ICG-ENHANCED FLUORESCENCE-GUIDED LAPAROSCOPIC SURGERY

3rd Edition

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1 Introduction

1.1 Historical and Scientific Background

Fluorescence is the property of certain molecules (fluorochromes) to emit fluorescent radiation when excited by a laser beam or exposed to near-infrared light (NIR) at specific wavelengths.1 Once the light energy is absorbed by the fluorochrome’s organic molecules, a promotion of delocalized electrons from ground state to a higher energy level occurs. Upon return from excited singlet state to ground state, energy is emitted in the form of photons, reaching the observer’s eye as fluorescence of a specific wavelength (Fig. 1.1).

Indocyanine green (ICG) dye was developed for near-infrared (NIR) photography by Kodak Research Laboratories in 1955 and was introduced in clinical practice since 1956.3,11 Initially, ICG was used in clinical applications to measure cardiac output,8,27 to study the anatomy of retinal vessels2 and to determine liver functional reserve before hepatic resection in cirrhotic livers.18 The ICG dye can be injected into the human blood stream with practically no adverse effects.1 ICG becomes fluorescent once excited with light of a specific wavelength in the NIR spectrum delivered by a specific light source or NIR laser device.7,21,34 Fluorescence can be detected using specific scopes and cameras, and then transmitted to a video screen, thus enabling the observer to visualize areas of anatomical interest where the dye has accumulated (e.g., biliary ducts, vessels, lymph nodes).

In recent years, ICG-enhanced fluorescence has been introduced in laparoscopic surgery to improve visualization and provide detailed anatomical information during surgery.29,39

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Fig. 1.1 Schematic drawing demonstrating the principle of fluorescence.

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Fig. 1.2 Electromagnetic spectrum with close-up view of the visible and near-infrared wavelength ranges.
ICG is a sterile, anionic, water-soluble but relatively hydrophobic, tricarbocyanine molecule with a molecular mass of 774.99 g/mol. Following intravenous injection, ICG is rapidly bound to plasma proteins, especially lipoproteins, with minimal leakage into the interstitium (Fig. 1.3). There are no known metabolites. ICG is rapidly extracted unaltered via the liver and almost completely excreted without conjugation in bile about 8 minutes after injection, depending on liver vascularization and function.\(^1\),\(^14\)

**Fig. 1.3** Schematic drawing showing intravenous administration of ICG.

For visualization of efferent lymph vessels, ICG is injected in the peritumoral area, commonly reaching the nearest draining lymph node within 15–20 minutes. After 1–2 hours, it binds to the regional lymph nodes, deposited into macrophages.\(^16\),\(^36\),\(^37\)

The standard dose commonly administered in clinical practice (0.1–0.5 mg/ml per kg of body weight) is well below the toxicity level.\(^1\)

ICG-enhanced fluorescence imaging offers major benefits during the following procedures:

- Fluorescence cholangiography during laparoscopic cholecystectomy to improve visualization of the biliary duct system.
- Fluorescence angiography for perfusion control during esophagogastric and colorectal surgery, for identification of vascular anatomy and perfusion control of solid organs.
- Intraoperative assessment of lymphatic drainage and sentinel lymph node (SLN) detection.
- NIR/ICG fluorescence-guided intraoperative identification of ureters after placement of ureteral catheters.

The KARL STORZ recommended set for ICG-enhanced fluorescence-guided laparoscopy is the IMAGE1 S™ RUBINA™ technology which includes a native 4K camera and is based on the modular IMAGE1 S™ camera platform. The video camera is connected to an ICG laparoscope equipped with a special filter for optimal reproduction during ICG-enhanced fluorescence and standard white light imaging. Apart from high-quality 4K video with natural color reproduction in white light conditions, there are three different NIR/ICG modes available (Overlay, Intensity Map and Monochromatic). The system offers a high level of user-friendly functionality. Switching from standard white light mode to NIR/ICG mode, and vice versa, is simply done via foot-pedal control or camera head buttons.

The NIR/ICG fluorescence Overlay mode can be adjusted so that the video image appears either in blue or in green color.

The NIR/ICG green color offers intensive fluorescence and detailed delineation against the surrounding tissue.

Conversely, choosing the NIR/ICG blue color offers the advantage of a more balanced fluorescence image, especially in well-perfused areas such as the liver. In this way, areas of high fluorescence intensity are less prone to appear overexposed.

In both white light mode and in the NIR/ICG fluorescence Overlay modes, visualization can be improved by the image enhancement functions (S-technologies) of the IMAGE1 S™ system. The surgeon can select the preferred S-technology as determined by the intended purpose.

The KARL STORZ IMAGE1 S™ system offers expanded compatibility and connectivity for further applications, as for instance, flexible endoscopy and open surgery procedures. For additional information about IMAGE1 S™ RUBINA™, see the addendum section of this brochure, see pp. 16.
ICG-Enhanced Fluorescence-Guided Laparoscopic Procedures

In all ICG-enhanced fluorescence-guided procedures performed by the authors, indocyanine green (VERDYE, Diagnostic Green) is used in the diluted form with sterile water.

2.1 ICG Fluorescence Cholangiography during Laparoscopic Cholecystectomy

The dye is injected intravenously at least 30 minutes before surgery to allow the agent to accumulate in bile.\textsuperscript{13,30}

In cases of elective cholecystectomy, ICG should be injected 3–10 hours prior to the procedure. In this way, it is made sure, that most of the agent has accumulated in the extrahepatic duct, while absence of fluorescence is typically noticeable in the liver parenchyma.

Following injection, the agent is concentrated in bile, resulting in visual enhancement of the biliary tree anatomy, especially in Calot’s triangle. During laparoscopic cholecystectomy, the use of ICG-enhanced fluorescence imaging has proven useful in both elective and acute settings.

Employed in an acute setting, diluted ICG should be administered as early as possible (at least 30 minutes prior to surgery). In such cases, concomitant background fluorescence is anticipated to occur in the liver parenchyma.

Even though there is variability between individuals, mainly related to liver function, BMI and inflammation grade, the ICG standard concentration for fluorescence-guided cholecystectomy is 0.1–0.2 mg / kg.\textsuperscript{1, 15, 31}

In a single-blind, randomized clinical trial Dip et al. showed that ICG fluorescence cholangiography (undertaken before and after dissection) is associated with a distinctly higher detection rate for all extrahepatic biliary structures as well as the junction between cystic duct and common bile duct, when compared to white light cholecystectomy alone. Contrasting the patients’ body mass index and inflammation grade with the detection rate of biliary structures, the trial revealed a statistically significant negative correlation.\textsuperscript{9}

If the individual anatomy of the cystic artery calls for intraoperative assessment, a small bolus of 2–3 ml of diluted ICG (0.2 mg/kg) can be injected. Fluorescence usually develops at the level of Calot’s triangle delineating the cystic artery after 60 seconds, and lasting for a mean time of nearly 35 seconds.

It is recommended to dilute a 25 mg-vial of ICG with 10 ml of sterile water.

- **Elective cholecystectomy**: 0.1 mg/kg of ICG solution administered 3–10 hours prior to the procedure if possible, in any case at least 30 minutes before surgery.
- **Acute cholecystitis**: 0.1 mg/kg of ICG solution administered at least 30 minutes prior to the procedure.

![Fig. 2.1 ICG-enhanced fluorescence imaging for visualization of biliary anatomy during elective laparoscopic cholecystectomy. Intraoperative views taken while using the green NIR/ICG Overlay mode. Prior to initiating dissection, the cystic duct (CD) is identified (a). In panel (b), the cystic duct (CD) and common bile duct (CBD) are identified.](image-url)
In most of the cases, right from the start of the procedure, ICG-enhanced fluorescence imaging allows to identify extra-hepatic biliary anatomy without or with minimal dissection of Calot’s triangle. This has proven to be useful not only in the normal course of the procedure, but also serves as a precautionary measure in the presence of anatomical variations or in certain conditions (e.g., inflamed tissue) posing an increased risk of iatrogenic injury. As a result, proper identification of vital structures and high-risk areas – which must be respected until dissection enables the key landmarks to be localized – is facilitated.

2.2 Intraoperative Assessment of Lymphatic Drainage and Sentinel Lymph Node Detection

ICG-enhanced fluorescence imaging may also be used for mapping lymphatic drainage pathways from various organs. The above method has been proposed for SLN biopsy in breast surgery, for surgical treatment of melanoma and gastrointestinal cancer, and – given the use of a dedicated telescope – for open surgery procedures. Among the clinical applications eligible for laparoscopic ICG-enhanced fluorescence imaging are the detection of intra-abdominal sentinel lymph nodes in patients with melanoma, lymphadenectomy in patients with metastatic melanoma and carcinomas of the prostate or endometrium.

It is recommended to dilute a 25 mg-vial of ICG with 20 ml of sterile water. No later than 10–15 minutes prior to the procedure, the dye is injected in the peritumoral area (a bolus of 0.5 – 1 ml used on each quadrant of the tumor) or – given a history of primary tumor removal – in the scar region. The detailed regimen for gastrointestinal tumors is as follows:

- For lymphatic mapping in gastric cancer surgery, including adenocarcinoma of the cardia in the lesser curvature, ICG is administered through esophagogastroduodenoscopy (EGD) 24 hours before surgery, allowing the lymphatic area and/or drainage pattern from the tumor to be visualized (Figs. 2.3a–c).

- In colon cancer surgery, ICG is administered in the peritumoral area at the beginning of surgery, allowing for lymphatic mapping after approx. 20–40 minutes (Figs. 2.4a–c, see overleaf).
2.3 ICG Fluorescence Angiography

ICG-enhanced fluorescence imaging may also be used to clarify vascular anatomy and to assess perfusion of solid organs or viscera, e.g., in procedures like laparoscopic gastrointestinal surgery.\textsuperscript{5, 6, 32}

The angiographic modality is effectively used to facilitate vascular dissection. This has been shown to be helpful under certain conditions when there is reason to suspect anatomical variations, as is the case in nephrectomy, liver resection, splenectomy, or vascular surgery. In such cases, ICG-enhanced fluorescence imaging provides a real-time video image of the individual distributive pattern of vascularity. The technique may also be used for assessment of organ perfusion and ischemia in applications such as liver resection,\textsuperscript{17} partial splenectomy, control of perfusion after kidney transplantation, and perfusion assessment of the gastric conduit during esophagectomy,\textsuperscript{35} just to mention a few.

One of the most widely accepted indications for ICG fluorescence angiography is laparoscopic colorectal resection. The technique is used to confirm adequate perfusion of the large bowel prior to anastomosis. Recent meta-analyses have demonstrated that the use of ICG fluorescence angiography is associated with a reduced rate of anastomotic leakage after colorectal surgery.\textsuperscript{19, 20}

Following injection of ICG into a central or peripheral vein the emerging fluorescence provides a “real-time snapshot” of colonic perfusion. This has been found to be very useful in defining the ideal plane of resection during mesenteric division, and allows to demonstrate ischemic or poorly-perfused areas after mesenteric division – i.e., prior to anastomosis – thus facilitating the assessment of vascularity after completion of anatomical reconstruction.

For perfusion assessment of the bowel, diluted ICG is injected using multiple boluses of 3 ml, each at a concentration of 0.2 mg/kg (usually 25 mg-vial of ICG diluted with 10 ml of sterile water).

Timing of ICG administration should be adapted to the substages of colorectal resection.

Left colectomy and anterior resection

\begin{itemize}
  \item Distal bowel resection and extraction of the colon.
  \item Intravenous ICG injection (3 ml) and identification of the perfused bowel prior to proximal resection (Figs. 2.5–2.6).
  \item Circular stapler is inserted into the rectum, the anvil is placed in the proximal colon, if mechanical anastomosis is to be performed.
  \item Intravenous ICG injection (3 ml) and perfusion assessment of bowel stumps.
  \item Anastomosis.
\end{itemize}

Optimal injection regimen

In order to induce real-time fluorescence angiography, ICG should be injected while the bowel or its vascularity pattern is shown on the video screen. Placing the distal tip of the scope in close proximity to the target area – without using the zoom function – has been found to improve visualization.

Occasionally, differences become noticeable between the planned resection line and the boundaries of well-perfused areas.

If extracorporeal bowel division is to be performed, whether for right or left-sided resections, adequate visualization is feasible with the operating room lighting turned off, because ambient illumination interferes with the fluorescence detection sensitivity of the video camera. Following completion of anastomosis, a reusable rectoscope may be introduced to assess perfusion of the rectal stump (Fig. 2.7).
Fig. 2.5 ICG-enhanced fluorescence-guided assessment of colonic perfusion after mesentery division during laparoscopic left colectomy. Intraoperative views taken during white light mode (a) and green NIR/ICG Overlay mode (b).

Fig. 2.6 ICG-enhanced fluorescence-guided assessment of colonic perfusion after mesentery division during laparoscopic left colectomy. Intraoperative views taken during Monochromatic NIR/ICG mode (a) and NIR/ICG Intensity Map mode (b). The tip of the forceps points to the boundary of the well-perfused area.

Fig. 2.7 ICG-enhanced fluorescence-guided perfusion assessment of the rectal stump during laparoscopic low anterior resection. Intraoperative view using the green NIR/ICG Overlay mode.
2.4 ICG-Enhanced Fluorescence-Guided Resection of Hepatic Metastases

ICG-enhanced fluorescence imaging aids in localizing hepatic metastases, thus enabling a targeted tumor removal in laparoscopic liver resection. An intravenous injection of 0.4 mg/kg ICG solution is given 36 hours prior to surgery. After this period, the normal liver parenchyma has eliminated most of the injected dye, whereas it is retained in adjoining non-diseased cells around the metastatic lesion which are deficient in normal bile secretion (Fig. 2.8a-g).

In this case, ICG-enhanced fluorescence imaging not only helps in localizing metastatic lesions, but also facilitates to determine the resection margins.

**Fig. 2.8** ICG-enhanced fluorescence-guided liver resection for metastatic hepatic lesions. The intraoperative images (a) to (g) were captured using the following visualization modes:

a. White light mode.

b. NIR/ICG Overlay mode.

c. NIR/ICG Intensity Map mode.

d. NIR/ICG Overlay mode (open surgery).

e. NIR/ICG Overlay mode (macroscopic view of the surgical specimen after extraction).

f. NIR/ICG Monochromatic mode showing the same specimen as in (e).

g. NIR/ICG Intensity Map mode showing the same specimen as in (e).
2.5 ICG-Enhanced Fluorescence Imaging for Visualization of Ureters in Laparoscopic Abdominal Surgery

ICG-enhanced fluorescence imaging can also be used for intraoperative identification of the ureters. As mentioned above, ICG is excreted in bile, thus it is not possible to localize the urinary system after intravenous ICG injection.

In order to enable identification of the ureters by NIR/ICG fluorescence, ureteral catheters (monolateral or bilateral, depending on surgery) are placed with a cystoscope directly before surgery. It is recommended to dilute 25 mg of ICG with 20 ml of sterile water and inject 2–3 ml of the solution into the renal pelvis through the open catheter. Following administration of ICG, the catheter(s) need(s) to be clamped and retracted causing ICG inflow followed by emergence of NIR fluorescence of the ureter(s) (Fig. 2.9)

Once the dye is instilled as described, NIR/ICG fluorescence allows to identify the ureters throughout the surgical procedure. The technique has been found to be very useful in complex cases of abdominal and pelvic surgery, like complicated diverticular disease or in the treatment of bulky tumors.22, 33

Fig. 2.9 ICG-enhanced fluorescence imaging for visualization of the left ureter during left colectomy. Intraoperative images (a, b) captured while using the green NIR/ICG Overlay mode.
ICG-Enhanced Fluorescence-Guided Laparoscopic Surgery

References


# IMAGE1 S™ RUBINA™ Technology for NIR/ICG Fluorescence Imaging

Based on the IMAGE1 S™ camera platform

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* Optional accessory.
ICG-Enhanced Fluorescence-Guided Laparoscopic Surgery

IMAGE1 S™ RUBINA™ Technology for NIR/ICG Fluorescence Imaging
based on the IMAGE1 S™ camera platform

1. **IMAGE1 S™ Camera Platform**
   - Modular architecture
   - Native 4K resolution and natural color rendering
   - S-Technologies in white light and in combination with the Overlay modes
   - Integrated unit communication via KS HIVE™

2. **Cold Light Fountain POWER LED RUBINA™**
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