Indocyanine green fluorescent cholangiography and intraoperative angiography with laparoscopic cholecystectomy: a randomized controlled trial

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Introduction
Laparoscopic cholecystectomy (LC) is the standard of care in the management of a diseased gall bladder. Sometimes it is complicated by bile duct injury, a significant cause of morbidity and mortality. Efforts are continuous to develop a standard technique to do it safely. Indocyanine green (ICG), fluorescent cholangiography was proposed to serve this cause.
Patients and methods
A double-blinded, randomized, controlled trial involved patients who underwent LC in Ain-Shams University Specialized Hospital from January 2020 till July 2021. Group A (*n*=60) underwent LC using the usual white light; group B (*n*=58) underwent LC with ICG florescence cholangiography and intraoperative ICG florescence arteriography.
Results
Females represented 78%, the mean age was 42.4 years, and the median BMI was 35.5. ICG was injected at a median time of 6.5 h before surgery. The blood loss was comparable between the two groups. In group B, all three structures were clearly identified in nearly all the patients. The common hepatic duct identification rate was 96.5% (*P*<0.001), cystic duct 98.2% (*P*=0.0175), and common bile duct was 94.8% (*P*<0.001). The operative time was significantly shorter in group B (*P*<0.001). None of the cases were converted to open and no biliary tree injuries were recorded in both groups and none of the patients injected or reinjected with the ICG experienced any symptoms or signs of allergy or reaction.
Conclusion
The near-infrared//(ICG cholangiography is an easy, safe, and effective technique to identify the extrahepatic biliary ducts, we recommend its routine use.

Keywords:
indocyanine green angiography, indocyanine green cholangiography, laparoscopic cholecystectomy, near-infrared/indocyanine green

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Introduction

Laparoscopic cholecystectomy (LC) is probably the most commonly performed laparoscopic procedure by general surgeons [1,2]. It was first performed in September 1985 [3]. Complications of LC range from simple surgical site infection, through more serious complications as bile duct injury (BDI) [4] or even death [1]. As the BDI is a significant cause of morbidity and mortality, efforts are continuous to develop a standard technique and effective educational models for young surgeons to avoid such complications [5].

In 1992, Strasberg *et al.* [6] proposed a technique to do the LC safely and in 1995 the term critical view of safety (CVS) was coined [4]. The CVS is a technique for the identification of the critical structures located in the Calot's triangle. It is composed of three elements: separation of the lower third of the gall bladder from the liver bed, clearing the area of the hepatocystic triangle from any fat or connective tissue, and third, two and only two structures remain attached to the gall bladder [4,6,7]. There is a paradox associated with the use of CVS. The 'critical view of safety paradox' is: the use of CVS is associated with lower BDI rates [7–11], but centers adopting the use of the CVS do not have lower rates of BDI [1,7,10,12]. Surprisingly and unfortunately even after four decades since its first description, surgeons may fail to differentiate between the CVS and the infundibular technique [7]. Even though it is usually recorded, in the operative notes, that

the surgeons achieved the CVS, evidence showed that it is not true in most of the cases. This is simply because the CVS cannot be achieved without fulfilment of all the three elements of this technique. Strasberg and Brunt [7] recommended the dictation of these three elements into operative notes as an excellent practice.

The suggested techniques to do a safe LC other than the CVS includes the infundibular technique, visualization of the common hepatic duct (CHD) and the common bile duct (CBD), and fundus-first cholecystectomy [7,13]. None of these techniques were backed up by clinical evidence. It is difficult to design and perform a randomized controlled trial to compare these techniques, as the sample size would be nearly 4500 patients per arm if calculated based on that the event rate; the BDI during the LC is 0.3% [7].

Adjuncts were suggested to increase the safety of LC, like routine intraoperative cholangiography (IOC) [14]. The IOC is time-consuming, needs additional personnel in the operation room, has the risk of radiation exposure for the patient and the medical staff, and requires a bulky machine [15], without any drop of rates of BDI [16]. The use of indocyanine green (ICG) florescence cholangiography in cholecystectomies was described more than a decade ago, in both open and LCs [17,18]. It emerged to be a better assessment tool for the extrahepatic biliary tree without the disadvantages of ordinary IOC.

The ICG is a tricarbocyanine dye. It was invented in 1955 for the photography industry by Kodak Laboratories [19]. In 1959, it was approved to be used as a medical dye [20]. It is a water-soluble lyophilized powder with a pH of 6.5 after being dissolved in water. The ICG exhibits florescence when subjected to the near-infrared (NIR) spectrum of light, as its peak spectral absorption stands at nearly 800 nm. When the ICG solution is injected in the plasma, its uptake is solely done by the liver cells, and it is excreted completely with the bile. The ICG solution can be safely injected intravenously, as reported allergies or toxicities were extremely rare [21]. The laparoscopic NIR/ICG IOC during LC was recently introduced in Egypt [22].

Patient and methods

This was a double-blinded, randomized, controlled trial that involved patients who underwent LC by authors A and D in Ain-Shams University Specialized Hospital in the period from January 2020 till July 2021.

The included patients were adults (from 18 to 75 years old), suffering from a gall bladder disease with valid indication for LC, who accepted to participate in the study. Patients with a history of previous biliary surgery, abdominal malignancy, and advanced chronic liver disease, as well as pregnant women were excluded from the study.

This study was registered at ClinTrials.gov PRS. An approval of the procedure was obtained from the Research Ethics Committee (REC), General Surgery Department, Ain-Shams University (IRB 00006379). Every patient signed an informed consent after full explanation of the process and the alternatives.

The sample size was calculated assuming that the identification rate of the cystic duct (CD) is 96% when using ICG cholangiography. The power study test revealed a total sample size of 118 patients, allocated 1 : 1 per group, were needed with 95% confidence.

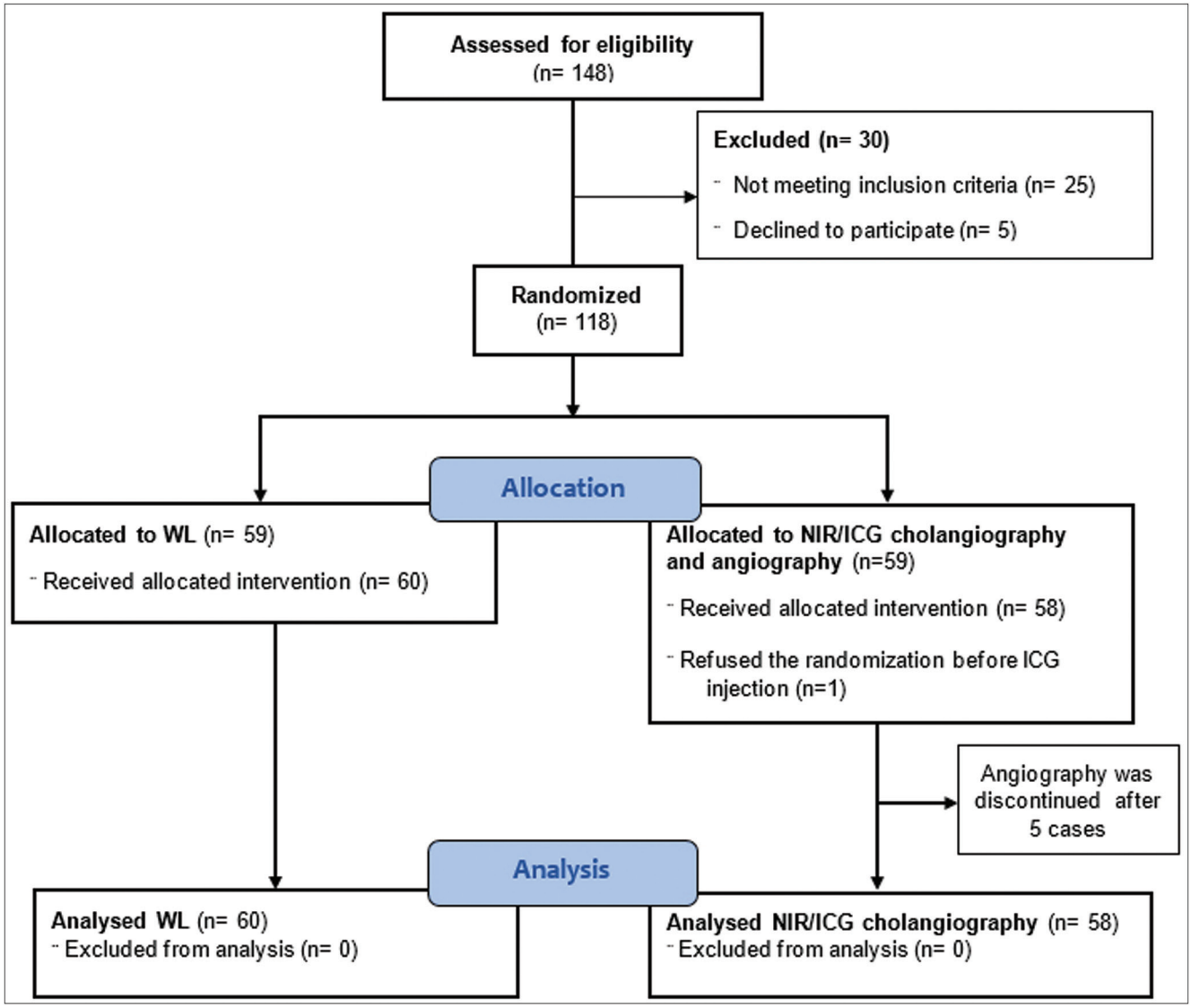
Recruited patients were randomly allocated into two groups using the number sequence generated by www.random.org. Group A patients underwent LC using the usual white light. This was the control group. In the second group, group B, patients underwent LC with ICG florescence cholangiography and intraoperative ICG florescence arteriography to detect the extrahepatic biliary tree and cystic artery. This was the test group. The workflow of the patients is shown in Fig. 1.

This was a double-blinded study, both patients and statistician were blinded to the surgical approach. Triple-blinded study was technically impossible due to surgeon involvement.

A full history, examination, and preoperative assessment were done for all the recruited patients. In all cases, the umbilical port was inserted using the Hasson's technique to achieve pneumoperitoneum, a 30-degree 10 mm scope was used, two to three working ports were inserted under vision. In group A patients the usual white light was used, the authors selected the CVS [4,6] as the technique of identification of the CD and artery. Group B patients were injected intravenously with the ICG solution, at least 1 h before the surgery, at a dose of 0.15 mg for each kilogram body weight. The NIR light was used to elaborate fluorescence for the cholangiography (Fig. 2). Reinjection of 0.05 mg/kg of the ICG solution, intravenously, was done during the dissection of Calot's triangle for the angiography.

For more consistency of structural identification, validity test was done by assessing the inter-examiner reliability using the recorded videos.

Figure 1



Workflow for participating patients according to Consort 2010 flow diagram.

The system used was the Image 1 S NIR/ICG and a Hopkins NIR/ICG 30-degree scope by Karl Storz Endoskope, Tuttlingen, Germany.

Primary outcomes: to identify the extrahepatic biliary system (the CD, CBD, CHD, and any possible anomalies present); to identify the cystic artery from its origin till its end and to detect any arterial anomaly.

Secondary outcomes: to detect the incidence of biliary or vascular injury resulted from misidentification of the structures, to compare the operative time, blood loss, and hospital stay between the two groups, and to detect reactions related to the use of ICG.

The obtained data were tabulated and coded for statistical analysis using Excel 365, Microsoft Corporation, Redmond, Washington, USA. Statistical analysis was done using open-source SOFA Statistics program, version 1.5.4, Paton-Simpson & Associates Ltd, Auckland, New Zealand. The χ^2 test was used with the categorical data, while independent t test and Mann–Whitney U test were used with the continuous data. The P values less than or equal to 0.05 were reported to be significant.

Definitions

CHD: the duct formed by the confluence of the right and left hepatic ducts till it joins with the CD [23].

CD: the duct joining the infundibulum of the gall bladder till it joins the CHD [23].

CBD: the duct formed by confluence of the CD and the CHD and it goes down to the ampulla of Vater [23].

Operative time: in this study, for the sake of accurate comparison, the operative time is measured from immediately after the insertion of the scope till the

start of extraction of the gall bladder specimen outside the body.

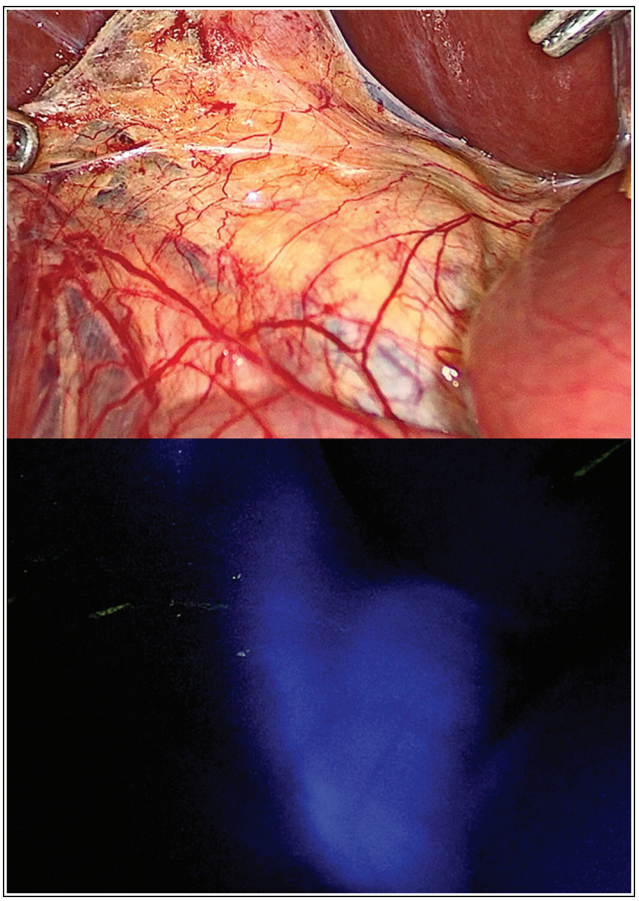
Results

Seventy-eight percent of the recruited patients were females. The mean age was 42.4 years, ranging from 25 to 73 years old and the median BMI was 35.5 kg/m^2. The main preoperative diagnosis was the chronic calculous cholecystitis (85.6%). The demographic data, the BMI, and the preoperative diagnosis are presented in Table 1.

The timing of injection of the ICG in group B was variable; it ranged from 1 to 19 h before the procedure with a median of 6.5 h (Fig. 3).

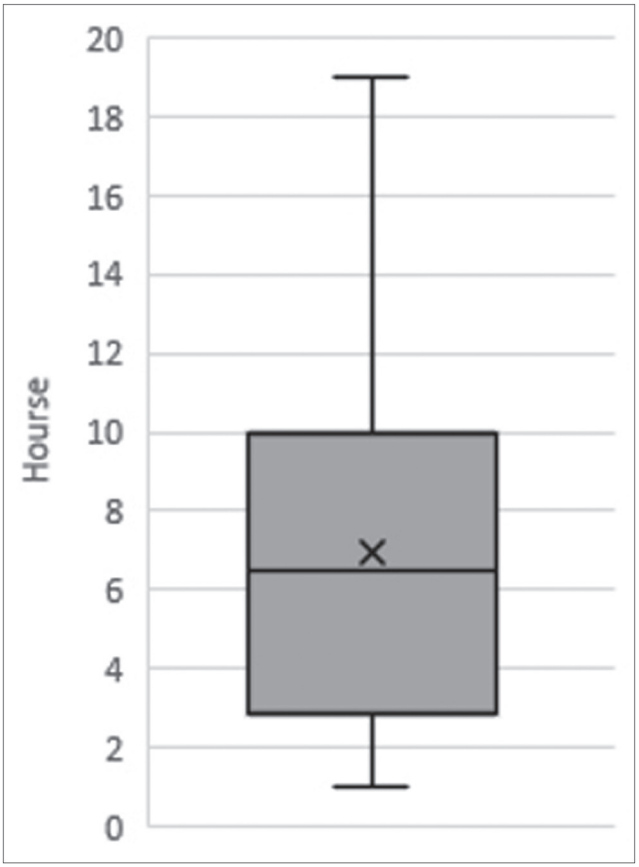
The blood loss was comparable between the two groups, where in group A the median blood loss was 0 ml in the range of 0–100 ml, while in group B the median

Figure 2



The cystic duct and the common hepatic duct before dissection with white light and near-infrared light.

Figure 3



Timing of the indocyanine green injection before the surgery.

Table 1 Demographic data, BMI, and the diagnosis

	All patients	WL	NIR/ICG	*P*
Sex [*n* (%)]				
Male	26 (22)	17 (28.3)	9 (15.5)	0.0931[§]
Female	92 (78)	43 (71.7)	49 (84.5)	
Age (mean±SD)	42.4 ± 11.8	41.95 ± 12.62	42.94 ± 11.05	0.649[^]
BMI [median (range)]	35.5 (20–49)	36 (20–49)	35 (23–47)	0.586[#]
Diagnosis [*n* (%)]				
ACC	16 (13.6)	9 (15)	7 (12)	0.5416[§]
CCC	101 (85.6)	50 (83.3)	51 (88)	
Polys	1 (0.8)	1 (1.7)	0	

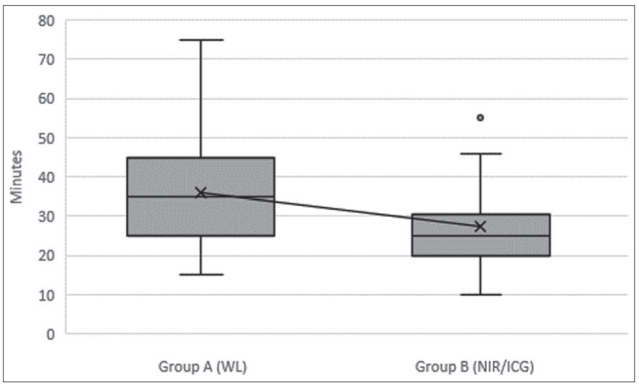
ACC, acute calculous cholecystitis; CCC, chronic calculous cholecystitis; ICG, indocyanine green; NIR, near-infrared; WL, white light. [§]χ^2 test. [^]Independent *t* test. [#]Mann–Whitney *U* test.

Table 2 The identification rates of the biliary structures

	All patients	WL	NIR/ICG	*P*
CHD [*n* (%)]				
Yes	83 (70.4)	27 (45)	56 (96.5)	<0.001*§
No	35 (29.6)	33 (55)	2 (3.5)	
CD [*n* (%)]				
Yes	109 (92.3)	52 (86.6)	57 (98.2)	0.0175*§
No	9 (7.7)	8 (13.4)	1 (1.8)	
CBD [*n* (%)]				
Yes	84 (71.2)	29 (48.3)	55 (94.8)	<0.001*§
No	34 (28.8)	31 (51.7)	3 (5.2)	

CBD, common bile duct; CD, cystic duct; CHD, common hepatic duct; ICG, indocyanine green; NIR, near-infrared; WL, white light. §χ^2 test. *Significant.

Figure 4



Operative time in the two groups.

blood loss was also 0 ml but in the range of 0–50 ml; the *P* value was 0.2973.

The visualization of the extrahepatic biliary structure is demonstrated in Table 2. In group B, where the NIR/ICG was used, all three structures were clearly identified in nearly all the patients, with a statistically significant difference when compared with the other group. Angiography was done for only five cases; the cystic artery was identified in three (60%).

The operative time is plotted in Fig. 4; it had a median of 35 min (15–75 min) in group A and a median of 25 min (10–55 min) in group B. This time variation had a statistically significant difference at *P* value less than 0.001. None of the cases were converted to open and no biliary tree injuries were recorded in both groups.

The hospital stay was the same in both groups. All the patients were discharged the next morning of the surgery.

None of the patients injected or reinjected with the ICG experienced any symptoms or signs of allergy or reaction.

Discussion

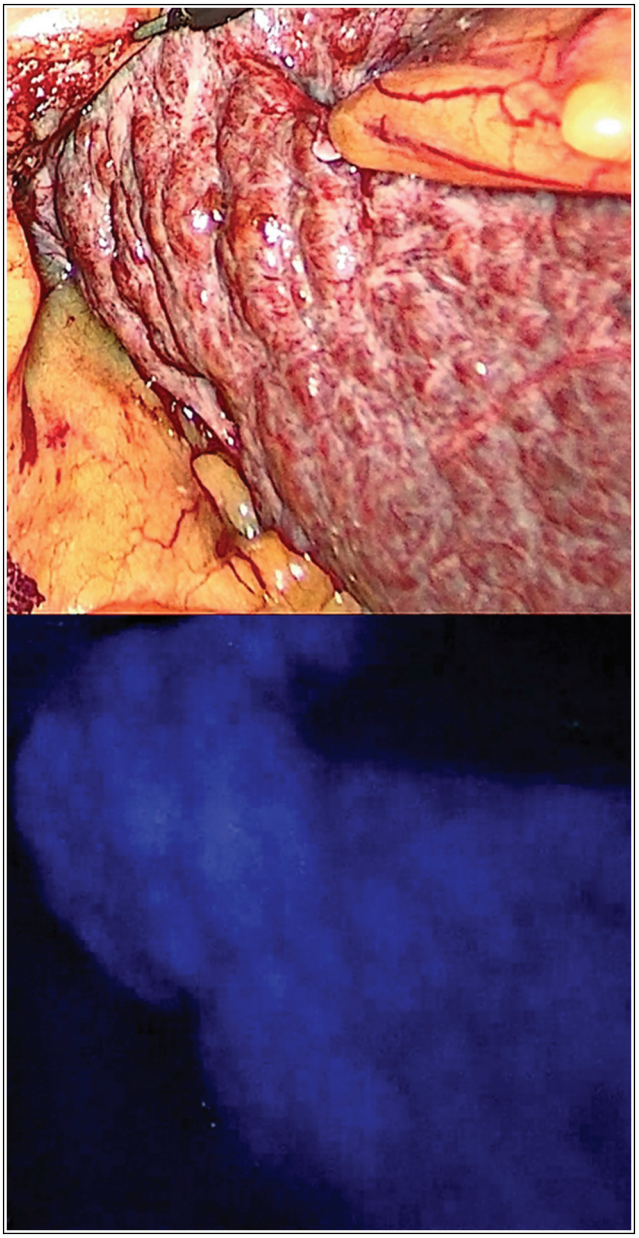
Ishizawa *et al.* [17] described a technique for IOC by injecting ICG dye either intra-biliary or intravenous, then exciting the dye by NIR light to produce fluorescence. Since then, the technique gained acceptance and improvement every day.

Most of the recruited patients, in this study, were females; in a similar study done on 108 patients, 69.5% of them were females [24]. The mean age of patients in this study is younger than that reported from similar studies conducted in Italy, Germany, Japan, and USA [24,25]. This is a predictable finding due to the younger nature of the Egyptian population. On the other hand, the median BMI in our study was higher than that of similar studies [25,26].

In this study, the ICG dye was injected at least 1 h before the induction of anesthesia, up to 19 h. In all cases the identification of the extrahepatic biliary structures was perfect, but for recording images or videos, the ICG injection more than 5 h gives a better result, as the tissue background fluorescence will markedly decrease, giving better contrast. Although cirrhotic patients were excluded from the study, it is worth mentioning that the presence of liver cirrhosis affects the extraction of the dye from the plasma and its excretion into the bile, so the liver shows strong fluorescence for a longer time (Fig. 5).

The identification of the extrahepatic biliary structures (Fig. 6), namely the CHD, CD, and the CBD, was significantly better in the NIR/ICG group, even before dissection of the tissues. The identification rate of the CHD was 96.5%, which was comparable with the data reported by Ishizawa *et al.* [17], Kaneko *et al.* [27], and Daskalaki *et al.* [28]. The CD could not be identified in a single patient with acute cholecystitis, making the identification rate of the CD 98.2%, some studies have reported a similar figure [28–30]. The CBD was not visualized only in three patients, one of

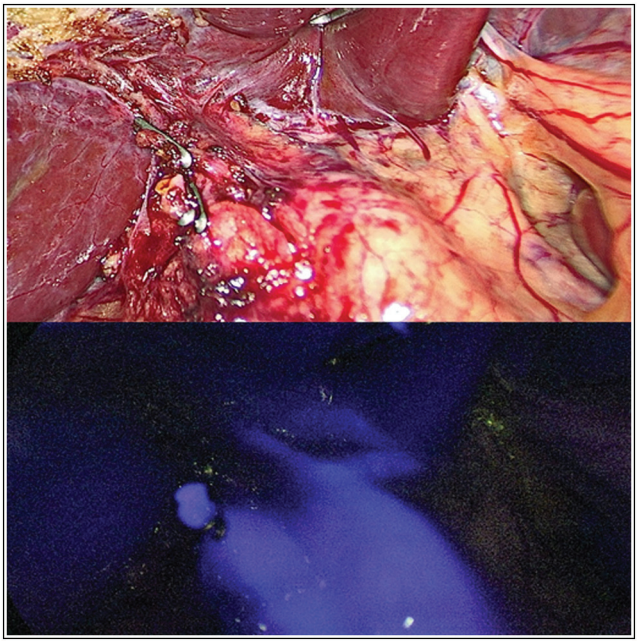
Figure 5



Cirrhotic liver with white light and with near-infrared light.

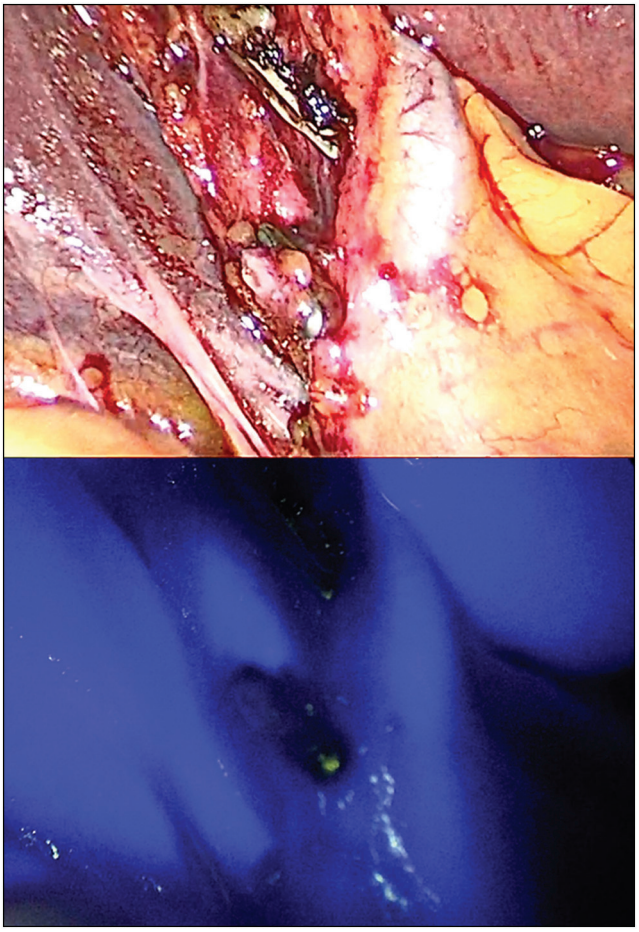
them was the patient in whom we did not identify both the CHD and the CD. But in the other two patients, the CBD was not identified because the CD was long and parallel to the CHD, so by definition, the CBD could never be identified. This biliary arrangement, the parallel CD, is an infrequent arrangement present only in 5–7% of the population [22]. During this study, we were also encountered with another infrequent arrangement, where the CD was joining the biliary tree just at the confluence of the right and left ducts, the carina (Fig. 7). After few cases we discontinued the intraoperative reinjection of ICG for angiography, for two main reasons; first, after the reinjection the background became annoyingly lit, which lowered the ability of the delineation of the extrahepatic biliary tree, which was the main concern. The second

Figure 6



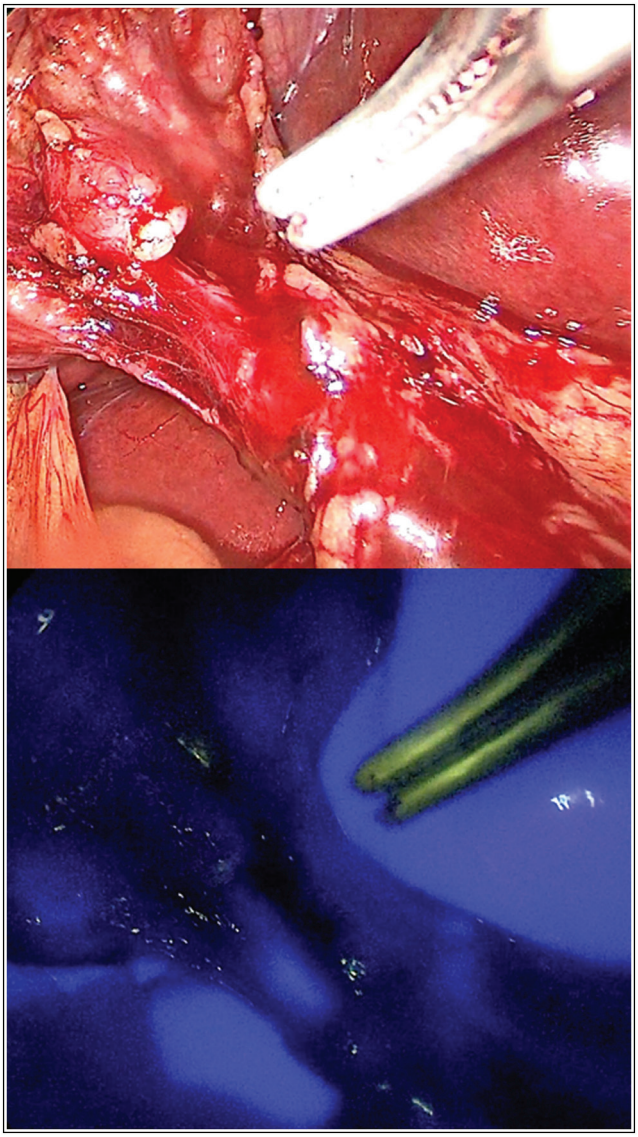
Right, left, common hepatic duct, cystic duct and common bile duct with white light and with near-infrared light.

Figure 7



Cystic duct insertion at the carina with white light and with near-infrared.

Figure 8



Cystic duct during dissection with white light and with near-infrared.

cause was that in most of the cases, the identification of the CD was enough to successfully identify the cystic artery. In a study that involved 28 patients who underwent NIR/ICG LC with reinjection of ICG of angiography, the cystic artery identification rate was only 89% [27]. We recommend sparing the use of this technique for some cases when arterial anomalies are expected and after the full identification of the biliary structures first.

The significantly shorter operative time in the NIR/ICG group was reported in this study as well as most of the studies with a similar structure [31,32]. This is due to the apparent benefit of the technique in the identification of the biliary system, even in acute cases (Fig. 8).

Conclusion

The use of the NIR/ICG cholangiography during the LC is an easy, safe, and effective technique to identify the extrahepatic biliary anatomy; we recommend its use routinely, especially in cases with acute inflammation. However for the ICG angiography, it should be spared only for certain cases and the reinjection of the ICG should be done only after the full identification of the biliary anatomy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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