FLUORESCENCE CHOLANGIOGRAPHY

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Fluorescence Cholangiography – The Advent of a New Era of Improved Visualization and Safety

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Table of Contents

1 An Unresolved Problem: Bile Duct Injury .......................................................... 7
  1.1. Current Methods for Bile Duct Visualization and Identification ............... 8
    1.1.1. Critical View of Safety Approach .................................................. 8
    1.1.2. Intraoperative Cholangiography ................................................. 8

2 NIR-Fluorescence: Seeing Beyond Human Vision ............................................. 8
  2.1. Basic Concepts of Fluorescence ............................................................. 8
  2.2. Fluorescence Cholangiography: Technique .......................................... 10
  2.3. Cystic Duct and Common Hepatic Duct Visualization ............................ 10
  2.4. Difficult Scenarios .................................................................................. 11
  2.5. Bile Duct Variability and Accessory Ducts .......................................... 11
  2.6. Why Routine Use of Fluorescence Cholangiography is Recommended ........ 12
    2.6.1. Feasible Without the Need for Cutting a Bile Duct ............................. 12
    2.6.2. Cost-Effective .................................................................................. 12
    2.6.3. Expeditious / Not Time-Consuming .............................................. 12
    2.6.4. Obviates the Use of X-Ray or Laser ............................................... 12
    2.6.5. Effective Imaging Modality .............................................................. 12
    2.6.6. The Role of Fluorescence Cholangiography in a Teaching Program ...... 13
    2.6.7. Fluorescence Cholangiography in Obese Patients ............................. 13
    2.6.8. Fluorescence Cholangiography and Bile Stones ............................... 13

3 References ....................................................................................................... 14
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Laparoscopic cholecystectomy is among the oldest laparoscopic procedures in surgery, with the first reported cases dating back to the mid-1980s. Since then it has become a common procedure with approximately 90% of cholecystectomies performed laparoscopically in Germany and the United States alone.

Many advantages have accrued from the laparoscopic approach as compared to the open procedure including earlier discharge of the patients, improved cosmetics, less abdominal pain and more rapid recovery. Nevertheless, the minimally invasive approach has been associated with shortcomings like a significant learning curve, loss of tactile feedback and increased risk of bile duct injury (BDI).

Undoubtedly, the main concern with laparoscopic cholecystectomy is related to the associated increase of BDI compared to that of the open surgery era (0.4 vs 0.2%). Bile duct injury is a rare, but serious complication during this procedure, which is most often due to misidentification of the extra-hepatic bile duct anatomy.

The reported incidence is 0.3–0.7% of cases. This translates to approximately 3,000 injuries out of the reported 750,000 laparoscopic cholecystectomies performed in the US in 2008 alone.

Bile duct injury (BDI) is associated with significant morbidity, and can effect relatively young patients who incur a substantial loss in quality of life as a consequence of multiple re-hospitalizations and re-interventions needed to repair the bile ducts.

When bile duct injuries occur, surgeons and hospitals often have to go through long and costly legal claims that usually favor the patients.

Conventional intraoperative cholangiography (IOC) has been advocated to decrease the incidence of BDI, but has not gained worldwide acceptance nor has it been shown to reduce BDIs. Strict observance of the ‘Critical-View-of-Safety’ has been proposed as the most suitable technique in order to prevent the occurrence of BDI, yet the incidence has not further decreased in the past decade, which is why it became desirable that other techniques or precautionary measures be adopted. Fluorescence Cholangiography (FC) is such a technique. By enhancing the visualization of the bile ducts in real time, accurate identification of the various structures is facilitated, which may help prevent injury. The technique requires no additional incisions and is easy to apply.

Fig. 1.1 Visual perceptual illusion is the cause of 97% of bile duct injuries.

Fig. 1.2 A bile duct injury is a life-changing event for the patient.

Key to acronym: Endoscopic retrograde cholangiopancreatography (ERCP).

Fig. 1.3 Consequences after a bile duct injury.

<table>
<thead>
<tr>
<th>Increased Hospital Stay</th>
<th>Reduced Quality of Life (QoL)</th>
<th>Increased Cost</th>
<th>Litigation</th>
</tr>
</thead>
</table>
| BDI adds an average of 32 days inpatient hospitalization and 10 days of outpatient care. | BDI decreases QoL 30 to 50% in the first year. | BDI increases 4.5 to 26 times the cost compared to an uncomplicated procedure. | BDI is the most frequent injury resulting in litigation. Average payout $ 508,341 USD.

An Unresolved Problem: Bile Duct Injury
1.1. Current Methods for Bile Duct Visualization and Identification

1.1.1. Critical View of Safety Approach

The complete exposure of Calot’s triangle – which is freed from all fatty and fibrous tissue, followed by mobilization of the lowest part of the gall bladder from its bed – was initially described in 1995 by Strasberg et al.\textsuperscript{34} who suggested this preliminary step to be taken with the main objective of identifying the cystic artery, the cystic duct and the main bile duct prior to cutting any structure at all. Although this has been reported in the literature as a critical step toward improving the safety of laparoscopic cholecystectomy, its implementation in routine clinical practice has not lead to a decrease in the rate of BDI.\textsuperscript{31–33}

1.1.2. Intraoperative Cholangiography

Intraoperative cholangiography (IOC) is a well-known technique that is used to demonstrate integrity of intra- and extra-hepatic bile ducts. For this purpose, a catheter has to be placed inside the bile ducts and with the administration of iodine and application of fluoroscopy, anatomical images from the relevant region are obtained.\textsuperscript{29}

The routine and selective use of IOC is still under debate.\textsuperscript{7} Proponents of the technique state that – given proper interpretation of the intraoperative fluoroscopic image – IOC is capable of decreasing the severity of BDI and allows identification of bile duct stones. Others find it challenging to cope with IOC, because it is said to be time-consuming and prone to the risk of misinterpretation of fluoroscopic images, so as to explain that – despite the use of this modality – bile duct injuries have not decreased. Others find it challenging to cope with IOC, because it is said to be time-consuming and prone to the risk of misinterpretation of fluoroscopic images, so as to explain that – despite the use of this modality – bile duct injuries have not decreased.

Up to now, no real-time intraoperative method has been shown to be useful to identify the extra-hepatic biliary anatomy during a laparoscopic cholecystectomy before clipping or cutting a bile duct structure. This brochure describes a novel technique that is based on the combined use of indocyanine green (ICG) – a fluorescent dye administered IV – and near-infrared (NIR) light allowing the surgeon to obtain additional information regarding biliary anatomy in real time during a laparoscopic procedure.

2.1. Basic Concepts of Fluorescence

In 1852, George Gabriel Stokes described the mineral Fluorite as emitting blue light following exposure to ultraviolet light. He termed the phenomenon as ‘Fluorescence’ and proposed that chemical compounds offering this property to be called ‘Fluorophores’.\textsuperscript{37}

The ability to emit fluorescence is very common in nature. The photosensitivity of delocalized electrons in aromatic ring structures is responsible for this. The absorbed light energy excites the delocalized electrons into a higher state of energy. When the electrons return to the ground state, the absorbed light energy is emitted as fluorescence. The emitted fluorescence is lower in energy as the absorbed exciting light energy is partially lost as heat.\textsuperscript{30}

The oldest known approved near-infrared (NIR) fluorescent dye in medicine, indocyanine green (ICG), has been discovered as a chemical compound suited for use in NIR fluorescence cholangiography.

ICG is a drug which has been approved for use in humans by the FDA since 1959 for cardiac and liver function tests. The tricarbon dye has an absorption maximum of $\lambda_{\text{Ex}} = 805$ nm and an emission maximum of $\lambda_{\text{Em}} = 835$ nm. On account of the inherent property of ICG to emit light in the NIR spectral range, disturbing effects of autofluorescence that may arise from the main blood components (hemoglobin and water) are virtually impossible. This results in a tissue detection depth for NIR fluorescence of up to 1 cm.\textsuperscript{1}
NIR-Fluorescence: Seeing Beyond Human Vision

Most commonly, ICG is intravenously administered where it binds to plasma proteins (albumin) thereby remaining in the bloodstream due to size exclusion. From the bloodstream, ICG is transported to the liver, where it is excreted via the bile into the duodenum. This exclusive excretion into bile makes it an ideal compound for delineation of the extra-hepatic biliary tree. In addition to bile duct imaging, ICG can be used for perfusion assessment and for the visualization of lymph channels and lymph nodes.

**Fig. 2.1** Principle of fluorescence.

**Fig. 2.2** Principle of perfusion assessment with ICG.

1. Intravenous injection of ICG
2. ICG binds to plasma proteins
3. Visualization of ICG in bloodstream with the KARL STORZ NIR/ICG System
4. NIR/ICG light source
2.2. Fluorescence Cholangiography: Technique

The procedure begins with the intravenous administration of 0.05 mg/kg of indocyanine green, ideally performed preoperatively when the IV line is placed, which allows at least 45 minutes prior to the surgery for it to be excreted from the liver and into the bile. Alternatively, if preoperative administration is not possible or was missed, the ICG can be administered directly after induction of anesthesia, but this will result in a less optimal viewing of the biliary anatomy due to residual ICG remaining in the liver.

Once the gallbladder is retracted, Calot’s triangle is illuminated using a special xenon light source that allows the use of both white light (WL) and NIR light. Switching or ‘toggling’ between these two modes is easily done using a foot pedal operated by the surgeon. Using this combination of WL and NIR imaging, the biliary ducts can be identified through the non-dissected tissue even earlier than in WL mode alone.25

2.3. Cystic Duct and Common Hepatic Duct Visualization

Fluorescent cholangiography is the first method that can be used in real time during a laparoscopic cholecystectomy in order to improve endoscopic visualization and facilitate identification of the extra-hepatic bile ducts. Accordingly, the use of this technology allows vital structures – which otherwise could not be identified with standard xenon white light alone – to be visualized by ICG-enhanced fluorescence, guiding the surgeon during dissection.25, 26

Figs. 2.3 Visualization of biliary structures through fat. Note the technique of ‘toggling’ between white light mode (WL) (a) and near-infrared (NIR) mode (b), which may be used as determined by surgeon’s preferences or by individual circumstances.
NIR-Fluorescence: Seeing Beyond Human Vision

2.4. Difficult Scenarios

Correct identification of the extra-hepatic bile duct is one of the main concerns of any surgeon undertaking a laparoscopic cholecystectomy. Preoperative workup of the patient includes laboratory tests, hepatobiliary ultrasound and, in some cases, MR imaging. Usually, these tests are capable of predicting the complexity of a planned laparoscopic cholecystectomy, but occasionally, a procedure that is seemingly ‘easy to do’ can turn into an unexpected nightmare.

In these situations, structures of the Calot’s triangle are difficult to see. When blood or fat covers the bile structures, Fluorescence cholangiography can be used efficiently to clarify the location of the ducts.

2.5. Bile Duct Variability and Accessory Ducts

Some authors report up to 2% of iatrogenic bile leaks after laparoscopic cholecystectomy, which is linked to an increase in the associated rate of morbidity. Unnoticed iatrogenic injuries to small subvesical or Luschka ducts are among the major factors contributing to postoperative complications after laparoscopic cholecystectomies. In 1753, Antoine Ferrein (1693–1769), a human anatomist, was the first to report on the presence of bile ducts within the left lateral or triangular ligament of the liver. These ducts were later described by Weber in 1842 as ‘aberrant biliary ducts’ located outside the hepatic parenchyma. In an attempt to elicit their course and drainage pathway, detailed studies were undertaken by Luschka in 1863, who called them ‘accessory’ instead of ‘aberrant’ ducts. Accessory ducts are present in 20–50% of the overall population. On account of their small diameter (typically 1–2 mm), intraoperative identification of accessory ducts is very difficult during a laparoscopic procedure. The vast majority of these minor bile duct injuries go unnoticed during laparoscopic procedures.

Based on initial experience from surgeons using fluorescence cholangiography on a routine basis, a detection rate of up to 7% of Luschka ducts has been reported. Once the ducts are recognized, they can be clipped to avoid further leaks. Fluorescence imaging of even small ducts may allow the surgeon to avoid Type-A bile duct injuries.
2.6. Why Routine Use of Fluorescence Cholangiography is Recommended

2.6.1. Feasible Without the Need for Cutting a Bile Duct

Fluorescence cholangiography can be performed without any incision in the bile duct. This is a main advantage of the technique, because unlike IOC, it can be performed in patients in whom the bile duct is friable. Trying to cannulate the cystic duct in order to perform an IOC in a patient suffering from severe cholecystitis or in the case of a short cystic duct, may provoke an injury.11

Initial studies show significant differences in feasibility rate between IOC and FC. One study concluded that FC was feasible on all patients in the trial, whereas IOC was feasible in only 93%.11

2.6.2. Cost-Effective

One of the surgeon's main concerns with a new technology is related to cost. According to published data, cost effectiveness has been demonstrated using FC as a routine precautionary measure. The rate of toxicity of ICG is less than 0.003%3 and the overall cost of the dye administered throughout the procedure is low. In 2014, costs for a FC were estimated between US$14 (cost of actual volume of ICG used) and US$100 (cost per vial).24 Additionally, FC has been shown to be far less expensive than IOC once the equipment is part of the medical armamentarium in the OR.12

2.6.3. Expeditious / Not Time-Consuming

Fluorescence cholangiography is not time-consuming and is significantly faster when compared to IOC. The average time to perform an FC is less than one minute, whereas the average IOC takes over seven minutes.12

2.6.4. Obviates the Use of X-Ray or Laser

The use of X-ray in the OR is time-consuming and associated with well-known risks for the OR staff. Fluorescence cholangiography uses NIR light produced by a xenon light source equipped with a specific filter. Unlike with the use of laser devices, which may necessitate a prior risk assessment by a laser safety commissioner, FC obviates the need for additional safety measures.

2.6.5. Effective Imaging Modality

FC works as a complement to traditional white light laparoscopy which helps the surgeon to more distinctly visualize the bile ducts.
2.6.6. The Role of Fluorescence Cholangiography in a Teaching Program

Considering that a laparoscopic approach is the current mainstay of care in the majority of cholecystectomy patients, it has in turn changed the way surgery is taught in residency programs. Undoubtedly, the control that a surgeon can have over a resident is reduced compared to open surgery. Instructions on where to proceed with dissection can be challenging because verbal communication is inherently prone to misunderstanding and observer-dependent interpretation of visual information.

Fluorescence cholangiography has been shown to be a very useful tool for surgeons who are in charge of teaching residents, in that it considerably facilitates proper identification of vulnerable biliary structures as compared to white light visualization alone.

<table>
<thead>
<tr>
<th></th>
<th>White light mode</th>
<th>NIR mode</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic duct</td>
<td>40%</td>
<td>99%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Common hepatic duct</td>
<td>35%</td>
<td>96%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cystic-common hepatic duct junction</td>
<td>24%</td>
<td>95.5%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 2.1 Percentage of extra-hepatic duct visualization with white light (WL) and near-infrared (NIR) light.10

2.6.7. Fluorescence Cholangiography in Obese Patients

In recent years, obesity has become a global problem. Occasionally, surgical treatment of obese patients can pose a challenge when proper visualization of structures of interest is obscured by fatty tissue.

The feasibility of fluorescence cholangiography and visualization of anatomical key structures has been analyzed on the basis of various groups of patients treated by laparoscopic cholecystectomies. Even though it is well known that penetration of NIR light may be reduced by fat, no significant differences nor differences in the visualization of cystic duct, common bile duct, and accessory duct were noted between the obese and non-obese groups (p-value 0.09, 0.16, and 0.66, respectively).10

2.6.8. Fluorescence Cholangiography and Bile Stones

Fluorescence cholangiography has been shown to be very effective in visualizing extra-hepatic biliary structures. In the presence of lithiasis, however, calculi may accumulate in the bile ducts, surrounded by bile. So far, no studies have demonstrated the visualization of bile stones using fluorescence cholangiography, and as such, it should be considered a complementary modality to IOC if preoperative laboratory results suggest the presence of bile stones.2
3 References


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