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).
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 elucidate 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 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.
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.

**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. 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. 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. After the liver resection, ICG fluorescence imaging can be used for detection of bile leakage on raw hepatic surfaces. 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.

**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. 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). 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. In case of liver cirrhosis, because of the liver cell malfunction of...
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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**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.
to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**References**


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