



Narrative review of fluorescence imaging-guided liver surgery

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Abstract: Indocyanine green (ICG) fluorescence imaging has come to be applied to hepatobiliary surgery not only visualization of bile duct but also for identification of subcapsular hepatic tumors and segmental boundaries. A large proportion of ICG molecules bind to high molecular-weight proteins such as albumin. ICG is selectively taken up to hepatocytes and excreted in the bile by an active transporter. Fusion ICG fluorescence images are obtained using a complementary metal-oxide semiconductor camera head and a near-infrared laser diode for ICG excitation. This method is helpful especially in cases of laparoscopic hepatectomy, wherein there is limited visual inspection and palpation in comparison with open surgery. ICG cholangiography is effective for visualizing the confluence of the left and right hepatic duct, decreasing the potential risks of bile duct stenosis or injury. ICG fluorescence imaging is also useful for the visualization of hepatic segment boundaries, which helps navigate the transection line in real time during hepatectomy. However, in the case of liver cirrhosis, the function of liver cells is depressed, and longtime ICG remains in the lesions; thus, the disappearance of fluorescence is delayed. ICG fluorescence imaging is a simple technology with the potential to improve the safety and quality of open, laparoscopic, and robotic hepatectomy.

Keywords: Indocyanine green (ICG); fluorescence imaging; liver surgery

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Introduction

Recently, fluorescence imaging systems have been developed to identify biological structures and confirming blood flow of organs during surgical treatment (1,2). As an example of such surgical technology, the use of an indocyanine green (ICG) fluorescence imaging-based navigation system has had a positive effect on the surgical treatment of skin, gastric and breast cancers (3-6).

In the field of hepatobiliary surgery, Aoki *et al.* reported the benefit of ICG fluorescence imaging for the first time by demonstrating the identification of segmental boundaries of the liver (7-9). In 2009, Ishizawa *et al.* reported the application of an ICG fluorescence imaging-based navigation technique to identify liver tumors (10,11). At the

same time, the fluorescence imaging-based cholangiography during laparoscopic cholecystectomy was reported as the first video article in a medical journal (12). Recently, Lehrskov *et al.* reported that fluorescence cholangiography was comparable to X-ray fluoroscopic cholangiography in terms of visualization of the critical junction during laparoscopic cholecystectomy (13). ICG fluorescence imaging has also been applied in various hepatectomy procedures as a tool for real-time intraoperative navigation.

In this study, we present a review of the clinical benefits of fluorescence imaging-guided liver surgery and demonstrate some practical tips. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/ls-20-102>).

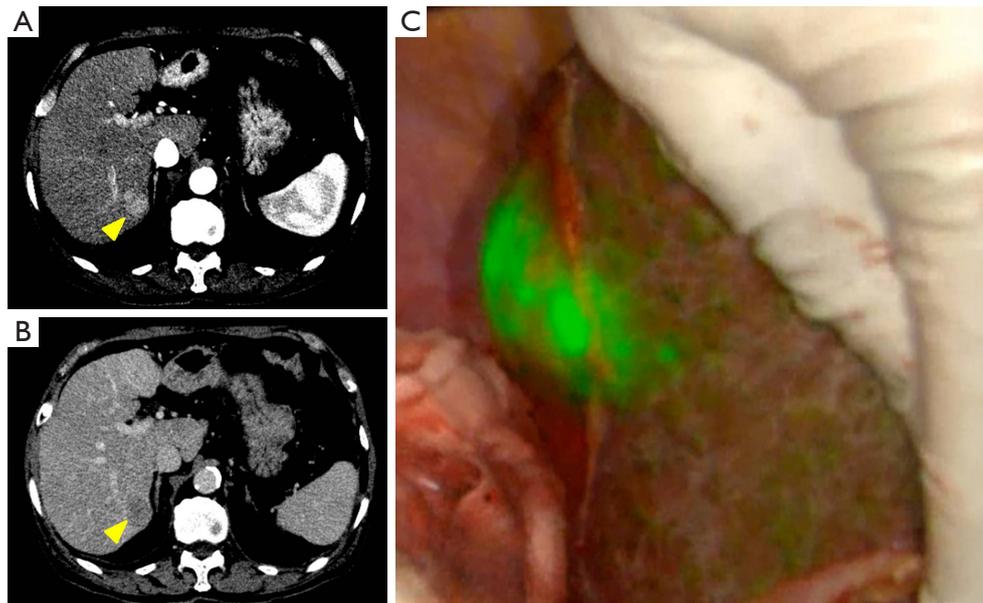


Figure 1 Preoperative computed tomography reveals hepatocellular carcinoma located in S7 (yellow arrowhead). (A) Arterial phase; (B) portal phase; (C) intraoperative ICG fluorescence imaging delineates the location of the hepatocellular carcinoma in S7.

Outline of the ICG system

ICG is a hydrosoluble molecule, which is rapidly and efficiently fixed to plasma proteins upon intravenous injection. Approximately 98–99% of ICG molecules bind to high molecular-weight proteins such as albumin. ICG is selectively taken up to hepatocytes and excreted in the bile by an active transporter (14). Fusion ICG fluorescence images are obtained using a complementary metal-oxide semiconductor camera head and a near-infrared laser diode for ICG excitation at a wavelength of 805 nm.

Detection of hepatic tumors using ICG

ICG fluorescence imaging system is worldwide used to detect hepatocellular carcinoma (HCC) and liver metastases, and this technique is especially useful for identifying subcapsular tumors during laparoscopic surgery because visual inspection and palpation of tumors are limited compared with open hepatectomy (15,16). The ICG fluorescence pattern of HCC and liver metastases is different.

The mechanism of ICG fluorescence imaging of HCC has been elucidated by immunohistochemical staining and gene expression analysis (7,17). The optimal timing and dose of ICG administration for this use have not yet

been proved. Generally, ICG (0.5 mg/kg body weight) is intravenously administered within 2 weeks before surgery in this method. ICG administration on the day before surgery in patients with decreased liver function should be avoided to reduce incidence of false-positives and background liver fluorescence. Further, in differentiated HCC, the expression levels of portal uptake transporters of ICG are well preserved, but biliary excretion disorder leads to retention of ICG in cancerous tissues (18) (*Figure 1*). However, in the case of poorly differentiated HCC, not only are the portal uptake transporters downregulated in cancerous tissues but the biliary excretion of ICG by surrounding non-cancerous hepatic parenchyma is also disordered, which results in rim-type fluorescence (18). It has been reported that the rim-type fluorescence signal found in patients with colorectal liver metastases is caused due to reduced bile excretion ability of the immature hepatocytes surrounding the tumor (19).

One of the disadvantages of ICG fluorescence imaging-based tumor detection is the relatively high false-positive rate. According to previous reports, out of the lesions newly detected only by fluorescence imaging of resected HCC specimens, 40–50% were non-cancerous lesions, such as regenerative nodules, atypical adenomatous hyperplasia, adenomatous hyperplasia, and bile duct proliferation

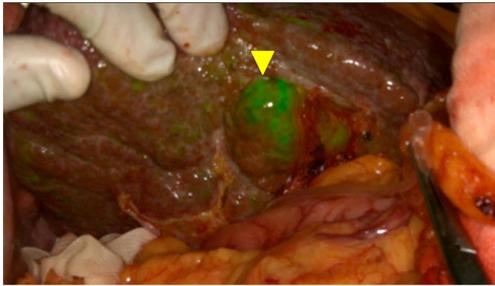


Figure 2 A false-positive nodule was identified in S5 during hepatectomy by intraoperative ICG fluorescence imaging for hepatocellular carcinoma (yellow arrowhead). The pathological diagnosis was a large cell regenerative nodule.

(10,20). For this reason, additional resection of these lesions should be recommended only when the other diagnostic modalities (re-evaluation of preoperative images, especially MRI, palpation/visual inspection, and/or intraoperative ultrasonography) also support a possibility of malignancy. *Figure 2* demonstrates a false-positive nodule detected only by intraoperative ICG fluorescent imaging. The pathological diagnosis was a large cell regenerative nodule.

Another disadvantage is that ICG fluorescence cannot detect tumors located deep in the liver. As hemoglobin or water absorbs little light at 805 nm, it is possible to visualize the fluorescence signals emitted by protein-bound ICG through 5–10 mm thick connective tissue (5,21).

ICG cholangiography

Generally, the anatomical structures of extrahepatic bile duct can be revealed by fluorescence imaging system after directly injecting 0.025–0.5 mg/mL ICG or intravenously injecting 2.5 mg ICG (ICG cholangiography). In 2019, an international multicenter randomized trial proved that ICG cholangiography was superior to white light alone when visualizing extrahepatic biliary structures (22). Ishizawa *et al.* reported intravenous injection of 2.5 mg ICG can also provide with fluorescent images of biliary tract without cannulation of the bile duct (23). These method decreases the risk of bile duct injury without the need to insert a trans-cystic tube for contrast material injection or to expose patients and medical staff to radiation.

ICG cholangiography is effective for visualizing the confluence of the left and right hepatic duct, decreasing the potential risks of bile duct injury or stenosis (16). After the liver resection, ICG fluorescence imaging can be used

for detection of bile leakage on raw hepatic surfaces (16). Marino *et al.* reported a 1:1-ratio case-matched cohort study of robotic liver resection, in which the surgical outcomes of 25 patients undergoing ICG cholangiography were compared with those of the group not receiving ICG cholangiography. Despite a similar operative time, the rates of postoperative bile leakage, R1 resection, and readmission were reduced in the group receiving ICG cholangiography (24).

Visualization of hepatic segments

Another feature of ICG fluorescence imaging is the visualization of the boundaries of hepatic segments, which helps anatomic resection to navigate the transection line in real time during hepatectomy. Anatomical resection is based on a theory to eradicate portal venous tumor extension and intrasegmental metastasis of HCC (25). In laparoscopic hepatectomy, we usually use a fluorescent imaging system to fuse images from the macroscopic view and the near-infrared ray view on a single monitor and the mode of monitoring could be switched with one button. There are two types of staining methods to reveal the borderline of the liver. The positive staining method involves directly injecting 0.25–2.5 mg/mL ICG solution into the portal vein branches of the hepatic segments to be removed. On the other hand, ischemic regions can be identified by injecting ICG intravenously after division or ligation of the corresponding portal branches (negative staining method) (8,9). The latter method is particularly useful in laparoscopic liver resection wherein injecting ICG solution into the branches of portal vein is technically demanding.

ICG fluorescence imaging keeps the demarcation line visualized during the whole parenchymal transection phase, which enables surgeons to intermittently check the proper anatomical borders. In our institution, laparoscopic segmentectomy is performed by the negative staining method with intravenous injection of ICG (2.5 mg) (*Figure 3*). The negative staining method visualizes the segmental borders not only on the liver surface, but also on the raw cut surface, which helps the surgeon follow the optimal direction during surgery (*Figure 4*). Berardi *et al.* reported that real-time navigation using the negative staining technique allowed surgeons to perform precise laparoscopic anatomical liver resection as planned by three-dimensional simulation in 98.7% of patients (26). In case of liver cirrhosis, because of the liver cell malfunction of

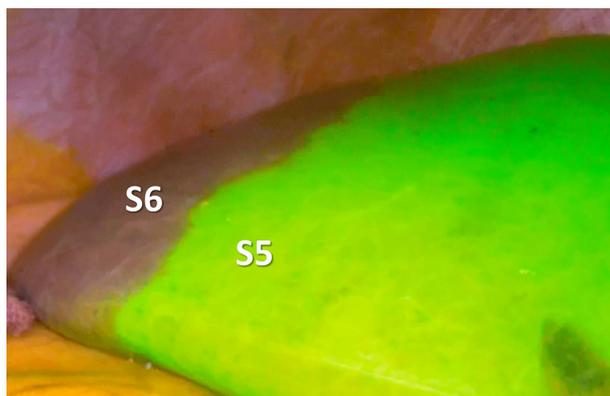


Figure 3 With the negative staining method of ICG fluorescence imaging reveals the boundaries between S5 and S6.

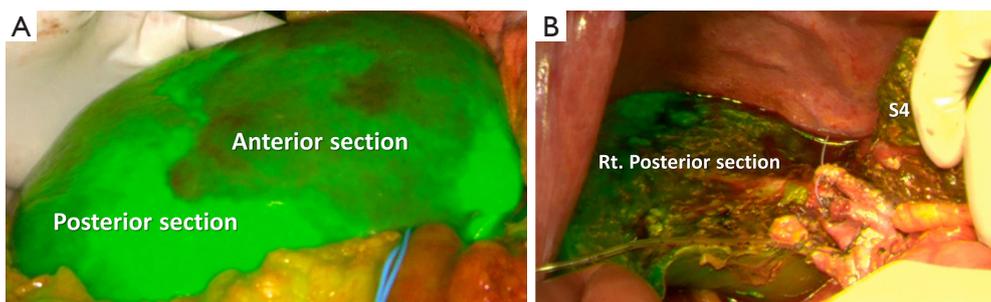


Figure 4 ICG fluorescence imaging using negative staining method. (A) Visualization of the segmental boundaries of right anterior section by ICG fluorescence imaging using the negative staining method. (B) ICG fluorescence was visible on the raw surface of the right posterior section and segment 4 after the resection of the right anterior section.

secretion and excretion, ICG will therefore remain in the liver parenchyma; thus, the disappearance of fluorescence is delayed (19,20,27).

Conclusions

ICG fluorescence imaging is a simple and useful method for visualizing liver tumors, the biliary tree, and boundaries of hepatic segments invisible to the naked eye. The application of ICG fluorescence imaging can improve the safety and quality of open, laparoscopic, and robotic hepatectomy.

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References

- Ogawa K, Fukunaga K, Takeuchi T, et al. Current treatment status of polycystic liver disease in Japan. *Hepatol Res* 2014;44:1110-8.
- Ardito F, Bianco G, Vellone M, et al. Long-term outcome after laparoscopic fenestration of simple liver cysts. *Surg Endosc* 2013;27:4670-4.
- Miyashiro I, Miyoshi N, Hiratsuka M, et al. Detection of sentinel node in gastric cancer surgery by indocyanine green fluorescence imaging: Comparison with infrared imaging. *Ann Surg Oncol* 2008;15:1640-3.
- Kitai T, Inomoto T, Miwa M, et al. Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. *Breast Cancer* 2005;12:211-5.
- Tsujino Y, Mizumoto K, Matsuzaka Y, et al. Fluorescence navigation with indocyanine green for detecting sentinel nodes in extramammary Paget's disease and squamous cell carcinoma. *J Dermatol* 2009;36:90-4.
- Kurihara T, Yamashita Y, Yoshida Y, et al. Indocyanine green fluorescent imaging for hepatic resection of the right hepatic vein drainage area. *J Am Coll Surg* 2015;221:e49-53.
- 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;32:1763-67.
- Ishizawa T, Zuker NB, Kokudo N, et al. Positive and negative staining of hepatic segments by use of fluorescent imaging techniques during laparoscopic hepatectomy. *Arch Surg* 2012;147:393-4.
- Inoue Y, Arita J, Sakamoto T, et al. Anatomical liver resections guided by 3-dimensional parenchymal staining using fusion indocyanine green fluorescence imaging. *Ann Surg* 2015;262:105-11.
- 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.
- Lim C, Vibert E, Azoulay D, et al. Indocyanine green fluorescence imaging in the surgical management of liver cancers: current facts and future implications. *J Visc Surg* 2014;151:117-24.
- Ishizawa T, Bandai Y, Kokudo N. Fluorescent cholangiography using indocyanine green for laparoscopic cholecystectomy: an initial experience. *Arch Surg* 2009;144:381-2.
- Lehrskov LL, Westen M, Larsen SS, et al. Fluorescence or X-ray cholangiography in elective laparoscopic cholecystectomy: a randomized clinical trial. *Br J Surg* 2020;107:655-61.
- Cherrick GR, Stein SW, Leevy CM, et al. Indocyanine green: observations on its physical properties, plasma decay, and hepatic extraction. *J Clin Invest* 1960;39:592-600.
- 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.
- Terasawa M, Ishizawa T, Mise Y, et al. Applications of fusion-fluorescence imaging using indocyanine green in laparoscopic hepatectomy. *Surg Endosc* 2017;31:5111-8.
- Shibasaki Y, Sakaguchi T, Hiraide T, et al. Expression of indocyanine green-related transporters in hepatocellular carcinoma. *J Surg Res* 2015;193:567-76.
- 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.
- van der Vorst JR, Schaafsma BE, Hutteman M, et al. Near-infrared fluorescence-guided resection of colorectal liver metastases. *Cancer* 2013;119:3411-8.
- Gotoh K, Yamada T, Ishikawa O, et al. A novel image-guided surgery of hepatocellular carcinoma by indocyanine green fluorescence imaging navigation. *J Surg Oncol* 2009;100:75-9.
- Landsman ML, Kwant G, Mook GA, et al. Light-absorbing properties, stability, and spectral stabilization of indocyanine green. *J Appl Physiol* 1976;40:575-83.
- Dip F, LoMenzo E, Sarotto L, et al. Randomized Trial of

- Near-infrared Incisionless Fluorescent Cholangiography. *Ann Surg* 2019;270:992-9.
23. 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.
 24. Marino MV, Di Saverio S, Podda M, et al. The application of indocyanine green fluorescence imaging during robotic liver resection: a case-matched study. *World J Surg* 2019;43:2595-606.
 25. Zhong XP, Zhang YF, Mei J, et al. Anatomical versus Non-anatomical Resection for Hepatocellular Carcinoma with Microscope Vascular Invasion: A Propensity Score Matching Analysis. *J Cancer* 2019;10:3950-7.
 26. Berardi G, Igarashi K, Li CJ, et al. Parenchymal sparing anatomical liver resections with full laparoscopic approach: Description of technique and short-term results. *Ann Surg* 2021;273:785-91.
 27. de Graaf W, Hausler S, Heger M, et al. Transporters involved in the hepatic uptake of Tc-99 m-mebrofenin and indocyanine green. *J Hepatol* 2011;54:738-45.

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