Special Journal of Open Research & Reviews

The Usefulness of Indocyanine Green Fluorescence in real-time visualization of Hepato-Biliary Surgery: Narrative review

Danilo[1] Coco, and Silvana[2] Leanza

****

Citation

Danilo Coco and Silvana Leanza. Usefulness of Indocyanine Green Fluorescence in real-time visualization of Hepato-Biliary Surgery: Narrative review. Special Journal of Open Research and Reviews, 2021, 2(1): 1-6

Highpoints

- This paper aims to report useful aspects of Indocyanine green fluorescence in the practice of different hepatobiliary surgery.
- Fluorescence imaging allows identification of:1. subcapsular tumors of the liver,2. Millimetric hepatocellular carcinoma (HCC),3. Intrahepatic cholangiocarcinoma (IC),4. Liver Metastases (LM),5. Various types of benign liver neoplasms and 6. non-pathological liver parenchyma.
- ICG fluorescence imaging is a quick, easy, fairly inexpensive, and harmless device with various surgical applications for visceral and HBP benign and malignant neoplasms.

Abstract

Background: Recent years have seen a substantial rise in the use of Fluorescence-Guided Surgery (FGS) to treat benign and malignant visceral, hepatobiliary and pancreatic neoplasms.

Aim: This paper aims to report useful aspects of Indocyanine green fluorescence in the practice of different hepatobiliary surgery.

Materials and Methods: Literature research was carried out including PubMed, Medline, Embase, Cochrane, and Google Scholar databases to identify articles reporting on the importance of ICG Fluorescence use in HPB Surgery.

Results: Fluorescence imaging allows identification of:1. subcapsular tumors of the liver,2. Millimetric hepatocellular carcinoma (HCC),3. Intrahepatic cholangiocarcinoma (IC),4. Liver Metastases (LM),5. Various types of benign liver neoplasms and 6. non-pathological liver parenchyma. These features increase accuracy and decrease complications during liver surgery.

Conclusion. Fluorcence cholangiography is used to obtain fluorescence images of the bile ducts after intrabiliaryinjection of 0.025−0.5 mg / mL ICG or 2.5 mg ICG intravenous injection. Innovations in imaging systems will increase the use of fluorescence imaging as an intraoperative navigation tool that can improve the safety and accuracy of open, laparoscopic, and robotic surgeries fluorescence imaging is a quick, easy, fairly inexpensive and harmless device with various surgical applications for visceral and HBP benign and malignant neoplasms.

Keywords: Indocyanine green; fluorescence imaging; liver surgery; biliary surgery; pancreatic surgery; biliary anatomy; Real-Time Surgery; Hepatectomy; Hepatocellular Carcinoma; Liver Metastases; Extra-hepatic bile duct; Cholangiocarcinoma.

Addresses: 1. Department of General Surgery, Ospedali Riuniti Marche Nord, Pesaro (PU), Italy. 2. Department of General Surgery, Carlo Urbani Hospital, Jesi (AN), Italy

Address for correspondence: Danilo Coco MD, Ospedali Riuniti Marche Nord, Pesaro (PU), Italy, Email: webcostruction@msn.com

Article history: **Received** Sept 17, 2021: **Accepted:** October 18, 2021: **Published:** December 6, 2021

Distribution and usage license: This open-access article is distributed by the terms and conditions of the Creative Commons Attribution 4.0 International License seen in this link (http://creativecommons.org/licenses/by/4.0/). You are free to use, distribute, and reproduce this article in any medium, provided you give correct credit to the original author(s) and the source, including the provision of a link to the Creative Commons license website. Pls show any modification's

****

Introduction

Fluorescenceguided surgery (FGS) is an intra operative navigation tool that allows the surge on better visualization of anatomical structures and/or better perception of the actual perfusion of an organ in real-time. (1,2). Since its approval (1954) by U.S. Food and Drug Administration, Indocyanine green (ICG) has been widely used in many clinical contexts. Then, in early 1990, ICG was initially used clinically for angiography of the ocular fundus. Technical developments in recent years, ICG Fluorescence Imaging (ICG-FI) has generated considerable attention for use of numerous surgical procedures, i.e.1. The monitoring of lymphatic nodes,2. Sentinel lymph nodes in breast cancer,3. Gastrointestinal cancers, 4.for testing blood supply during coronary artery bypass grafting, 5.for cleavage of cerebral aneurysm.For what concern HPB surgery, no attention was given to ICG-FI until Japanese Surgeons visualized hepatobiliary structures in the late 2000s using ICG-FI.(3,4,5,6).ICG fluorescence imaging (FI) technique helps monitor hepatic surgical procedures and

provides the surgeon with Real-Time Visualization (RTV) of complex fluorescent structures that would be undetectable under traditional white light. Extrahepatic bile duct anatomy and hepatic tumors can be highlighted and hepatic segments can be highlighted based on the fluorescence properties of ICG and its biliary excretion. RTV and location of hepatic tumors can help surgeons perform therapeutic liver resections even with sparing parenchyma hepatectomies, thereby reducing postoperative complications (7).

These features increase accuracy and decrease complications during liver surgery. Fluorescence cholangiography is used to obtain fluorescence images of the bile ducts after intrabiliary injection of 0.025−0.5 mg / mL ICG or 2.5 mg ICG intravenous injection. Innovations in imaging systems will increase the use of fluorescence imaging as an intraoperative navigation tool that can improve the safety and accuracy of open laparoscopic and robotic surgery. (8,9). Through the production of fluorescence cholangiography for hepatic tumors, ICG was observed to accumulate around adenocarcinoma foci in cancerous tissue,i.e. HCC, and in non-cancerous hepatic parenchyma. (9,10).

The limitation of fluorescence imaging is the low tissue penetration ability. In other words, when lesions are>10 mm deep from the surface of the liver, they cannot be visualized as fluorescences. However, fluorescence imaging is expected to complement preoperative and intraoperative imaging modalities that sometimes fail to diagnose subcapsular hepatic malignancies, whereas fluorescence imaging has visualized them well. (11,12). In the last few years, fluorescence imaging using the fluorescent properties of indocyanine green (ICG) has become widespread in several medical and surgical specialties. Due to its relatively low cost and high availability. (13)

Aim: This paper aims to report useful aspects of Indocyanine green fluorescence in the practice of different hepatobiliary surgery.

Materials and Methods

Literature research was carried out including PubMed, Medline, Embase, Cochrane, and Google Scholar databases to identify articles reporting on the importance of ICG Fluorescence use in HPB Surgery.

Inclusion and exclusion criteria

The keywords used were “ICG," "Fluorescence," and "Real-Time Surgery.",”Hepatectomy, Hepatocellular Carcinoma,” Liver Metastases” Extra-hepatic bile duct” cholangiocarcinoma”. We analyzed all full-texts, randomized and nonrandomized clinical trials, and observational studies. We exclude all manuscripts that reported the use of ICG in another field of surgery.

Outcomes (Result)

A Deutch study demonstrated ICG Fluorescence Guided Surgery during hepatectomy allows Real-Time monitoring of intraoperative liver function remnant. The study analyzed the use of ICG injection after arterial and portal vein clamping of the affected liver, gave a real-time function of nonaffected liver diminishing the probability of post-Hepatectomy Liver Failure (PHLF). ICG can be used before hepatectomy to simulate the situation after resection and after hepatectomy to control the non-resected liver. For each measurement, the surgeon used an aqueous solution of ICG 0.25mg/kg body weight intravenous injection.

This method helped surgeons in decision making before hepatectomy in a small liver avoiding the augmented risk of PHLF over 5-8%.(14). A study from Japan demonstrated that ICG near-infra- Fluorescence can facilitate the visualization of HCC and could help in visualizing hepatic perfusion, tumor perfusion, and the demarcation line after clamping. This method seems to reduce the difficulties during laparoscopic surgery.

The surgeon introduced 2.5mg of ICH following clamping or closure of the proximal glissonean pedicles.ICG injection delineated the fluorescent parenchyma from non-fluorescent helping the visualize of the

resection line. (15). A Chinese study showed the use of ICG observed with Photo Dynamic Eye (PDE) to delineate boundaries of HCC lesions and to find small HCC tumors not visualized pre-operatively in 50 patients.

They concluded that ICG-PDE is a very simple but safe tool that helps the surgeon to have a real-time imaging of HCC, a very safe method to guide liver resection and margin and high sensibility to receive new small HCC. (16,17). In 2009, Ishizawa et al.(6) reported the first NIR/ICG fluorescence application in liver tumor identification. Eight of 63 HCCs were identified with NIRF imaging that was otherwise imperceptible; 8% of false-positives rate was reported (10).

By 2013, the series progressed to 170 subjects and 276 HCCs. The false-positive rate dropped to 1%, while 273 of 276 lesions (99%) were identified under NIRF, including 21 grossly unidentifiable lesions. Morita et al.(18) further evaluated the ICG fluorescence imaging and showed that ICG fluorography identified 73 of 76 (96%) preoperatively diagnosed HCC lesions. Overall, the sensitivity of NIRF for HCCs was 96% and its positive predictive value was 71.5%. Kudo et al.(11) devised the technique for laparoscopic ICG fluorescence imaging and evaluated the efficacy for identifying subcapsular liver cancers in laparoscopic hepatectomy.

It was described that like palpation during open hepatectomy, this technique enables real-time identification of subcapsular liver cancers, subsequently facilitating estimation of the required extent of hepatic mobilization and determining the location of an appropriate hepatic transaction line. In 2008, Aoki et al.(5)reported an intraoperative technique for identifying segment and subsegment of the liver with high-sensitivity NIRF imaging for anatomical hepatic resection.

Stained subsegments and segments of the liver were identifiable in 33 (94.3%) of the 35 patients. Alternatively, Uchiyama et al(19) advocated combining fluorescence navigation system (PDE) using ICG and contrast-enhanced intra-operative US with Sonazoid for detection of liver sections and segments and demonstrated it to be a useful and safe tool for performing liver resection. Recent studies proved that ICG fluorescence imaging accurately identified primary and metastatic liver tumors (20.21,22) that had been intravenously injected for a routine liver function test in 37 patients with hepatocellular carcinoma (HCC) and 12 patients with metastasis of colorectal carcinoma (CRC) before liver resection. ICG-fluorescent imaging identified all of the microscopically confirmed HCCs (n ¼ 63) and CRC metastases (n 28) in surgical specimens.

Discussion

ICG Fluorescence allows the development of Real-Time Surgery (RTS) as a rapid tool to ensure complete tumor resection, to underline a clear boundary between pathologic and normal tissue, to visualize the vascular hepatic system, and to detect new hepatic lesions particularly for tiny liver metastases <5mm and superficial hepatic lesions that cannot be observed before surgery. (17).

Further, the use of ICG Fluorescence can be used to control liver function tests and accumulates in HCC allowing to follow resection margin and to discover new small HCC. ICG-fluorescent imaging identified all of the microscopically confirmed HCCs and CRC liver metastases in the surgical specimens. (22). The time between ICG injection and hepatectomy of 1 to 28 days has also been the topic of several publications while others proposed an intraoperative injection. (18, 20, 23, 24, 25, 26, 27,28).

Even administration routes of ICG were differently applied, related to preoperative or intraoperative ICG use (e.g. portal vein or right vein of the stomach, central venous catheter, or peripheral vein)(29). Several studies have reported that an intravenous ICG of 0.25-0.5mg/kg from 12-24h to 14 days before surgery is the best choice. (18,30,31,32,33). ICG can be used in various ways. Administering ICG into the portal vein or right vein of the stomach. In this way, the

fluorescence of normal liver tissue developed within 1–2 min administering. ICG through a central venous catheter. In this way, the fluorescence of normal liver tissue developed uniformly in 5–10 min. Moreover, central venous ICG administration resulted in slightly slower and weaker fluorescence, but with an increased dose, the results significantly improved.

The interval is related to liver function: poor liver function and cirrhosis will take much longer to extract ICG from the blood to the bile, as well as a complete cellular washout. (34). Liu et al. developed the combination of the fluorescence goggle system and transarterial hepatic ICG delivery and showed the transarterial route of ICG facilitated rapid and selective uptake of ICG in HCC, providing higher imaging contrast between the tumors and normal hepatic tissue than the IV method. Well-differentiated HCCs have been detected as uniformly and highly fluorescing lesions, while poorly differentiated HCCs and metastases of CRC were detected as rim-fluorescing lesions with low lesion-to-liver contrast. (22).

Fluorescent images of the biliary tract can be obtained by intrabiliary injection of ICGto obtain clear fluorescence images of the bile ducts following intrabiliary injection of ICG, diluted ICG solution (approximately 0.025 mg/mL) should be used for imaging.When the intrahepatic bile duct anatomy and the extrahepatic biliary system must be identified, ICG should be diluted with radiographic contrast agents, enabling radiographic cholangiography easily and immediately following fluorescence cholangiography(6). Fluorescence cholangiography could also be performed following intravenous injection of ICG because ICG excreted into bile can act as a source of fluorescence.

This technique involves the intravenous injection of small amounts of ICG, usually 2.5 mg, diluted into a 1 mL solution.ICG should be administered at least 15 minutes before imaging to obtain better signal-to-background contrast (6,23).Theoretically, our fluorescent imaging technique could be used to delineate any lesions retaining ICG in surgical specimens cut into 10-mm sections because near-infrared light penetrates human tissues to a depth of about 5-10 mm. (35). Intraoperative ICG-fluorescent imaging is still useful because it not only aids visual inspections and palpation but also compensates for drawbacks in intraoperative ultrasonography in observing small lesions located just beneath the liver surface. Furthermore, this technique can be used to detect residual cancerous tissues on the raw surface of the remnant liver after resection. Other advantages of our ICG-fluorescent technique are its safety and feasibility. ICG is already used worldwide to evaluate liver function before resection. The reported incidence of adverse reactions after the intravenous injection of ICG is quite small (approximately 0.003%). (36)

Conclusions

The current findings indicate that an ICG–FI navigation technology is a new real-time intraoperative imaging method. This technique is promising for hepatic resection and clinical exploration in colorectal liver metastases, in HCC(17), in boundaries, in liver function tests, and in the study of the extra and intrahepatic biliary tree. Intraoperative ICG fluorescence imaging navigation enabled the high sensitivity for identifying tiny and grossly unidentifiable liver cancer tumors in real-time, enhancing the accuracy of liver resection and operative cancer staging. (29)Despite the various benefits of FI-ICG based in hepatobiliary surgery, there are some drawbacks; these include limited tissue penetration and poor specificity.

Intraoperative Ultrasound remains the gold standard for the detection of deeper tumors and FI-ICG is complemental. Further clinical studies are required to assess the sensitivity and specificity of FI-ICG based during hepatobiliary surgery.

Conflicts of interest: none declared.

Financial support: none declared.

Acknowledgments: Silvana Leanza MD for reviewing the manuscript

Human Rights Statement: Not applicable

References

1. Diana M. Enabling precision digestive surgery with fluorescence imaging. Transl Gastroenterol Hepatol 2017; 2: 97 [PMID: 29264435 DOI: 10.21037/tgh.2017.11.06]

2.Gioux S, Choi HS, Frangioni JV. Image-guided surgery using invisible near-infrared light: fundamentals of clinical translation. Mol Imaging 2010; 9: 237-255 [PMID: 20868625].

3.Kubota K, Kita J, Shimoda M, et al. Intraoperative assessment of reconstructed vessels in living-donor liver transplantation, using a novel fluorescence imaging technique. J Hepatobiliary Pancreat Surg 2006;13:100-4.

4. Mitsuhashi N, Kimura F, Shimizu H, et al. Usefulness of intraoperative fluorescence imaging to evaluate local anatomy in hepatobiliary surgery. J Hepatobiliary Pancreat Surg 2008;15:508-14.

5. Aoki T, Yasuda D, Shimizu Y, et al. Image-guided liver mapping using fluorescence navigation system with indocyanine green for anatomical hepatic resection. World J Surg 2008;32:1763-7.

6. Ishizawa T, Tamura S, Masuda K, et al. Intraoperative fluorescent cholangiography using indocyanine green: a biliary road map for safe surgery. J Am Coll Surg 2009;208:e1-4.

7.Giorgio Rossi1, Antonio Tarasconi1, Gianluca Baiocchi2, Gian Luigi de'Angelis3, Federica Gaiani2, Francesco Di Mario3, Fausto Catena1, Raffaele Dalla Valle4, Fluorescence guided surgery in liver tumors: applicationsand advantages,Acta Biomed 2018; Vol. 89, Supplement 9: 135-140 DOI: 10.23750/abm.v89i9-S.7974.

8.Takeaki Ishizawa1, Akio Saiura1, Norihiro Kokudo, Clinical application of indocyanine green fluorescence imaging during hepatectomy, Hepatobiliary Surg Nutr 2016;5(4):322-328

9. Ishizawa T, Masuda K, Urano Y, et al. Mechanistic background and clinical applications of indocyanine green fluorescence imaging of hepatocellular carcinoma. Ann Surg Oncol 2014;21:440-8.

10. Ishizawa T, Fukushima N, Shibahara J, et al. Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Cancer 2009;115:2491-504.

11.Kudo H, Ishizawa T, Tani K, et al. Visualization of subcapsular hepatic malignancy by indocyanine-green fluorescence imaging during laparoscopic hepatectomy. Surg Endosc 2014;28:2504-8.

12. Kawaguchi Y, Nagai M, Nomura Y, et al. Usefulness of indocyanine green fluorescence imaging during laparoscopic hepatectomy to visualize subcapsular hard-to-identify hepatic malignancy. J Surg Oncol 2015;112:514-6.

13. Reinhart MB, Huntington CR, Blair LJ, Heniford BT, Augenstein VA. indocyanine green: historical context, current applications, and future considerations. Surg Innov 2016; 23: 166-175 [PMID: 26359355 DOI: 10.1177/1553350615604053]

14. Thomas MN, Wenninger E, Angela M, et al. Intraoperative simulation of remnant liver function during anatomic liver resection with indocyanine green clearance (LIMON) measurements. HPB (Oxford). 2015: 17 (6): 471-476. Doi: 10.1111/hpb.12380

15. Urade T, Sawa H, Iwatani Y, Abe T, Fujinaka R, Murata K, Mii Y, Man-I M, Oka S, Kuroda D. Laparoscopic anatomical liver resection using indocyanine green fluorescence imaging. Asian J Surg. 2020 Jan;43(1):362-368. doi: 10.1016/j.asjsur.2019.04.008. Epub 2019 Apr 28.

16. Zhang YM, Shi R, Hou JC, Liu ZR, Cui ZL, Li Y, Wu D, Shi Y, Shen ZY. Liver tumor boundaries identified intraoperatively using real-time indocyanine green fluorescence imaging. J Cancer Res Clin Oncol. 2017 Jan;143(1):51-58. doi: 10.1007/s00432-016-2267-4. Epub 2016 Sep 14.

17. Shih-Wei Huang1,2, Jing-Jim Ou, Hon Phin Wong1,2 The use of indocyanine green imaging technique in a patient with hepatocellular carcinoma, Transl Gastroenterol Hepatol 2018;3:95.

18. Morita Y, Sakaguchi T, Unno N, Shibasaki Y, Suzuki A, Fukumoto K, Inaba K, Baba S, Takehara Y, Suzuki S, Konno H (2013) Detection of hepatocellular carcinomas with near-infrared fluorescence imaging using indocyanine green: its usefulness and limitation. Int J Oncol 18:232–241.

19. Uchiyama K, Ueno M, Ozawa S, et al. Combined intraoperative use of contrast-enhanced ultrasonography imaging using a son avoid and fluorescence navigation system with indocyanine green during anatomical hepatectomy. Langenbecks Arch Surg 2011;396:1101-7.

20. Lieto E, Galizia G, Cardella F, et al. Indocyanine Green Fluorescence Imaging-Guided Surgery in Primary and Metastatic Liver Tumors. Surg Innov 2018;25:62-8.

21. Satou S, Ishizawa T, Masuda K, et al. Indocyanine green fluorescent imaging for detecting extrahepatic metastasis of hepatocellular carcinoma. J Gastroenterol 2013;48:1136-43.

23. Ishizawa T, Bandai Y, Ijichi M, et al. Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy. Br J Surg 2010;97:1369-77.

24. Gotoh K, Yamada T, Ishikawa O, et al. A novel imageguided surgery of hepatocellular carcinoma by indocyanine green fluorescence imaging navigation. J Surg Oncol 2009;100:75-9.

24. Ishizawa T, Masuda K, Urano Y, et al. Mechanistic background and clinical applications of indocyanine green fluorescence imaging of hepatocellular carcinoma. Ann Surg Oncol 2014;21:440-8.

25. Kudo H, Ishizawa T, Tani K, et al. Visualization of subcapsular hepatic malignancy by indocyanine-green fluorescence imaging during laparoscopic hepatectomy. Surg Endosc 2014;28:2504-8.

25. Tanaka T, Takatsuki M, Hidaka M, et al. Is a fluorescence navigation system with indocyanine green effective enough to detect liver malignancies? J Hepatobiliary Pancreat Sci 2014;21:199-204.

26. Kitagawa N, Shinkai M, Mochizuki K, et al. Navigation using indocyanine green fluorescence imaging for hepatoblastoma pulmonary metastases surgery. Pediatr Surg Int 2015;31:407-11.

27. Boogerd LS, Handgraaf HJ, Lam HD, et al. Laparoscopic detection and resection of occult liver tumors of multiple cancer types using real-time near-infrared fluorescence guidance. Surg Endosc 2017;31:952-61.

28. Peyrat P, Blanc E, Guillermet S, et al. HEPATOFLUO: A prospective monocentric study assessing the benefits of indocyanine green (ICG) fluorescence for hepatic surgery. J Surg Oncol 2018;117:922-7.

29. Zhang YM, Shi R, Hou JC, et al. Liver tumor boundaries identified intraoperatively using real-time indocyanine green fluorescence imaging. J Cancer Res Clin Oncol 2017;143:51-8.

30. Tsujino Y, Mizumoto K, Matsuzaka Y, Niihara H, Morita E (2009) Fluorescence navigation with indocyanine green for detecting sentinel nodes in extramammary Paget's disease and squamous cell carcinoma. J Dermatol 36:90–94.

31. Lim C, Vibert E (2013) Identification of metastatic liver cancer. Fluoresc Imaging 31:18–24

32. Lim C, Vibert E, Azoulay D, Salloum C, Ishizawa T, Yoshioka R, Mise Y, Sakamoto Y, Aoki T, Sugawara Y et al (2014) Indocyanine

green fluorescence imaging in the surgical management of liver cancers: current facts and future implications. J Visc Surg 151(2):117–124

33. Kawaguchi Y, Aoki T, Ishizawa T, Arita J, Satou S, Kaneko J, Sakamoto Y, Sugawara Y, Hasegawa K, Kokudo N (2013) Education and imaging: hepatobiliary and pancreatic: identification of recurrent hepatocellular carcinoma by intraoperative fluorescent imaging. J Gastroenterol Hepatol 28(3):587.

34. Sheng QS, Lang R, He Q, et al. Indocyanine green clearance test and model for end-stage liver disease score of patients with liver cirrhosis. Hepatobiliary Pancreat Dis Int 2009;8:46-9.

35. Kim S, Lim YT, Soltesz EG, et al. Near-infrared fluorescent type II quantum dots for sentinel lymph node mapping. Nat Biotechnol. 2004;22:93-97.

36. Cherrick GR, Stein SW, Leevy CM, Davidson CS. Indocyanine green: observations on its physical properties, plasma decay, and hepatic extraction. J Clin Invest. 1960;39:592-600.

37. Liu Y, Zhao YM, Akers W, et al. First-in-human intraoperative imaging of HCC using the fluorescence goggle system and transarterial delivery of near-infrared fluorescent imaging agent: a pilot study. Transl Res 2013;162:324-31.

Submit your paper for publication to the Special Journal of Open Research and Reviews Politics and Economic Sustainability (Spec. j. open res. rev.) seen online at the link below https://sjorr.spparenet.org/submit/ or by email attachment to us at editorialoffice@spparenet.org