# Non-radiographic intraoperative fluorescent cholangiography is feasible

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**ABSTRACT**

**INTRODUCTION:** Intraoperative fluorescent cholangiography (IFC) with concomitant fluorescent angiography was recently developed for non-invasive identification of the anatomy during laparoscopic cholecystectomy. The objective of this study was to assess the time required for routine-use of IFC and to evaluate the success rate of the procedures.

**MATERIAL AND METHODS:** A total of 35 patients scheduled for laparoscopic cholecystectomy and operated by the same surgeon were consecutively enrolled. A standardised protocol with IFC including angiography was performed during laparoscopic cholecystectomy. Intraoperative time and exposure of predefined anatomical structures were recorded.

**RESULTS:** The median time used for IFC was 2.6 minutes (range: 1.5-11.4 minutes) corresponding to a median of 6.2% (range: 3.0-15.2%) of the operation time. The junction between the cystic duct, the common bile duct and the common hepatic duct was identified by IFC in all patients. In 29 of the 35 patients (83%; 95% confidence interval: 71-96%), the cystic artery was visualised by fluorescent angiography. No adverse effects or complications were recorded.

**CONCLUSION:** Routine-use of IFC with fluorescent angiography during laparoscopic cholecystectomy is feasible and associated with an acceptable time expenditure and a satisfactory success-rate.

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**TRIAL REGISTRATION:** The Regional Ethics Committee approved the study (J. No. H-3-2013-FSP45). The study is registered with clinicaltrials.gov (ID: NCT02136095).

Laparoscopic cholecystectomy is a common laparoscopic procedure. Bile duct injury is a rare, but serious complication (0.2-0.5%) which is most often due to misidentification of the extra-hepatic bile duct anatomy during the operation [1-5]. Intraoperative cholangiography is advised when the bile duct anatomy is unclear. It has been debated whether routine use of intraoperative cholangiography during laparoscopic cholecystectomy is advisable, but there is no clear consensus [6-8].

Intraoperative fluorescent cholangiography (IFC) is a new method for non-invasive visualisation of the biliary anatomy during laparoscopic cholecystectomy [9-11]. The method implies preoperative injection of the nontoxic fluorescent dye indocyanine-green (ICG), which is excreted by the liver into the bile. The laparoscopic fluorescence imaging system allows online switching between normal laparoscopy and fluorescent imaging whenever needed. This provides real-time, continuous and angle-independent visualisation during dissection without X-ray radiation. In addition, IFC provides the possibility of performing peroperative fluorescent angiography to visualise small and large artery branches [12, 13]. However, IFC cannot detect stones in the common bile duct, since the retro-duodenal part of the common bile duct is not visible when using IFC.

Compared with conventional cholangiography, IFC may provide a faster, more useful and less invasive delineation of the anatomy owing to the possibility of prompt switching between normal and cholangiographic imaging. Recent studies have evaluated the feasibility of IFC (ability to perform useful biliary and angiographic identification) with promising results [9-13]. Until now, no studies have evaluated the time expenditure associated with IFC when used routinely.

The primary objective of this study was to assess the time expenditure associated with IFC with concomitant angiography. The secondary objective was to evaluate the success-rate of the procedures.

## MATERIAL AND METHODS

The study was prospective and patients were enrolled consecutively. We included patients undergoing laparoscopic cholecystectomy by a single surgeon between September and December 2013 at a single-centre university department with unrestricted referral of patients (and 600 laparoscopic cholecystectomies performed annually). The included patients represented all patients undergoing laparoscopic cholecystectomy by one surgeon during the study period. The inclusion criteria were age ≥ 18 years and obtained informed consent. The exclusion criteria were iodine or ICG hypersensitivity, liver or renal insufficiency, thyrotoxicosis, pregnancy or lactation.

### Laparoscopic fluorescence imaging system

We used the Olympus Laparoscopic Imaging System for ICG Fluorescence Observation. This system provides a 30-degree 10-mm rigid lens laparoscope, a xenon light source and a camera head mounted with switchable light filters in order to make fluorescent emission visible

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when the system is in fluorescence imaging mode (FI mode). Both filters are easily operated by a switch and a lever on the camera head allowing the operator to change between FI mode and normal white light mode. The system creates a monochrome image on the monitor in which fluorescence appears light green on a dark background, where surrounding structures are dimly visible.

**Indocyanine-green administration**

2.5-7.5 mg of ICG (0.05 mg/kg) was injected intravenously directly after induction of anaesthesia. ICG rapidly binds to plasma proteins and is exclusively and entirely excreted by the hepatic parenchymal cells into the bile, starting within a few minutes after injection of ICG.

**Intraoperative fluorescent cholangiography and angiography during laparoscopic cholecystectomy**

Laparoscopic cholecystectomy procedures were performed in accordance with Danish and international guidelines (Critical View of Safety Technique) [14, 15]. The operations were initialised as usual, but the operation field was routinely inspected in the FI mode before dissection of Calot´s triangle. Blunt laparoscopic instruments were carefully used to keep aside overlying structures (liver or fat tissue) in order to visualise extra-hepatic biliary ducts. During dissection, the FI mode was used when needed until critical view of safety was obtained. Before division of any tubular structure, the FI mode was routinely used again, and fluorescent angiography was performed by re-injecting the same dose of ICG as initially used. After division of the cystic duct and artery, the FI mode was applied again to check for bile leakage.

**Data collection**

Intraoperative FI-mode-time was registered by a study nurse. The operating surgeon completed a structured questionnaire immediately after each operation regarding patient characteristics (age, body mass index, American Society of Anesthesiologists score, indication for operation, allergy and ICG dose) and anatomical identification by IFC (visible cystic duct, common bile duct, common hepatic duct, right and left hepatic ducts, cystic artery, aberrant bile ducts, and/or other abnormalities).

Successful IFC was defined as IFC exposure of the junction between the cystic duct, common bile duct and common hepatic duct. Successful fluorescent angiography was defined as adequate visualisation of the cystic artery within Calot´s triangle by the method.

Follow-up for detection of post-operative complications was obtained by a check in the joint regional journal system (OPUS) for relevant contacts to hospitals in the Capital Region of Denmark in the 30-day period following laparoscopic cholecystectomy. Final gallbladder pathology was recorded on the same occasion.

**Statistics**

Data were described by simple descriptive statistics using medians and ranges, percentages as well as 95% confidence intervals (95% CI), when appropriate. The study was explorative in nature and the patient inclusion number was not based on a pre-study power calculation, but instead defined by a fixed study period.

**Ethics**

Informed consent was obtained from all patients. The Regional Ethics Committee approved the study prior to inclusion of patients. Our department had permission from the Danish Health and Medicines Authority to use ICG in the present study.

*Trial registration:* The Regional Ethics Committee approved the study (J. No. H-3-2013-FSP45). The study is registered with clinicaltrials.gov (ID: NCT02136095).

## RESULTS

During the study period, 36 patients were eligible, but one patient was excluded due to lactation, and we thus analysed 35 patients (26 female, 9 male). The median age was 48 years (range: 18-74 years) and the median body mass index was 28 kg/m$^2$ (range: 19-38 kg/m$^2$). The indications for laparoscopic cholecystectomy were: symptomatic cholecystolithiasis (n = 15), history of chol-

**TABLE 1**

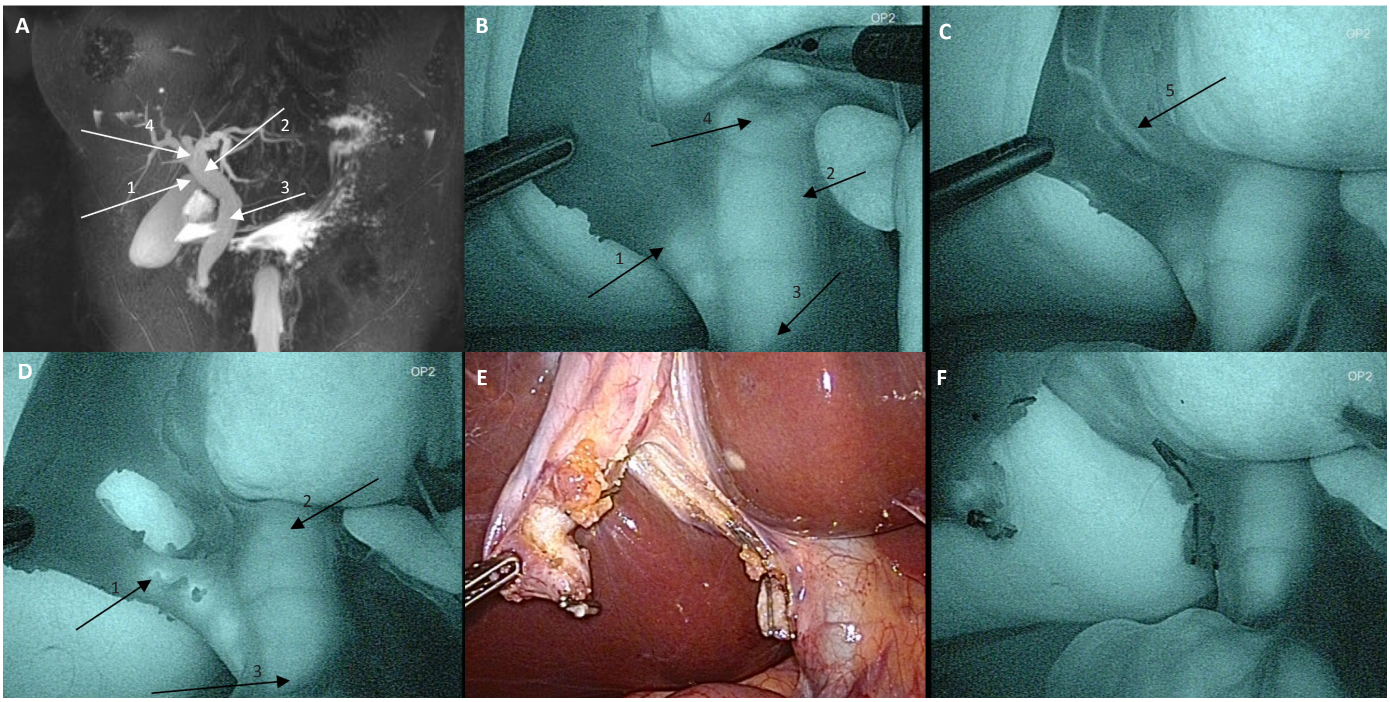
Operation time and time spent on intraoperative fluorescent cholangiography according to indication for operation.

| Indication for operation | Operation time, min., median (range) | IFC time, min., median (range) | IFC time/ operation time, %, median (range) |
|---|---|---|---|
| Symptomatic cholecystolithiasis (n = 15) | 38 (22-45) | 1.9 (1.5-4.8) | 6.0 (3.7-15.2) |
| History of cholecystitis (n = 13) | 67 (25-135) | 3.1 (1.6-9.3) | 6.9 (3.0-13.2) |
| History of CBD stone (n = 5) | 60 (41-89) | 3.3 (1.8-11.4) | 6.9 (3.5-13.5) |
| Acute cholecystitis (n = 2) | 62 (42-82) | 2.5 (2.3-2.6) | 4.3 (3.2-5.4) |

CBD = common bile duct; IFC = intraoperative fluorescent cholangiography.

FIGURE 1

An example of biliary duct and cystic artery anatomy in a patient with a history of impacted common bile duct stone delineated by: magnetic resonance imaging (**A**), intraoperative fluorescent cholangiography (IFC) before dissection of Calot's triangle (**B**), fluorescent arteriography 10-20 seconds after intravenous reinjection of indocyanine-green (**C**), IFC after dissection of Calot's triangle (**D**) and white light image + IFC after division of cystic duct and artery (**E** and **F**).




1 = cystic duct; 2 = common hepatic duct; 3 = common bile duct; 4 = confluence of hepatic ducts; 5 = cystic artery.

ecystitis (n = 13), history of common bile duct stone (n = 5) and acute cholecystitis (n = 2). The final gallbladder diagnoses were: cholelithiasis (n = 5), chronic cholecystitis (n = 23) and acute/chronic cholecystitis (n = 7).
A total of 24 operations were performed in an ambulatory-surgery setting and 11 operations in an in-hospital setting.

### Time spent on intraoperative fluorescent cholangiography

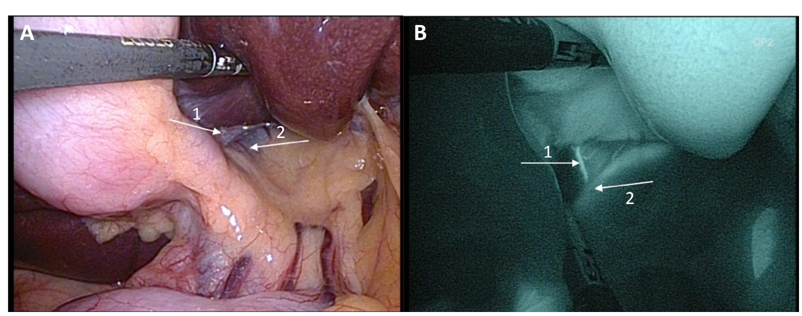
The median operation time was 43 minutes (range: 22-135 minutes). The median time spent on performing the IFC procedure including angiography was 2.6 minutes (range: 1.5-11.4 minutes), corresponding to a median of 6.2% (range: 3.0-15.2%) of the total operation time, **Table 1**.

### Bile duct identification using intraoperative fluorescent cholangiography

The junction between the cystic duct, common bile duct and common hepatic duct was identified by IFC during the operation in all patients. In 19 patients (54%; 95% CI: 38-71%), the confluence of the right and left hepatic ducts was visualised (**Figure 1**).

FIGURE 2

White light image (**A**) and intraoperative fluorescent cholangiography image (**B**) of extra-hepatic biliary duct anatomy identifying an aberrant bile duct (1) entering into the common hepatic duct (2) before any dissection of Calot's triangle.



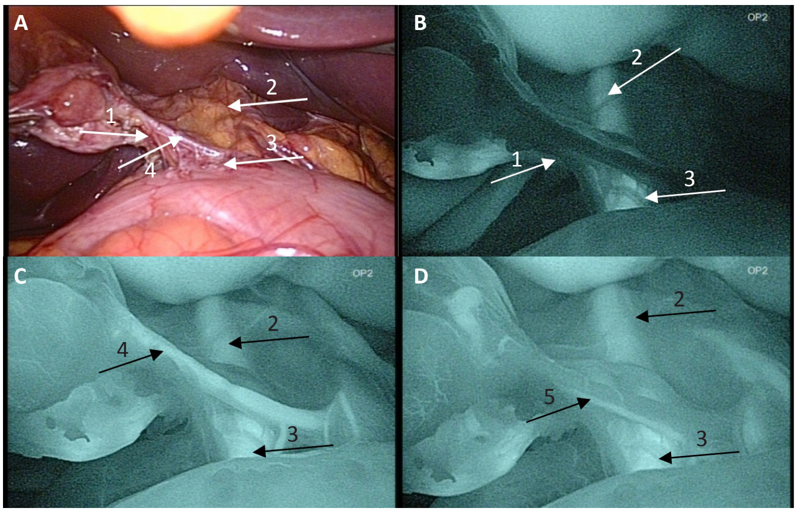

In one patient, an extra-hepatic aberrant bile duct entering into the common hepatic duct was identified by IFC and left intact (**Figure 2**).

### Visualisation of the cystic artery by fluorescent angiography

In 29 of the 35 patients (83%; 95% CI: 71-95%), the cystic artery was visualised by fluorescent angiography during

FIGURE 3

An example of intraoperative fluorescent cholangiography with fluorescent angiography demonstrated by a white light image (**A**) and intraoperative fluorescent cholangiography images before (**B**) and during (**C**) the arterial phase, 10-20 seconds after intravenous reinjection of indocyanine-green. A few seconds later (**D**) was taken, showing fluorescent enhancement of cystic veins.




1 = cystic duct; 2 = common hepatic duct; 3 = common bile duct; 4 = cystic artery; 5 = cystic vein.

the arterial phase around 10-20 seconds after intravenous re-injection of ICG (**Figure 3**). In patients with a non-inflamed gallbladder, arteriography was successful in four of five cases (80%; 95% CI: 45-115%), whereas it was successful in 25 of 30 patients (83%; 95% CI: 70-96%) with an inflamed gallbladder. In one patient, an abnormal course of the cystic artery on the right side of the gallbladder was visualised. In no patients, the right branch of the hepatic artery was considered to be in danger of misinterpretation.

### Adverse effects and complications

We observed no adverse effects to ICG injection, and no complications to the operations were recorded within 30 days. The median follow-up period was 44 days (range: 30-58 days). All patients were discharged as planned preoperatively.

## DISCUSSION

The present study reports the first Scandinavian experience with routine use of IFC in unselected patients undergoing laparoscopic cholecystectomy. The IFC procedures were performed within an acceptable time expenditure of 6% of the operation time. IFC provided a clear delineation of the relevant biliary structures in all patients, and in most cases the course of the cystic artery was visualised as well. IFC imaging was generally satisfactory in quality.

Prior to the study we defined successful IFC as the visualisation of the junction between the common hepatic duct, the cystic duct and the common bile duct (and not the right and left hepatic duct confluence). The hepatic duct confluence was visible in only 54% of our patients, probably due to an intrahepatic location of the confluence in the remaining patients. During laparoscopic cholecystectomy, especially the extra-hepatic biliary ducts are in danger of misinterpretation, and in order to obtain the critical view of safety, it is the junction between common hepatic duct, cystic duct and common bile duct, which is of vital importance.

Our results are consistent with those of other initial reports on the subject [9-13]. Ishizawa et al, Schols et al and Sherwinter evaluated the feasibility of IFC (capability to identify biliary ducts), with success rates equal to ours (a near 100% detection rate for relevant biliary ducts) [9-11]. Schols et al also measured the time used for identification of biliary ducts with and without fluorescent imaging in a non-randomised setting and reported a significantly reduced time to identification with fluorescent imaging available [10]. In addition, Schols et al and Kaneko et al evaluated fluorescent angiography with success rates in line with those reported in the present study (cystic artery identification in 87% and 89% of patients, respectively) [12, 13].

In several of our operations, the arteriography was performed after starting the dissection of Calot's triangle, which might have caused coagulation of the artery. Overlying fat or dense connective tissue may also have impeded success due to limited penetration of fluorescent light. It could therefore be advisable to do a first attempt on arteriography before touching Calot's triangle, and then repeat it at the following steps during the dissection, if needed.

According to the literature, IGC administration (0.05 mg/kg) can be repeated several times with a minimal risk for the patient. A hyper-sensitive reaction to ICG in patients with no history of allergy to iodine is described in 0.003% [9-12]. ICG has been used for several decades in various specialities, e.g. for measurement of liver blood-flow, and it has proven to be extensively non-toxic with a tolerable daily dose of up to 5 mg/kg [9, 16].

Intraoperative X-ray cholangiography demands puncture and cannulation of a bile duct (preferably the cystic duct) after dissection of Calot's triangle. The invasiveness of the procedure entails a risk of bile leakage and duct injury. IFC does not require bile duct cannulation and it provides real-time, continuous and angle-independent visualisation during dissection without X-ray radiation. No studies have compared the time employed by IFC versus conventional intraoperative cholangiography for the purpose of bile duct identification (and safe dissection). IFC may prove to be more time-effective than intraoperative cholangiography. IFC is, however, unable to diagnose biliary stones in the retro-duodenal part of the common bile duct. Future studies should compare these modalities in a randomised set-up, preferably in complicated gallbladder disease.

In addition, a randomised clinical trial to demonstrate if routine use of IFC can prevent bile-duct injuries would be highly interesting. Such a study would require thousands of patients due to the low rate of this severe complication, and it may be difficult to perform.

Further studies could compare IFC with magnetic resonance imaging cholangiography in order to validate the findings of IFC. Other studies should focus on optimising the dose and timing of ICG injection. Finally, it could be evaluated if IFC can influence the learning curve of trainees performing laparoscopic cholecystectomy.

Despite a generally successful first experience with IFC, our study did reveal some obstacles. When ICG is injected right before the operation, the liver background fluorescence is significant during the whole operation. To some extent, this phenomenon can impair discrimination of bile ducts from liver tissue. In one study, this problem was handled by injecting ICG one day before surgery and the results were good [17]. However, this practice is not compatible with a same-day ambulatory surgery concept.

Another limitation of IFC is the reduced ability of the fluorescent light to penetrate tissues of a certain thickness (5-10 mm). Therefore, IFC may fail to delineate the biliary structures before dissection of Calot's triangle if they are covered with dense connective tissue or a thick layer of fat tissue. The method may still be useful in such situations, because the biliary structures can be safely approached by gradually dissecting the area with intermittent fluorescence imaging for early detection and saving of biliary ducts buried in connective or fat tissue.

## CONCLUSION

Routine use of IFC with fluorescent angiography during laparoscopic cholecystectomy can be performed routinely with a minimal use of operation time and a high success rate.

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