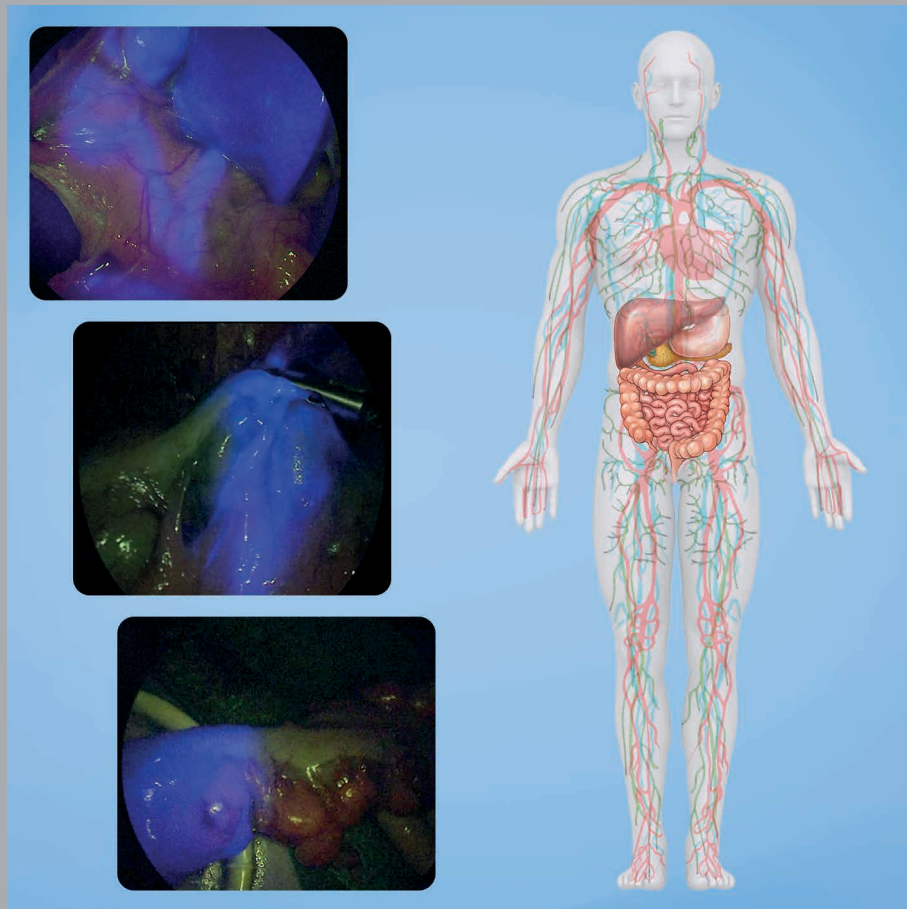


Endo:Press®

# ICG-ENHANCED FLUORESCENCE- GUIDED LAPAROSCOPIC SURGERY

2<sup>nd</sup> Edition



Luigi BONI  
Simona MACINA  
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## ICG-Enhanced Fluorescence-Guided Laparoscopic Surgery – 2<sup>nd</sup> 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.<sup>1</sup> 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).

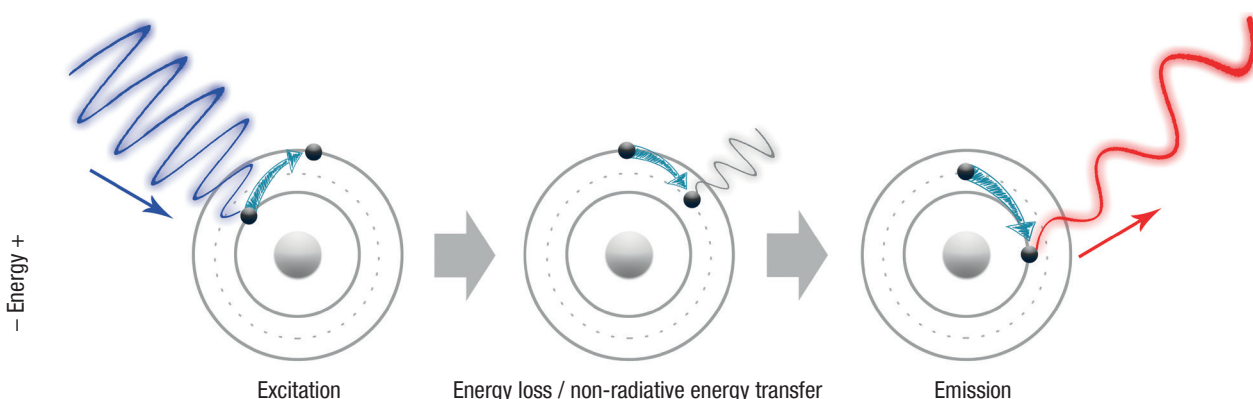


Fig. 1.1 Schematic drawing demonstrating the principle of fluorescence.

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.<sup>3, 10</sup>

Initially, ICG was used in clinical applications to measure cardiac output,<sup>8, 23</sup> to study the anatomy of retinal vessels<sup>(2)</sup> and to determine liver functional reserve before hepatic resection in cirrhotic livers.<sup>17</sup>

The ICG dye can be injected into the human blood stream with practically no adverse effects.<sup>1</sup> ICG becomes fluo-

rescent once excited with light of a specific wavelength in the NIR spectrum delivered by a Xenon light source or NIR laser device.<sup>7, 18, 29</sup> 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.<sup>25, 34</sup>

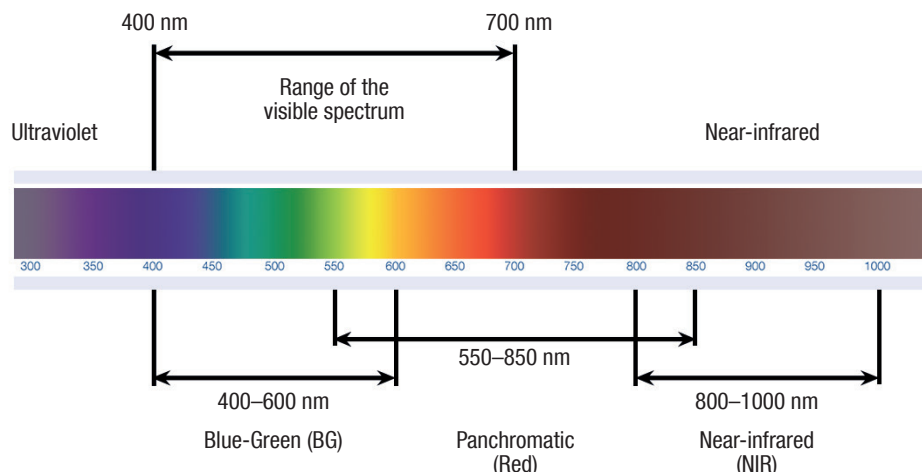
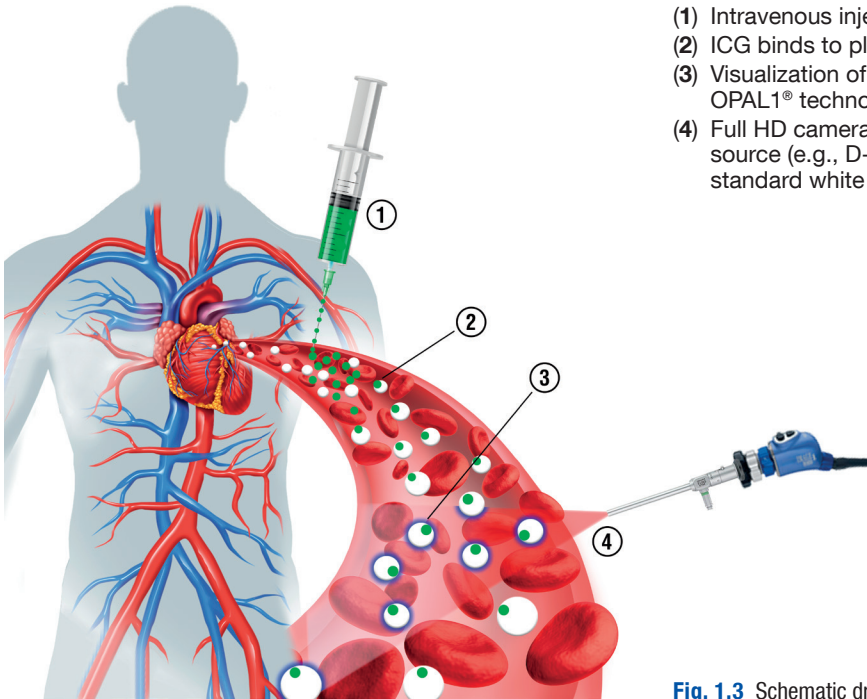


Fig. 1.2 Electromagnetic spectrum with close-up view on the visible and near-infrared wavelength ranges.

ICG is a sterile, anionic, water-soluble but relatively hydrophobic, tricarboyanine molecule with a molecular mass of 774,99g/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.<sup>1, 13</sup>



- (1) Intravenous injection of ICG
- (2) ICG binds to plasma proteins
- (3) Visualization of ICG in bloodstream using KARL STORZ OPAL1® technology for NIR/ICG imaging.
- (4) Full HD camera system coupled to a Xenon cold light source (e.g., D-LIGHT P) which can be operated in standard white light mode and in NIR/ICG mode.

**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 minutes. After 1–2 hours, it binds to the regional lymph nodes, deposited into macrophages.<sup>15, 32, 33</sup>

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

ICG-enhanced fluorescence imaging provides for improved visualization of the biliary duct system and tracing of the flow of bile, intraoperative evaluation of lymphatic drainage, sentinel lymph node mapping, identification of vascular anatomy, and for perfusion control of solid organs, colon and rectum.

The KARL STORZ recommended set for ICG-enhanced fluorescence-guided laparoscopy includes a high-end full HD camera system IMAGE1 S™ that can be operated in dual mode for both white light and fluorescence imaging. 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 superb full HD image quality in white light mode and backlight illumination with true color gamut, 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.

When used in NIR/ICG fluorescence mode, the KARL STORZ OPAL1® technology can be adjusted such that the video image appears either in blue or in green color.

Using the NIR/ICG green mode offers intensive fluorescence and detailed delineation against the surrounding tissue. As a concomitant effect, the background appears with slight brightening.

Conversely, use of the NIR/ICG blue mode 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.

Visualization in both modes is improved by use of the IMAGE1 S™ system, which comes with various imaging modules that can be selected according to surgeon's preferences.

The KARL STORZ IMAGE1 S™ system offers expanded compatibility and connectivity for further applications such as 3D imaging, 4K imaging, flexible endoscopy, and open surgery procedures. For additional information, see the addendum section of this brochure, page 17.

## 2

## ICG-Enhanced Fluorescence-Guided Laparoscopic Procedures

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

Once the solution is prepared in the operating room, it is injected into a peripheral vein or in the area around the tumor at a specific concentration depending on the patient's weight and clinical situation.

### 2.1 ICG-enhanced Fluorescence-Guided Laparoscopic Cholecystectomy

The dye is injected intravenously at least 30 minutes before surgery to allow the agent to accumulate in bile.<sup>12, 26</sup>

In cases of elective cholecystectomy, ICG should be injected 6–10 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 under NIR light has proven useful in both elective and acute settings.

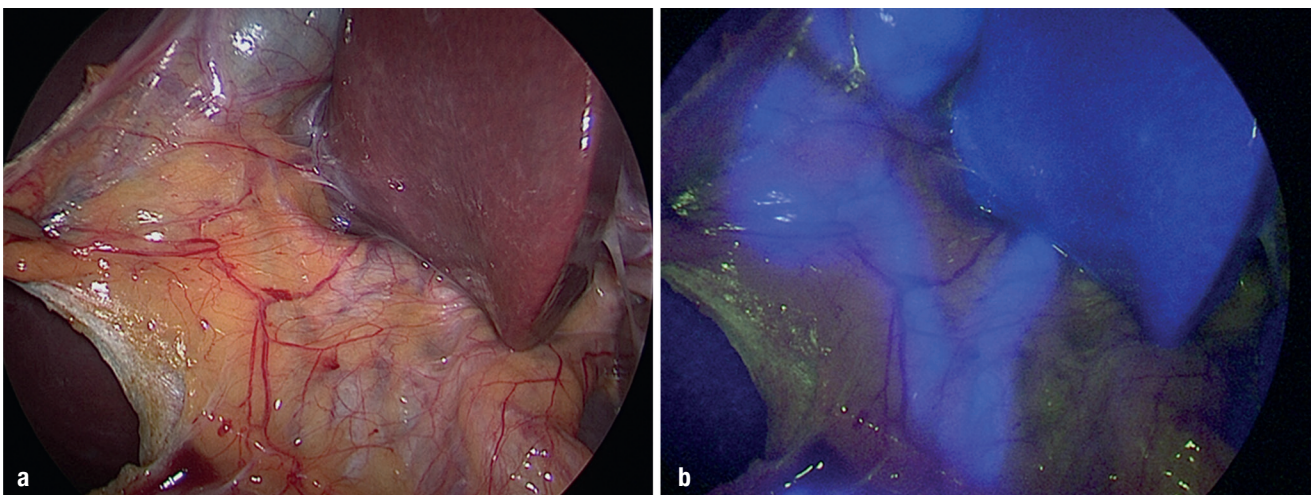
Employed in an acute setting, diluted ICG should be administered as early as possible (at least 30 minutes prior to surgery). In such cases, concomitant background fluorescence is anticipated to occur in the liver parenchyma.

Even though there is variability between individuals, mainly related to liver function, the ICG standard dose for fluorescence-guided cholecystectomy is 0.1–0.2 mg / kg.<sup>1, 14, 27</sup>

Based on the standard protocol employed in the authors' clinical practice, a 25 mg-bottle of ICG is diluted using 10 ml of sterile water.

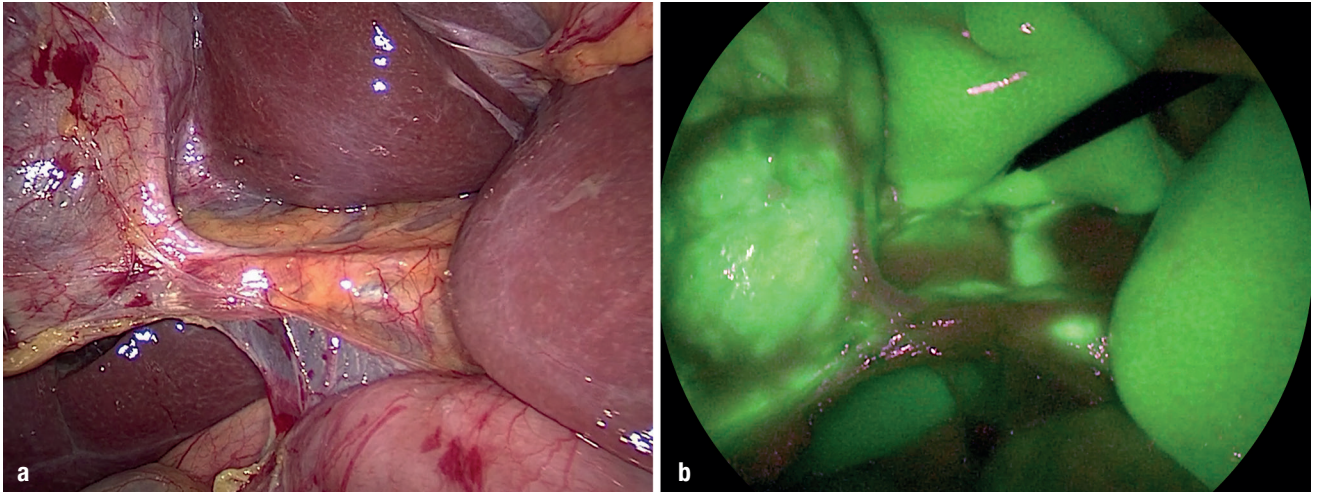
- **Elective cholecystectomy:** 4 ml of ICG solution administered 6–10 hours\* prior to the procedure if possible, in any case at least 30 minutes before surgery.
- **Acute cholecystitis:** 5–7 ml of ICG solution administered at least 30 minutes prior to the procedure.

According to reports in the literature, use of this technique allows to identify the biliary anatomy in virtually all cases (100% sensitivity) and, in particular, the junction between cystic duct and common bile duct<sup>4, 9, 13, 29, 31</sup> irrespective of whether or not the tissue to be visualized is inflamed (Figs. 2.1–2.4).

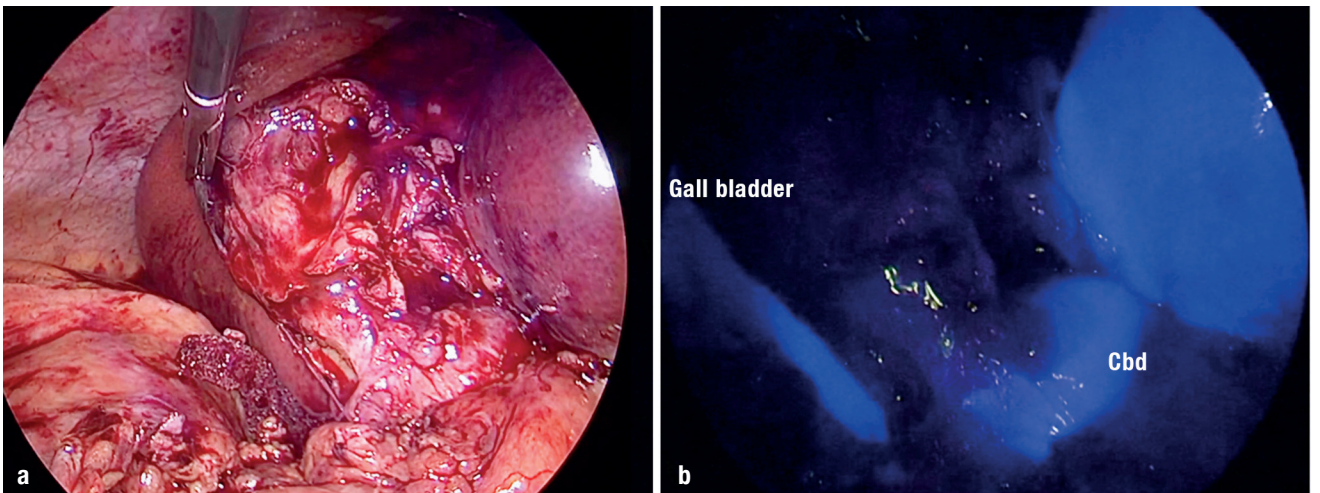


**Fig. 2.1** ICG-enhanced fluorescence imaging for visualization of biliary anatomy during elective laparoscopic cholecystectomy. Intraoperative views taken during white light mode (a) and NIR/ICG blue mode (b).

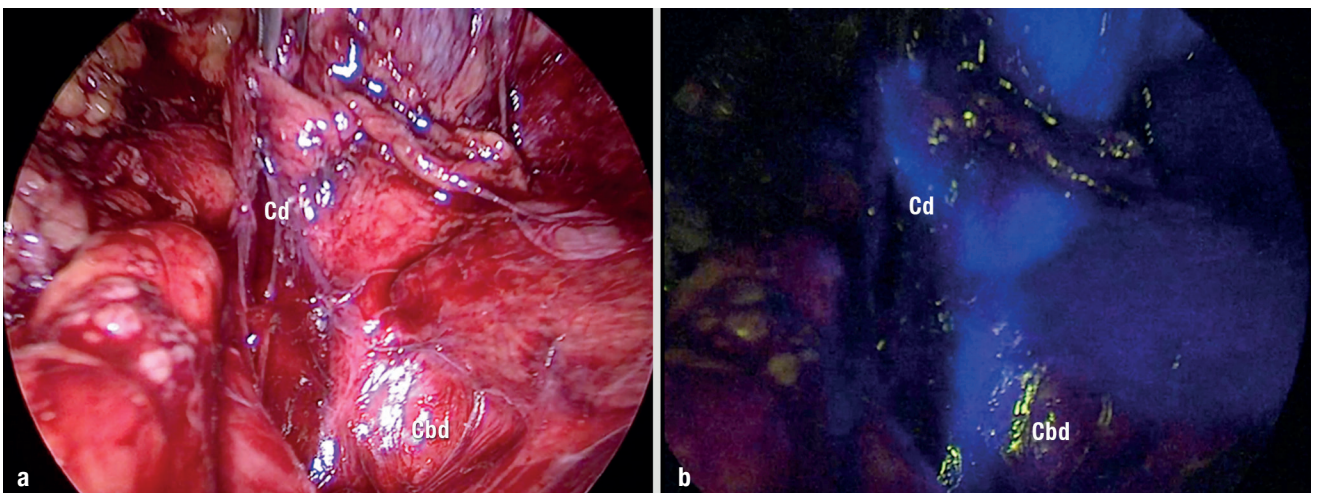




**Fig. 2.2** ICG-enhanced fluorescence imaging for visualization of biliary anatomy during elective laparoscopic cholecystectomy (diluted ICG administered 1 hour prior to the procedure). Intraoperative views taken during white light mode (**a**) and NIR/ICG green mode (**b**).



**Fig. 2.3** ICG-enhanced fluorescence imaging for visualization of biliary tree anatomy with signs of acute cholecystitis managed by laparoscopic cholecystectomy. Intraoperative views taken during white light mode (**a**) and NIR/ICG blue mode (**b**). Common bile duct (**Cbd**).



**Fig. 2.4** ICG-enhanced fluorescence imaging for visualization of biliary tree anatomy with signs of acute cholecystitis managed by laparoscopic cholecystectomy. Intraoperative views taken during white light mode (**a**) and NIR/ICG blue mode (**b**). Common bile duct (**Cbd**); Cystic duct (**Cd**).



If the individual anatomy of the cystic artery calls for intraoperative assessment, a small bolus of 2–3 ml of 0.2 mg/ml/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 (Fig. 2.1).

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., the presence of inflamed tissue) posing an increased risk for iatrogenic injury. As a result, proper identification of vital structures and high-risk areas – that 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

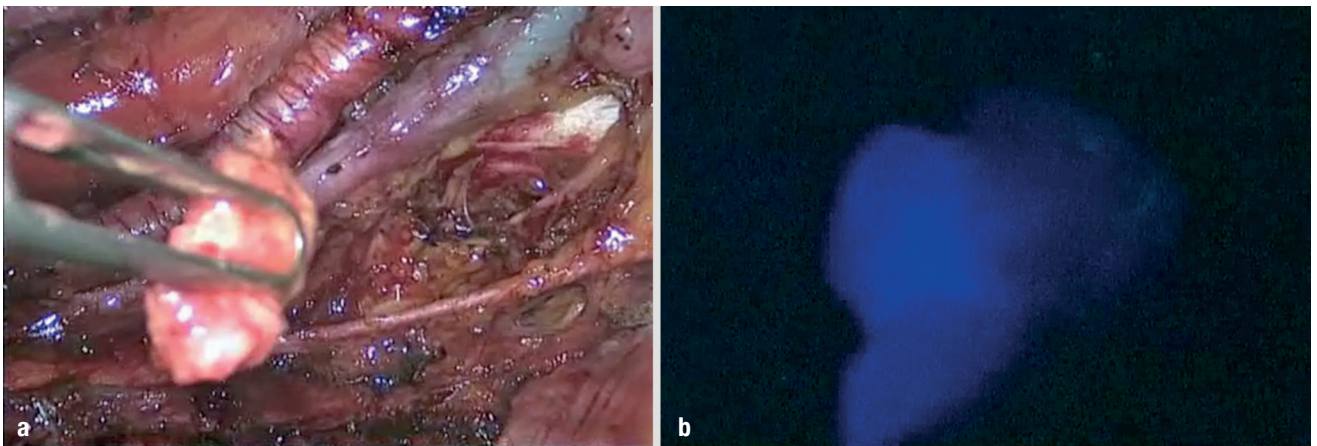
ICG-enhanced fluorescence imaging may also be used for mapping lymphatic drainage pathways from various organs.<sup>1</sup>

The above method has been proposed for sentinel lymph node biopsy in breast surgery, for surgical treatment of melanoma and gastrointestinal cancer, and – given the use of a dedicated video camera – for open surgery procedures.<sup>11, 20–22</sup>

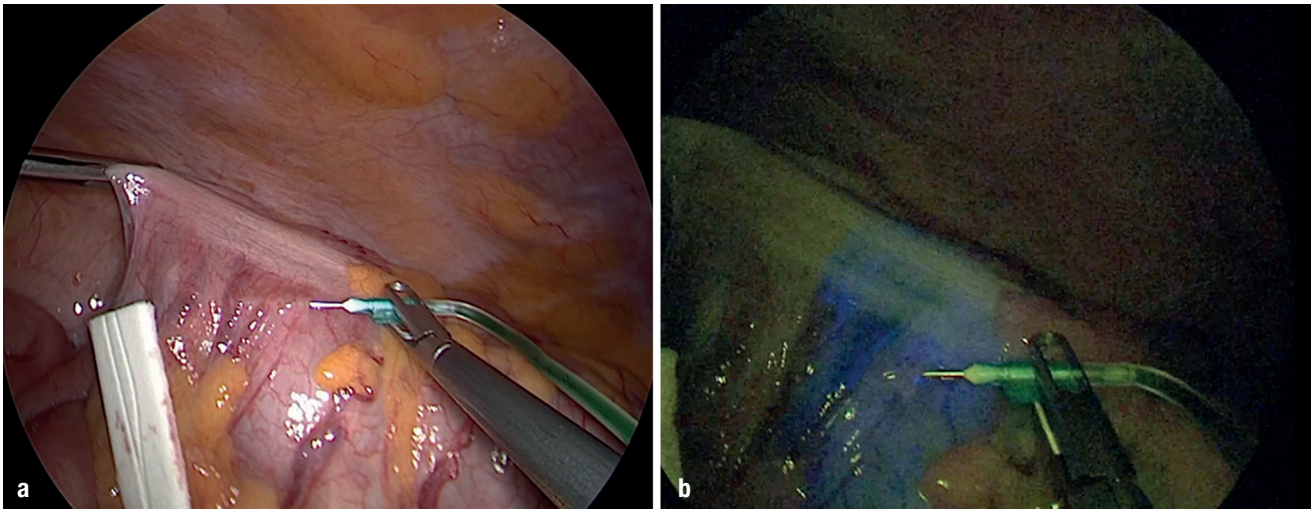
In these cases, it is recommended to dilute 25 mg of ICG with 20 ml of sterile water. No later than 10–15 min. prior to the procedure, the dye is injected in the peritumoral area (a bolus of 0.5–1 ml used on each quadrant of the tumor) or – given a history of primary tumor removal – in the scar region. This is to ensure that proper diffusion into the lymphatic vessels occurs.

Among the clinical applications eligible for laparoscopic ICG-enhanced fluorescence imaging are the detection of intra-abdominal sentinel lymph nodes in patients with melanoma (Fig. 2.5), lymphadenectomy in patients with metastatic melanoma<sup>14</sup> and carcinomas of the prostate<sup>19</sup> or endometrium.<sup>24</sup>

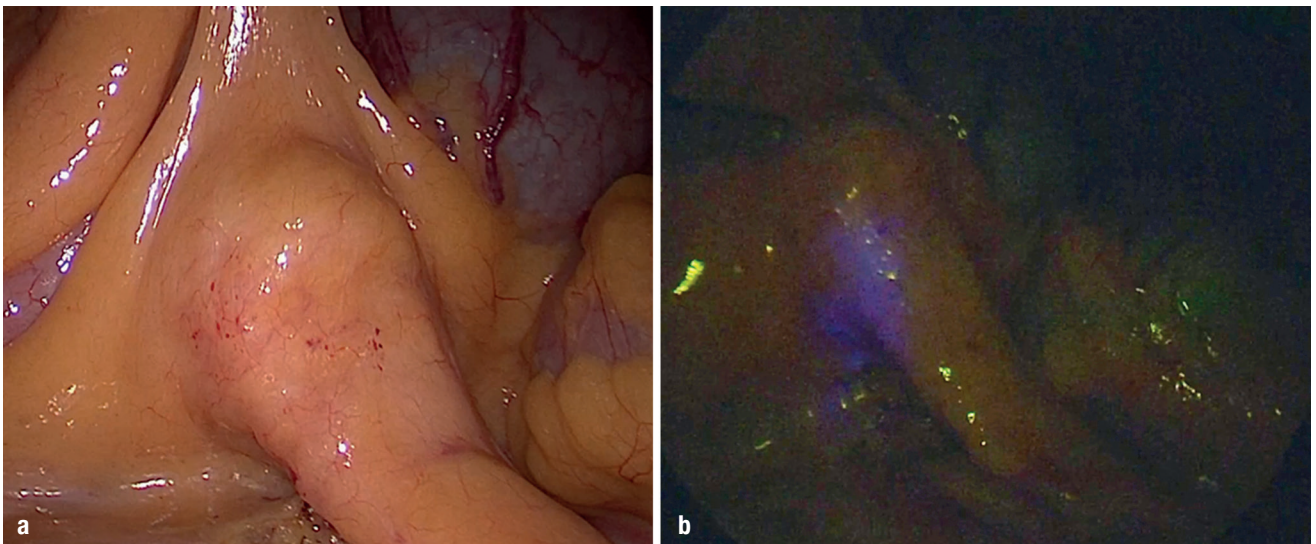
ICG-enhanced fluorescence imaging after peritumoral ICG injection may be used for lymph node mapping in the treatment of colorectal and gastrointestinal carcinomas. If used for lymphatic mapping in gastric cancer surgery, including adenocarcinoma of the cardia in the lesser curvature, 25 mg of ICG should be diluted in 20 ml of sterile water (a bolus of 0.5 ml used on each quadrant of the tumor), allowing the lymphatic area and/or drainage pattern from the tumor to be visualized (Figs. 2.6–2.8).



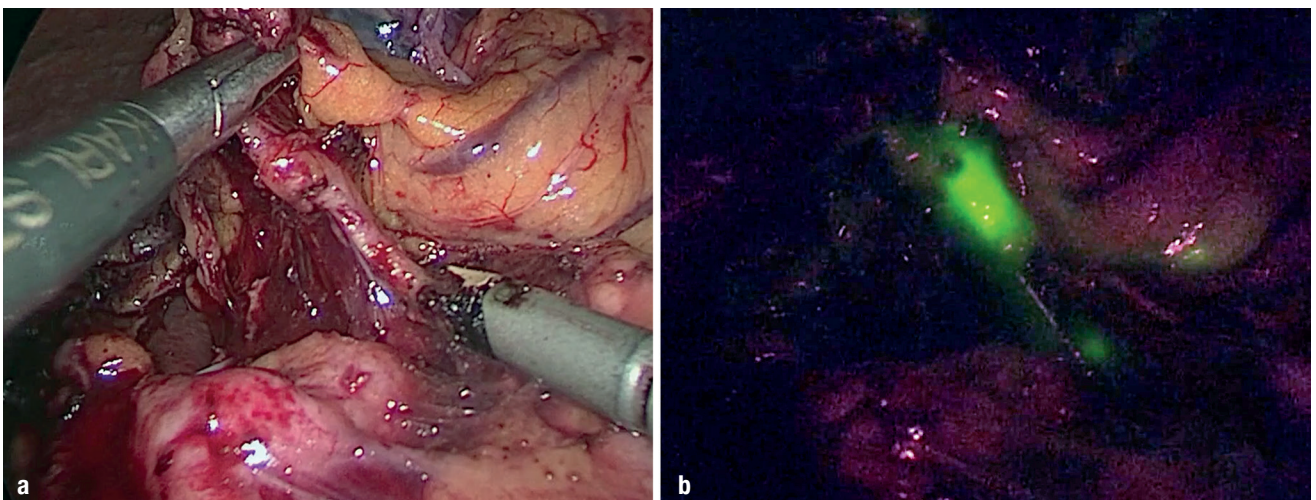
**Fig. 2.5** ICG-enhanced fluorescence imaging during radical pelvic and para-aortic lymphadenectomy (removal of the iliac and sacral lymph nodes) for treatment of metastatic melanoma of the left lower leg. Intraoperative views taken during white light mode (a) and NIR/ICG blue mode (b).



**Fig. 2.6** ICG-enhanced fluorescence-guided lymph node mapping during laparoscopic right hemicolectomy. Intraoperative views of peri-tumoral ICG injection shown in white light mode (a) and NIR/ICG blue mode (b).



**Fig. 2.7** ICG-enhanced fluorescence-guided lymph node mapping during laparoscopic right hemicolectomy. Detection of the ileocolic lymph nodes along the lymphatic drainage pathways. Intraoperative views taken during white light mode (a) and NIR/ICG blue mode (b).



**Fig. 2.8** ICG-enhanced fluorescence-guided lymph node mapping during laparoscopic gastrectomy. Intraoperative views taken during white light mode (a) and NIR/ICG green mode (b).



### 2.3 ICG-Enhanced Fluorescence-Guided Colorectal Resection

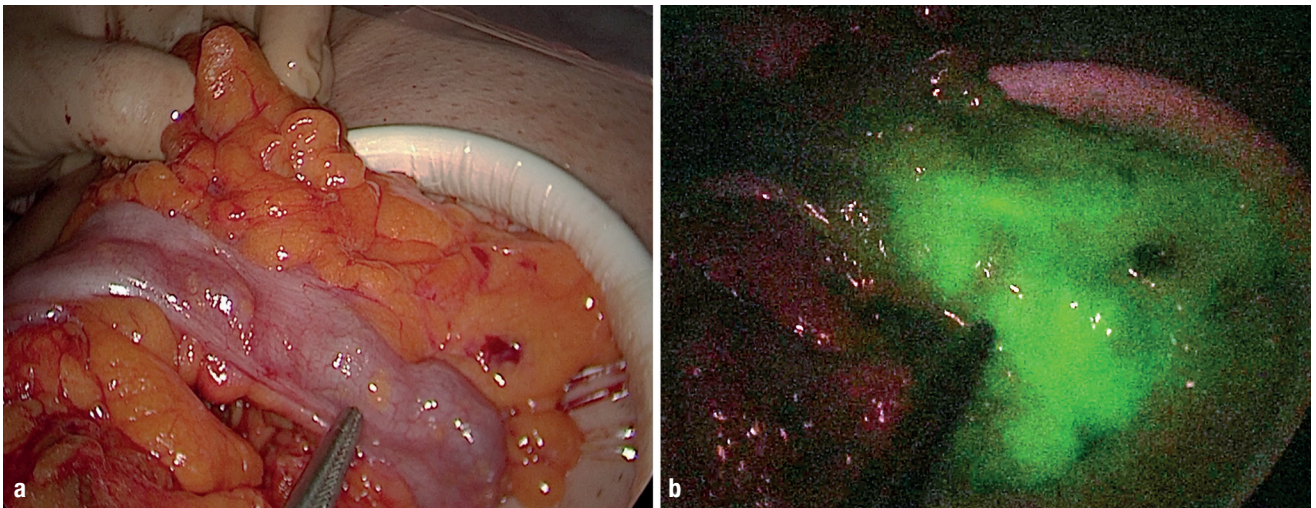
ICG-enhanced fluorescence imaging may also be used during laparoscopic colorectal resection in order to confirm adequate perfusion of the large bowel prior to anastomosis.<sup>5, 6, 28</sup>

ICG-enhanced fluorescence imaging is performed after ICG injection into a central or peripheral vein and 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.

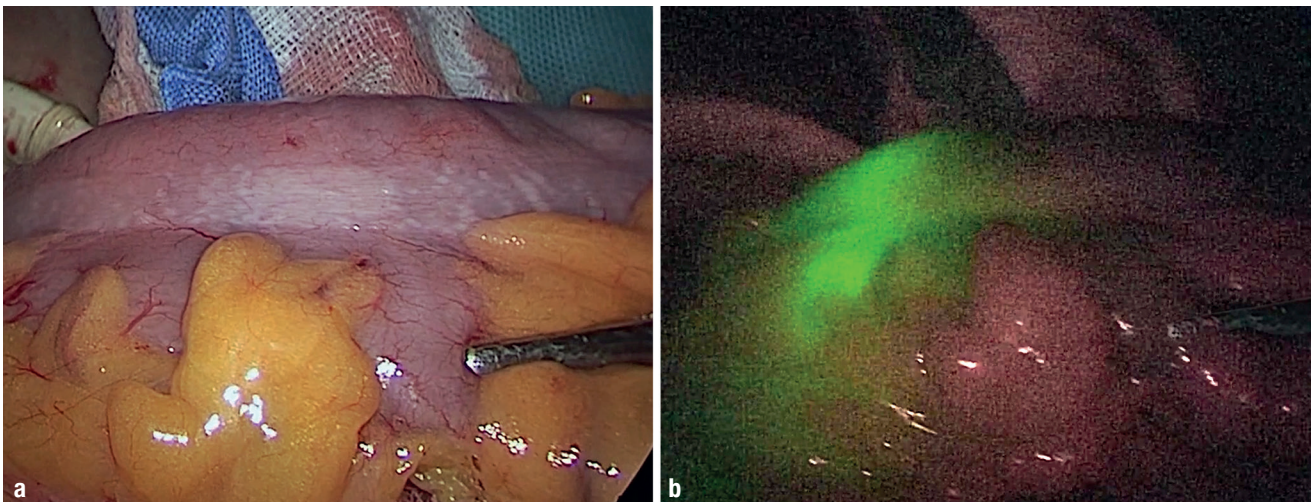
For perfusion assessment of the bowel, diluted ICG is injected using two boluses of 3 ml, each at a concentra-

tion of 0.2 mg/kg. The first bolus is administered after mesenteric division facilitating resection by providing relevant information on well-perfused areas (Fig. 2.9). The second bolus is given prior to bowel anastomosis to confirm adequate vascularization. Occasionally, differences become noticeable between the planned resection line and the boundaries of well-perfused areas (Fig. 2.10).

If extracorporeal bowel division is to be performed, whether for right or left-sided resections, adequate visualization is feasible only with the operating room lighting turned off, because ambient illumination has been found to interfere 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. 2.11).

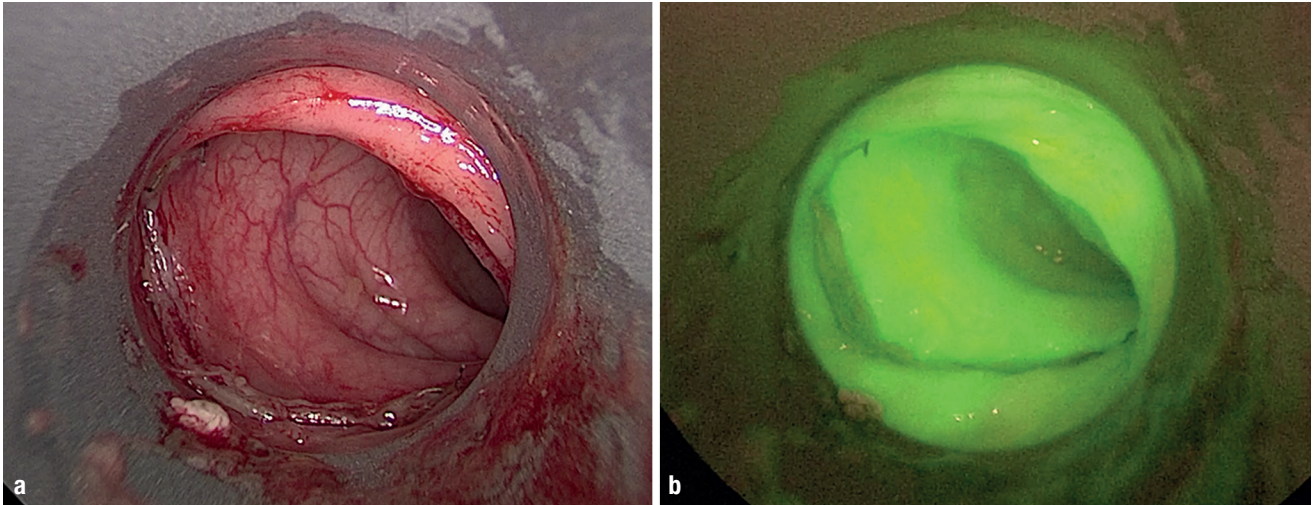


**Figs. 2.9** ICG-enhanced fluorescence-guided assessment of colonic perfusion during laparoscopic hemicolectomy. Intraoperative views taken during white light mode (a) and NIR/ICG green mode (b).



**Figs. 2.10** Note the difference between the planned resection margin in WL mode (a) and the boundaries of the well-perfused segment shown under fluorescence angiography (b). Intraoperative views taken during white light mode (a) and NIR/ICG green mode (b).



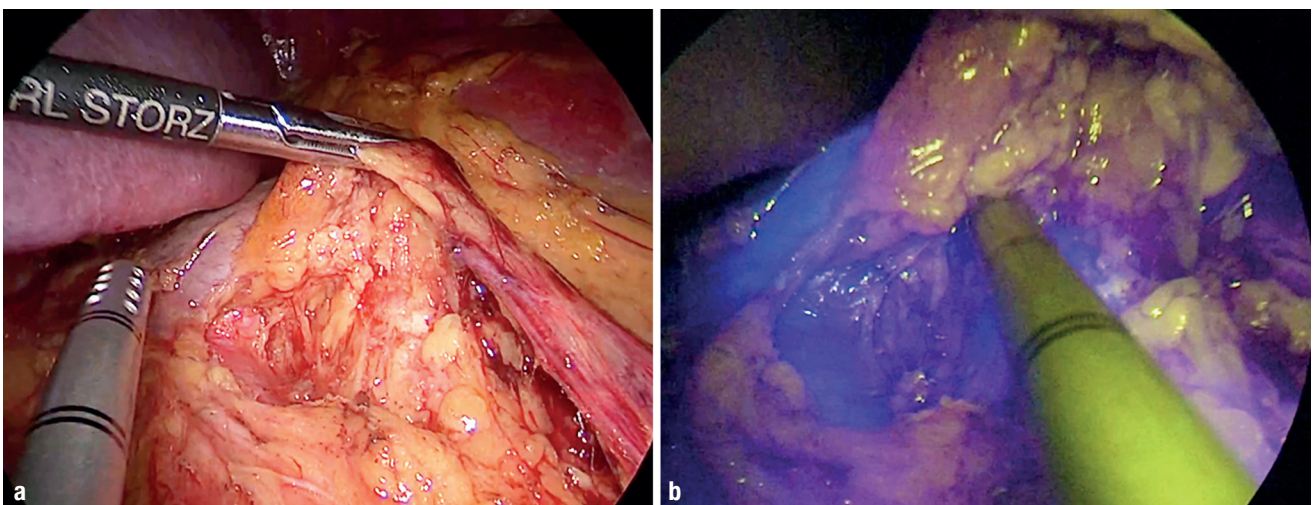


**Figs. 2.11** ICG-enhanced fluorescence-guided perfusion assessment of the rectal stump during laparoscopic low anterior resection. Intraoperative views taken during white light mode (a) and NIR/ICG green mode (b).

## 2.4 ICG-Enhanced Fluorescence Imaging for Vascular Mapping and Assessment of Perfusion in Solid Organs

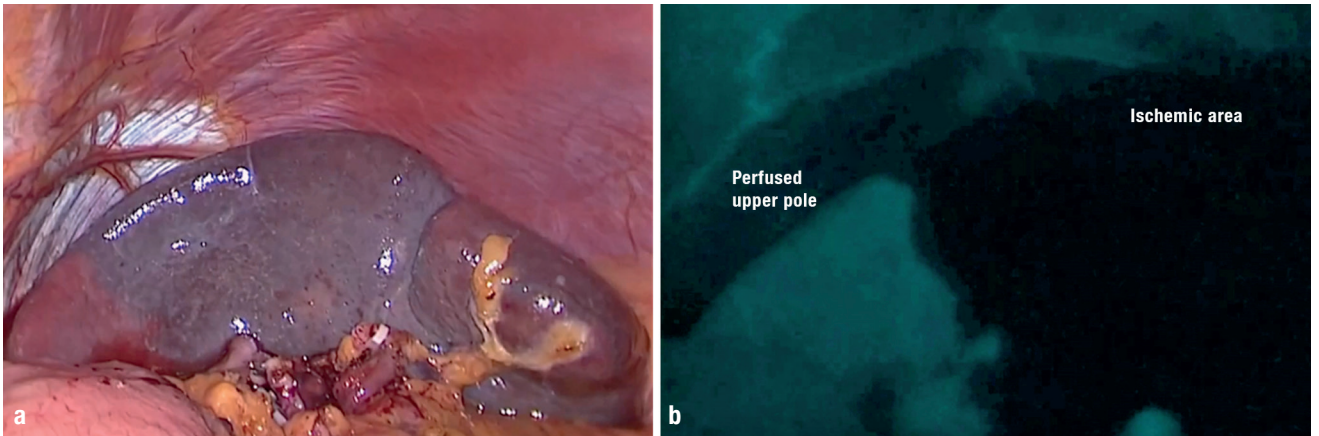
In view of its “angiographic” properties, ICG-enhanced fluorescence imaging is used effectively to facilitate vascular dissection. This has been shown to be helpful under certain conditions when there is reason to suspect the presence of anatomical variations, as is the case in nephrectomy (Fig. 2.12), 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.

ICG-enhanced fluorescence-guided assessment of organ perfusion and ischemia may also be used in applications such as liver resection,<sup>16</sup> partial splenectomy (Fig. 2.13), control of perfusion after kidney transplantation (Fig. 2.14), and assessment of the perfusion of gastric conduit during esophagectomy,<sup>30</sup> just to mention a few.

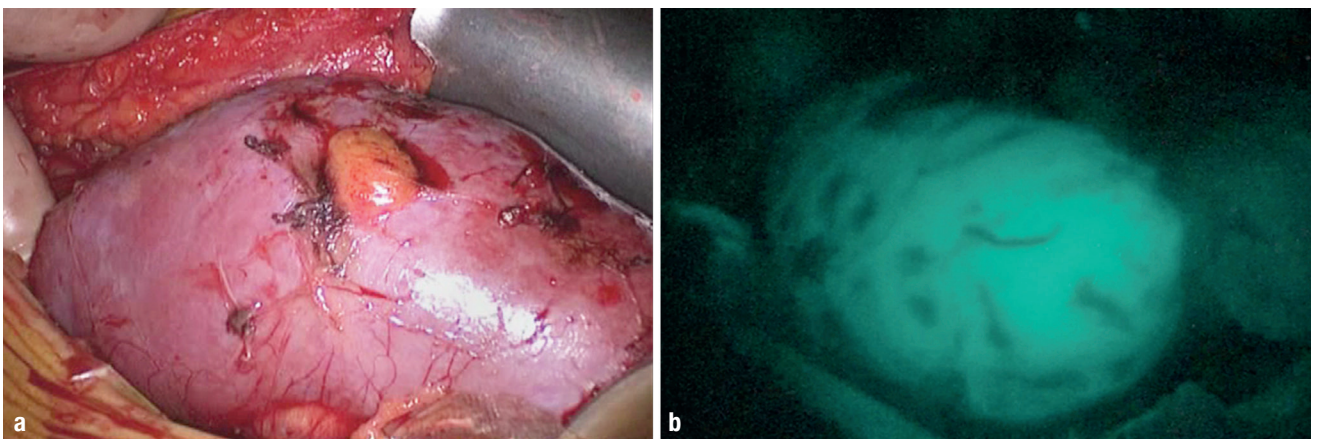


**Figs. 2.12** Visualization of vascular anatomy using ICG-enhanced fluorescence imaging during laparoscopic nephrectomy. Intraoperative views taken during white light mode (a) and NIR/ICG blue mode (b).





**Figs. 2.13** Assessment of perfusion of the spleen using ICG-enhanced fluorescence imaging. Intraoperative views taken during white light mode (a) and NIR/ICG green mode with SPECTRA A\* (b).



**Figs. 2.14** ICG-enhanced fluorescence-guided assessment of kidney perfusion following transplantation. Intraoperative views taken during white light mode (a) and NIR/ICG green mode with SPECTRA A\* (b).

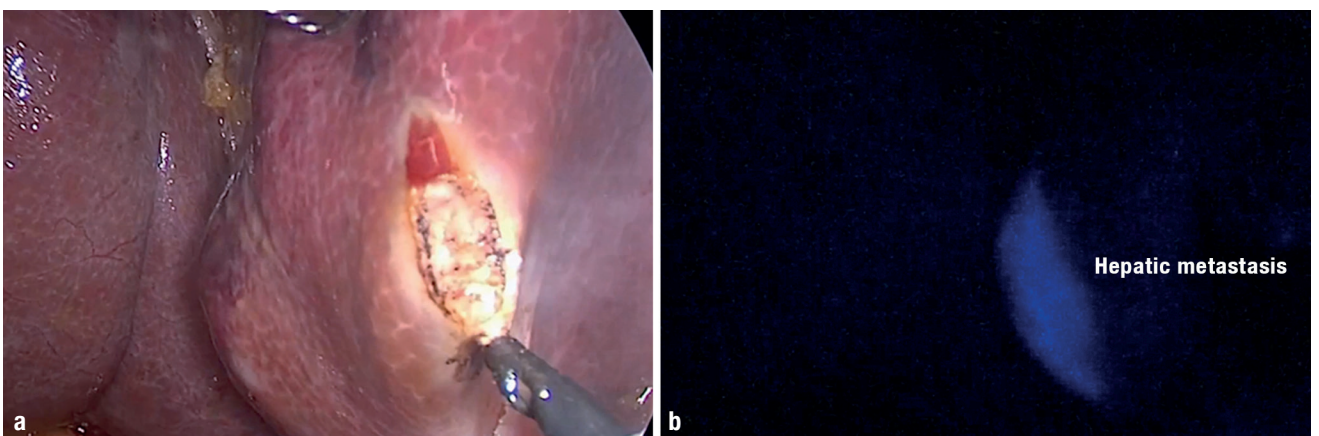
\* SPECTRA A: Not for sale in the U.S.A.

## 2.5 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 the procedure. 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 that are deficient in normal bile secretion (Fig. 2.15).

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



**Figs. 2.15** ICG-enhanced fluorescence-guided liver resection for metastatic hepatic lesions. Intraoperative views taken during white light mode (a) and NIR/ICG blue mode (b).

## 3

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