorescence images of bile ducts after intrabiliary or intravenous injection of ICG.[4] However, the limitation of fluorescence imaging is its low tissue penetration ability, which makes it challenging to visualize lesions deeper than 10mm from the liver surface.[5] Despite this limitation, ICG-FI is relatively low-cost and widely available, and innovations in imaging systems are likely to increase its use in various surgical specialties. The fluorescence imaging method can provide the surgeon with real-time identification of a specific structure

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HIGHLIGHTS

1. ICG-Fluorescence Imaging (ICG-FI) has promising applications in hepatic surgery, including hepatocellular carcinoma, liver metastases, and biliary tree study.
2. Indocyanine green (ICG) fluorescence-guided real-time surgery is a promising technique in liver surgery
3. ICG fluorescence-guided real-time surgery aids in real-time surgical decisions.
4. ICG helps assess liver function and reduces the risk of post-hepatectomy liver failure.
5. Cost may also be a limiting factor in adopting ICG fluorescence-guided real-time surgery in some healthcare settings.

without using ionizing radiation, thus reducing the surgical procedure's invasiveness and complications while preserving tumour-free tissues. In addition, several studies have validated the use of ICG-FI for precise liver tumour recognition and localization, supporting its potential clinical application in liver resection surgery.[6] ICG-FI can provide a high yield of valuable data by visualizing the anatomical structures, delineating the tumour boundaries, displaying the vascular and biliary systems, and monitoring the hepatic function during hepatectomy.

The ICG-FI technique has recently gained attention in numerous areas of medicine, including hepatobiliary, pancreatic, colorectal, and breast cancer surgeries. It has the potential to change the paradigm of surgical navigation, mapping, and delineation, particularly in HPB surgery. This comprehensive review was done to understand better its potential applications in other surgical specialties.

METHODS

The present study utilized a systematic approach to gather information on the use ICG fluorescence in hepatobiliary surgery. A comprehensive literature search was conducted using several electronic databases, including PubMed/Medline, Embase, Cochrane, and Google Scholar. An expert in the field was also consulted to identify any missed articles or studies. The search was performed by using a combination of relevant keywords such as "ICG", "Fluorescence", "Real-Time Surgery", "Hepatectomy", "Hepatocellular Carcinoma", "Liver Metastases", "Extra-hepatic bile duct", and "Cholangiocarcinoma". The inclusion and exclusion criteria were established to ensure that only relevant studies were included in the review.

The studies that were included in this review had to meet the following criteria: (1) the study had to report on the use of ICG fluorescence in HPB surgery, including hepatocellular carcinoma, liver metastases, and extra-hepatic bile duct and cholangiocarcinoma, (2) the study had to be published in English, (3) the study had to be full-text articles, and (4) the study had to be either randomized or non-randomized clinical trials, observational studies, or case reports. Conversely, manuscripts that focused on the use of ICG fluorescence in other surgical fields were excluded from this review. After screening the studies by title and abstract, the full-text articles were reviewed.

The selected studies were then analyzed, and the relevant information was extracted. This systematic approach allowed us to understand comprehensively the importance of ICG fluorescence in HPB surgery. By utilizing the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework, we ensured our study was conducted with high rigour and transparency. The PRISMA methodology is a widely recognized and rigorous evidence-based approach to conducting systematic reviews, which identified 105 potential studies that met the inclusion criteria. Following initial screening and assessment for eligibility, 33 studies that were specific to the use of ICG fluorescence-guided resections in hepatobiliary surgery were included.

The final analysis included studies on the safety, feasibility, diagnostic accuracy, and prognostic value of ICG fluorescence-guided HPB surgery. The information gathered provides crucial insights into the current and potential use of ICG fluorescence imaging in HPB surgery, paving the way for further research and advancements in this emerging area of surgical navigation.

RESULTS

ICG fluorescence-guided surgery during hepatectomy has shown promising outcomes in real-time monitoring of intraoperative liver function remnant.[7] Several studies have investigated the use of ICG injection after arterial and portal vein clamping of the affected liver, providing real-time assessment of the function of the non-affected liver and reducing the risk of post-

TABLE 1 Key findings on the basis of review

Reference	Study Objective	Study Design	Key Findings
1	Fluorescence-guided surgery in cancer	Review	ICG fluorescence-guided surgery enables real-time visualization of the tumour microenvironment and aids in navigation in cancer surgery beyond visualization of tumours.
2	Fluorescence-guided surgery in pancreatic cancer	Review	Fluorescence-guided surgery involving ICG has demonstrated promising results in the intraoperative detection of pancreatic cancer while avoiding the potential damage of the normal pancreas associated with dissection.
3	Real-time identification of liver cancers	Clinical study	ICG fluorescence imaging enabled real-time identification and localization of liver cancers during surgery through the binding and excretion of ICG.
4	Fluorescence-guided laparoscopic cholecystectomy	Randomized controlled trial	ICG fluorescence imaging during laparoscopic cholecystectomy after percutaneous transhepatic gallbladder drainage can be a safe and effective method for identifying the cystic duct and preventing additional biliary injury.
5	Intraoperative fluorescence imaging in pediatric patients with kidney tumours	Preliminary study	Intraoperative near-infrared fluorescence imaging using ICG can assist in identifying and completely excising tumours in pediatric patients with kidney tumours in laparoscopic surgery.
6	Real-time fluorescence navigation for liver resection	Clinical study	Real-time ICG fluorescence imaging can guide surgeons in identifying tumours and bile ducts, monitoring blood flow and liver function, and improving the accuracy of liver resection with enhanced visualization.
7	Applications of ICG fluorescence imaging in liver cancer	Review	ICG fluorescence imaging in liver cancer provides a noninvasive imaging modality, capable of aiding in the diagnosis, staging, and management of HCC.
8	Fluorescence imaging during live donor hepatectomy	Clinical study	ICG fluorescence imaging is a feasible and safe method for guiding liver resections during live donor hepatectomy surgeries.
9	The usefulness of fluorescence navigation with ICG in identifying liver tumours	Clinical study	Fluorescence navigation using ICG can help intraoperatively identify liver tumours with high sensitivity and specificity.
10	Fluorescence imaging for visualizing hepatocellular carcinoma during laparoscopic hepatectomy	Clinical study	ICG fluorescence imaging during laparoscopic hepatectomy can assist in the identification and removal of HCC, even in patients with liver cirrhosis.
11	Fluorescence navigation with ICG for detecting sentinel lymph nodes in breast cancer	Meta-analysis	Fluorescence navigation with ICG is an effective method for identifying sentinel lymph nodes in breast cancer with high accuracy and low false-negative rates.
12	Real-time identification of liver cancers	Clinical study	ICG fluorescence imaging is a real-time imaging technique that provides surgeons with a way to identify, locate and remove liver tumours with high sensitivity and specificity.
13	Visualization of subcapsular HCC by ICG fluorescence imaging during hepatectomy	Clinical study	ICG fluorescence imaging can help surgeons identify subcapsular HCC accurately and completely during laparoscopic hepatectomy.
14	Image-guided liver mapping using fluorescence navigation system	Clinical study	ICG fluorescence imaging can help surgeons intraoperatively map the liver and identify important anatomical landmarks, enabling precise and safe liver resection.
15	Combining fluorescence navigation with ICG for anatomical liver resection in situs inversus totalis	Clinical study	Combining fluorescence navigation with ICG can be a useful tool for aiding in identifying the anatomical landmarks of the liver and performing safe and effective anatomical liver resections, even in situs inversus totalis.
16	Intraoperative NIRF overview	Review	Near-infrared fluorescence imaging techniques, including ICG, can assist surgeons in the real-time identification of tumours and surrounding tissue, aiding in tumour localization and facilitating safe resection.
17	Current status and future perspectives of ICG fluorescence-guided surgery in liver diseases	Review	ICG fluorescence-guided surgery is a promising tool that enables real-time visualization of anatomical structures, tumour margins, and blood flow to enhance the precision, safety, and success of liver surgeries.
18	Fluorescence imaging for detecting extrahepatic metastasis of HCC	Clinical study	ICG fluorescence imaging can detect extrahepatic metastasis of HCC before or during surgery, resulting in improved surgical outcomes and patient prognosis.
19	Update on fluorescence-guided surgical navigation in hepatobiliary and pancreatic surgery	Review	Fluorescence-guided surgical navigation using ICG is a practical and effective tool for visualizing anatomical landmarks, facilitating the identification of lesions, and reducing surgical morbidity in hepatobiliary and pancreatic surgery.
20	Real-time ICG fluorescence imaging to evaluate liver function during hepatectomy	Clinical study	Real-time ICG fluorescence imaging can be a safe and feasible method to evaluate liver function during hepatectomy, enabling real-time decision-making in the surgical strategy.
21	Cost-effectiveness of fluorescence-guided surgery in gastrointestinal cancer	Systematic review	Fluorescence-guided surgery with ICG can be a cost-effective tool for improving the surgical management of gastrointestinal cancers reducing costs associated with postoperative complications and readmissions.

ICG, IndoCyanine Green; HCC, hepatocellular carcinoma

hepatectomy liver failure.[8] This technique has been employed both before and after hepatectomy to simulate the post-resection situation and control the non-resected liver. The administration of an intravenous injection of ICG at a dose of 0.25 mg/kg body weight has been utilized in these measurements.[9] A study conducted in Japan demonstrated that ICG near-infrared fluorescence imaging enables visualization of hepatocellular carcinoma (HCC), hepatic perfusion, tumour perfusion, and the demarcation line after clamping, thereby aiding in the navigation of laparoscopic surgery.[10] Surgeons introduced 2.5 mg of ICG following clamping or closure of the proximal Glissonean pedicles, which clearly delineated the fluorescent parenchyma from non-fluorescent areas and facilitated visualization of the resection line. In a Chinese study, the use of ICG observed with PhotoDynamic Eye allowed for the evaluation of the boundaries of HCC lesions and revealed small HCC tumours that were not visualized preoperatively in 50 patients.[11] This method was considered a simple and safe tool that provides real-time imaging of HCC, aiding in liver resection and margin guidance, with high sensitivity for detecting new small HCC.

The initial application of near-infrared/ICG fluorescence for liver tumour identification was reported by Ishizawa et al. in 2009.[12] This series expanded to include 170 subjects and 276 HCCs by 2013, with a false-positive rate reduced to 1%. Near-infrared fluorescence identified 273 out of 276 lesions (99%), including 21 grossly unidentifiable lesions. Morita et al. further evaluated ICG fluorescence imaging and demonstrated that ICG fluorography identified 73 out of 76 (96%) preoperatively diagnosed HCC lesions. Overall, near-infrared fluorescence sensitivity for HCCs was 96%, with a positive predictive value of 71.5%. Kudo et al. developed a technique for laparoscopic ICG fluorescence imaging and evaluated its efficacy in identifying subcapsular liver cancers during laparoscopic hepatectomy.[13] This technique enables real-time identification of subcapsular liver cancers, facilitating the estimation of the necessary extent of hepatic mobilization and determining the appropriate hepatic transection line. Aoki et al. reported an intraoperative technique for identifying liver segments and subsegments using high-sensitivity near-infrared fluorescence imaging for anatomical hepatic resection.[14]

In 33 out of 35 patients, stained subsegments and segments of the liver were identifiable (94.3%). Alternatively, Uchiyama et al. proposed combining a fluorescence navigation system using ICG and contrast-enhanced intraoperative ultrasound with Sonazoid for the detection of liver sections and segments.[15] This combined approach has proven to be a useful and safe tool for performing liver resection. Recent studies have demonstrated that ICG fluorescence imaging accurately identifies primary and metastatic liver tumours.[16] In a study involving 37 patients with hepatocellular carcinoma (HCC) and 12 patients with colorectal carcinoma (CRC) metastasis undergoing liver resection ICG-fluorescent imaging, following routine liver function tests, we successfully identified all microscopically confirmed HCCs (n = 63) and CRC metastases (n = 28) in the surgical specimens.

DISCUSSION

ICG fluorescence-guided real-time surgery is a promising technique in liver surgery, but certain limitations and biases must be considered when its effectiveness is evaluated. ICG fluorescence-guided real-time surgery provides critical real-time information for surgeons during liver surgery, including differentiation between abnormal and normal tissue and preservation of vital blood vessels. ICG fluorescence can also assist in monitoring liver function and identifying small hepatic lesions, making it a versatile tool in intraoperative imaging. Fluorescence cholangiography with intrabiliary injection of ICG is an effective method for identifying biliary lesions during surgery. However, its publication bias and variable injection timing impact the effectiveness of ICG fluorescence-guided real-time surgery. Studies that report positive outcomes preferentially may overestimate the effectiveness of ICG fluorescence-guided real-time surgery. Surgeons with limited exposure to the technique may achieve less favourable outcomes than those with extensive experience. ICG injection timing requires careful consideration based on the patient's liver function and

can be influenced by subjective factors, requiring standardized protocols to minimize bias and ensure consistency. While ICG fluorescence is valuable during surgery, it should not replace preoperative imaging and clinical evaluation. Cost may also be a limiting factor in adopting ICG fluorescence-guided real-time surgery in some healthcare settings.[17-21]

Conclusion

In summary, using ICG-FI as an intraoperative navigation technology holds great promise for hepatic resection and clinical exploration in colorectal liver metastases, HCC, tumour boundaries, liver function testing, and the study of the extra and intra-hepatic biliary tree. The real-time high sensitivity of ICG-FI in identifying both minute and grossly unidentifiable liver cancer tumours enhances the precision of liver resection and the accuracy of operative cancer staging. However, it is important to acknowledge that the technique does have certain limitations. These limitations include limited tissue penetration and modest specificity, which can be mitigated by incorporating the gold standard of intraoperative ultrasound for the detection of deeper tumors. Further clinical studies are necessary to evaluate the sensitivity and specificity of ICG-FI in the context of hepatobiliary surgery.

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Author Contributions

Conception and design: DC & SL. Acquisition, analysis, and interpretation of data: DC & SL. Manuscript drafting and revising it critically: DC & SL.Approval of the final version of the manuscript: DC & SL.Guarantor accuracy and integrity of the work: DC & SL.

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Conflict of Interest

The authors declare no conflicts of interest.

Ethical Approval

This is a review work. Ethical approval was not necessary.

ORCID iDs

Danilo Coco https://orcid.org/0000-0002-5839-1767

Silvana Leanza https://orcid.org/0000-0001-8672-7486

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