Near-infrared fluorescence cholangiography assisted laparoscopic cholecystectomy (FALCON): an international multicentre randomized controlled trial

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ORIGINAL ARTICLE

Near-infrared fluorescence cholangiography assisted laparoscopic cholecystectomy (FALCON): an international multicentre randomized controlled trial

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Abstract

Aim To assess the added value of Near InfraRed Fluorescence (NIRF) imaging during laparoscopic cholecystectomy.

Methods This international multicentre randomized controlled trial included participants with an indication for elective laparoscopic cholecystectomy. Participants were randomised into a NIRF imaging assisted laparoscopic cholecystectomy (NIRF-LC) group and a conventional laparoscopic cholecystectomy (CLC) group. Primary end point was time to 'Critical View of Safety' (CVS). The follow-up period of this study was 90 postoperative days. An expert panel analysed the video recordings after surgery to confirm designated surgical time points.

Results A total of 294 patients were included, of which 143 were randomized in the NIRF-LC and 151 in the CLC group. Baseline characteristics were equally distributed. Time to CVS was on average 19 min and 14 s for the NIRF-LC group and 23 min and 9 s for the CLC group (p 0.032). Time to identification of the CD was 6 min and 47 s and 13 min for NIRF-LC and CLC respectively ($p < 0.001$). Transition of the CD in the gallbladder was identified after an average of 9 min and 39 s with NIRF-LC, compared to 18 min and 7 s with CLC ($p < 0.001$). No difference in postoperative length of hospital stay nor occurrence of postoperative complications was found. ICG related complications were limited to one patient who developed a rash after injection of ICG.

Conclusion Use of NIRF imaging in laparoscopic cholecystectomy provides earlier identification of relevant extrahepatic biliary anatomy: earlier achievement of CVS, cystic duct visualisation and visualisation of both cystic duct and cystic artery transition into the gallbladder.

Laparoscopic cholecystectomy (LC) is one of the most commonly performed laparoscopic procedures. The most feared complication during laparoscopic cholecystectomy is bile duct injury. Bile duct injury as a result of laparoscopic cholecystectomy is rare with an incidence of 0.3–0.7% [1–5] but

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often results in severe morbidity and even mortality, lower quality of life and extra costs [6–9].

Misidentification of extra-hepatic bile duct anatomy during laparoscopic cholecystectomy is the main cause of bile duct injury [10]. Examples of such misidentification are mistaking the common bile duct for the cystic duct and aberrant hepatic ducts for the cystic duct or cystic artery. In order to reduce the risk of bile duct injury, techniques to enhance proper identification of the anatomy are needed. One of those techniques is the Critical View of Safety (CVS) technique which was introduced by Strasberg in 1995 [11]. The CVS technique is the gold standard nowadays to perform a safe cholecystectomy with identification of the cystic duct (CD) [13–15]. However, according to a study by Nijssen et al. [16], only in 10% of laparoscopic cholecystectomies CVS is actually established. A study by Gonzales et al. [17] showed that CVS was reached significantly more often in elective than in emergency surgeries. Nassar et al. found that in 1 out of 6 consecutive laparoscopic cholecystectomies, CVS could not be established [18]. This could mean that in daily practice it is more difficult to establish CVS than previously assumed. A problem in achieving CVS could be a persistent difficulty in recognizing the relevant anatomical structures. Additional imaging techniques might improve identification of these structures.

Near-infrared fluorescence (NIRF) imaging after intravenous injection of indocyanine green (ICG) is a promising technique for easier intraoperative recognition of biliary anatomy [19]. By real-time identification of the cystic duct and common bile duct, NIRF imaging may improve the outcome of laparoscopic cholecystectomy [16, 27, 28]. ICG is cleared quickly and exclusively by the liver after intravenous administration and has a well-known pharmacokinetic and safety profile. Neither radiological support nor additional intervention such as opening the cystic or common bile duct are required, making it an easy, real-time technique to use during surgery. Encouraging results derived from early clinical studies suggest routine use of ICG fluorescence laparoscopy could be warranted [20]. One of the first studies by Ishizawa et al. [21] showed that with the use of NIRF and ICG, the cystic duct was visible before dissection, which was confirmed by Schols et al. [22]. A systematic review by Liu et al. confirmed that the technique is a safe and feasible new way for biliary tract identification in laparoscopic cholecystectomy [23]. Experts and early adopters of this technique advocate that any gallbladder surgery would profit from this imaging, [24] and NIRF should be considered both safe and effective [25]. An Asia–Pacific consensus document states that "fluorescence cholangiography can help identify extrahepatic biliary anatomy" and thereby aid in safe dissection of critical structures [37]. Another recent study showed that routine use of fluorescent cholangiography during laparoscopic cholecystectomy is a cost-effective surgical strategy [26].

Despite these earlier promising results, clinical acceptance in daily practice requires more high-quality clinical data. A first randomized trial has been published in which higher detection rates of all essential biliary structures were found, when comparing NIRF imaging with conventional laparoscopic cholecystectomy [27]. In a previous study, our group established the time gained until identification of these essential anatomical structures by using NIRF imaging [22]. Preferably, an endpoint is chosen that is directly related to bile duct injury. This is practically impossible because of its low incidence resulting in unrealistic high numbers of patients to be included. Therefore, other endpoints have to be selected that are related to safety and efficiency of the procedure, likely decreasing the chance of bile duct injury. We believe gain in time until identification of essential structures results in earlier awareness of the exact anatomy, contributing to safety of the procedure. Therefore, the primary objective of the present randomized clinical trial was to evaluate whether earlier establishment of Critical View of Safety could be obtained using the NIRF imaging technique during laparoscopic cholecystectomy.

Methods

The FALCON trial is a multinational randomized controlled clinical trial with 6 participating centres: three in The Netherlands and single centres in Italy, Germany and the United Kingdom. The study protocol was approved by the Institutional Review Board of the Maastricht University Medical Center/Maastricht University (reference number METC142049), registered at clinicaltrials.gov (NL47718.068.14) and performed according to the declaration of Helsinki [28]. The design of the FALCON trial has been published previously [29]. A flow chart of methods used is shown in Fig. 1.

Participants

Adult patients [18 years or older] undergoing elective laparoscopic cholecystectomy were invited to participate by their surgeon during a regular outpatient visit. Inclusion criteria were normal liver and renal function, no hypersensitivity for iodine or ICG, able to understand the nature of the study procedures, willing to participate and provide written informed

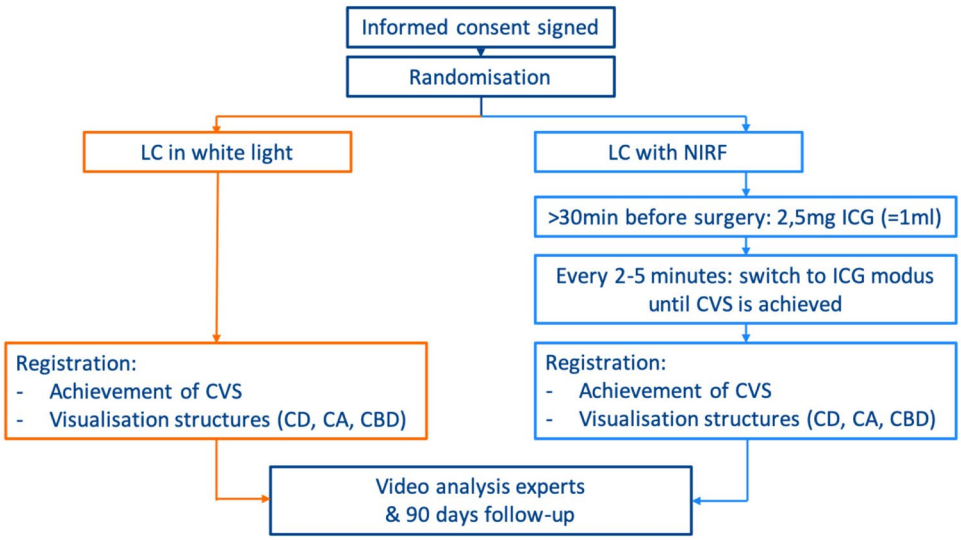

Fig. 1 Study flow chart *LC* laparoscopic cholecystectomy, *NIRF* Near infrared fluorescence imaging, *ICG* indocyanine green, *CVS* critical view of safety, *CD* cystic duct, *CA* cystic artery, *CBD* common bile duct

consent, Physical Status Classification of ASA I/ASA II, planned for elective cholecystectomy.

Exclusion criteria were Age < 18 years, liver or renal insufficiency, known iodine or ICG hypersensitivity, pregnancy or breastfeeding, not being able to understand the nature of the study procedure, a Physical Status Classification of ASA III or above, and acute surgery for cholecystitis. Conversion to open cholecystectomy, before CVS was established, was a reason for study withdrawal from time point analysis. Patients were included in the study after signing informed consent. All participants were randomized in either the control group or intervention group. Block randomization using blocks of six, with sealed envelopes and stratification per participating centre was used. After signing the informed consent form, the next sealed envelope in line was opened by the coordinating investigator. Blinding of patients or surgeons was not possible with this study design.

Intervention

Participants in the intervention group underwent a laparoscopic cholecystectomy following the CVS-technique with the use of near-infrared fluorescence cholangiography (NIRF-LC). In all cases 3 or 4 trocars were used, depending on the preference of the surgeon. To establish CVS, three criteria should be met. The hepato-cystic triangle must be cleared of fat and fibrous tissue; the lowest one third of the gallbladder must be mobilized from the liver; two, and only two structures must be seen entering the gallbladder [11, 12].

A NIRF imaging system (Karl Storz GmbH, Tuttlingen, Germany) was used in this procedure. This is a commercially available laparoscopic fluorescence imaging system, including a plasma light guide and a 30-degree, 10-mm laparoscope applicable for white light, autofluorescence, and ICG imaging. The system was used for intraoperative conventional imaging [called the "WL" (white light)-mode] and near-infrared fluorescence imaging [called the "ICG" (Indocyanine green)-mode]. The system was equipped with a foot pedal, allowing the surgeon to easily switch from WL-mode to ICG-mode, and back. Because of the instantaneous changing of images and the stable position of the laparoscope, anatomical orientation could be maintained. However, direct fluorescence image-overlay on the conventional anatomical image was not possible with this system. During surgery, the NIRF imaging system was switched from white to NIRF light at least every 5 min until identification of CVS.

To obtain fluorescence imaging of the biliary tract and cystic artery a NIRF contrast agent was administered. At least 30 min before incision, 2.5 mg of Indocyanine Green (ICG) (2.5 mg/ml) (Diagnostic Green, Aschheim, Germany) was injected intravenously. A repeat injection of 2.5 mg was administered for concomitant arterial and biliary fluorescence delineation after achievement of CVS in patients included in the Maastricht University Medical Center and the Leiden University Medical Center.

The control group underwent a laparoscopic cholecystectomy as in standard care following the CVS-technique without the use of intraoperative cholangiography.

Experience of the surgical team

The operation was performed by a surgeon or surgical resident. This person is called the first surgeon. The position of assistant (second surgeon) in the procedure could be taken by a surgical resident or surgeon. At least one

member of the team needed to have performed more than 50 procedures as first surgeon.

Outcome measures

The primary outcome measure was time to identification of CVS, measured from the first look at the liver hilum (i.e. after first release of organs or adhesions obstructing this view). CVS was defined established if the following three criteria were met:

1 Mobilization of the gallbladder infundibulum for one-third of the length of the gallbladder from the liver bed.
2 Circumferential exposure of the cystic duct and confirmation of its transition in the gallbladder.
3 Circumferential exposure of the cystic artery and confirmation of its transition in the gallbladder.

Secondary outcome measures were Time until identification of the cystic duct (CD), Time until identification of the common bile duct, Time until identification of the transition of the CD into the gallbladder, Time until identification of the transition of the cystic artery (CA) into the gallbladder, Intraoperative bile leakage from the gallbladder or cystic duct, bile duct injury, postoperative length of hospital stay, complications due to injected ICG, conversion to open cholecystectomy, 90 days all-cause postoperative complications. Also, the presence of signs of cholecystitis were noted and the difficulty of the procedure as experienced by the surgical team on a scale of 1–5.

Patient follow-up was 90 days postoperatively.

Data management

A Case Report Form was completed intra-operatively. A structure was scored as 'identified' if its localization was confirmed with great certainty by the first surgeon performing the laparoscopic cholecystectomy. The first surgeon was consulted to decide whether the team agreed that CVS was established. In accordance with regular care, all laparoscopic surgical procedures were digitally recorded. An expert panel, consisting of three highly experienced laparoscopic surgeons, analysed the data using video recordings: time until identification of the cystic duct and of its transition into the gallbladder; time until identification of the cystic artery and its transition into the gallbladder; when and whether CVS was established. All clinical data were prospectively registered in a database.

Sample size

Sample size calculation was based on pilot data from the same research group [22, 30]. In these studies, identification of the cystic duct and common bile duct were established respectively 11 and 10 min earlier using fluorescence laparoscopic imaging compared to conventional laparoscopic imaging. A sample size of 131 for each randomization arm was calculated to detect a reduction in 'time to establishment of CVS' of at least 5 min with a power of 80% and an α of 0.05. Assuming a withdrawal rate of 15% (due to usual reasons for drop-out in combination with technical difficulties concerning the video recordings) during the trial, a total of 308 ($n = 2 \times 131$ /0.85) would be required.

Statistical analysis

Descriptive statistics were used to summarize characteristics of the study population.

The primary outcome measure was time to identification of CVS, which was analysed using the independent-samples *t*-test. All numerical secondary outcomes such as time until visualization of cystic duct and cystic artery were analysed using the independent samples *t*-test. All categorical secondary outcomes such as bile duct injury and conversion to open surgery were analysed using a using a Pearson's Chi-Square test. We computed interaction terms to evaluate whether surgical difficulty and BMI would modify the effect of NIRF. These analyses were considered exploratory.

To quantify agreement between experts in the panel on intra-operative observations, the intra-class correlation coefficient (ICC) was calculated for all measured time-points during surgery in a random set of included surgeries. With the use of the ICC, values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.9 indicate excellent reliability [31].

Analyses were performed using SPSS Statistics 27 (IBM, Armonk, New York, USA). All tests except the ICC were two-tailed and the significance level was set at $p < 0.05$.

Results

Patient characteristics

A total of 294 patients were included in this study between January 2016 and September 2019, of which 143 (48.6%) were randomized in the NIRF-LC and 151 (51.4%) in the CLC group. No patients were lost to follow-up. See also the flowchart in Fig. 2. Demographic data are given in Table 1. Mean age was 53.1 years in the NIRF-LC group, and 53.1 years in the CLC group. 61.3% versus 65.5% of patients were female. Average BMI was 27.52 in the NIRF-LC group and 27.6 in CLC group ($p = 0.948$). 88.4% of

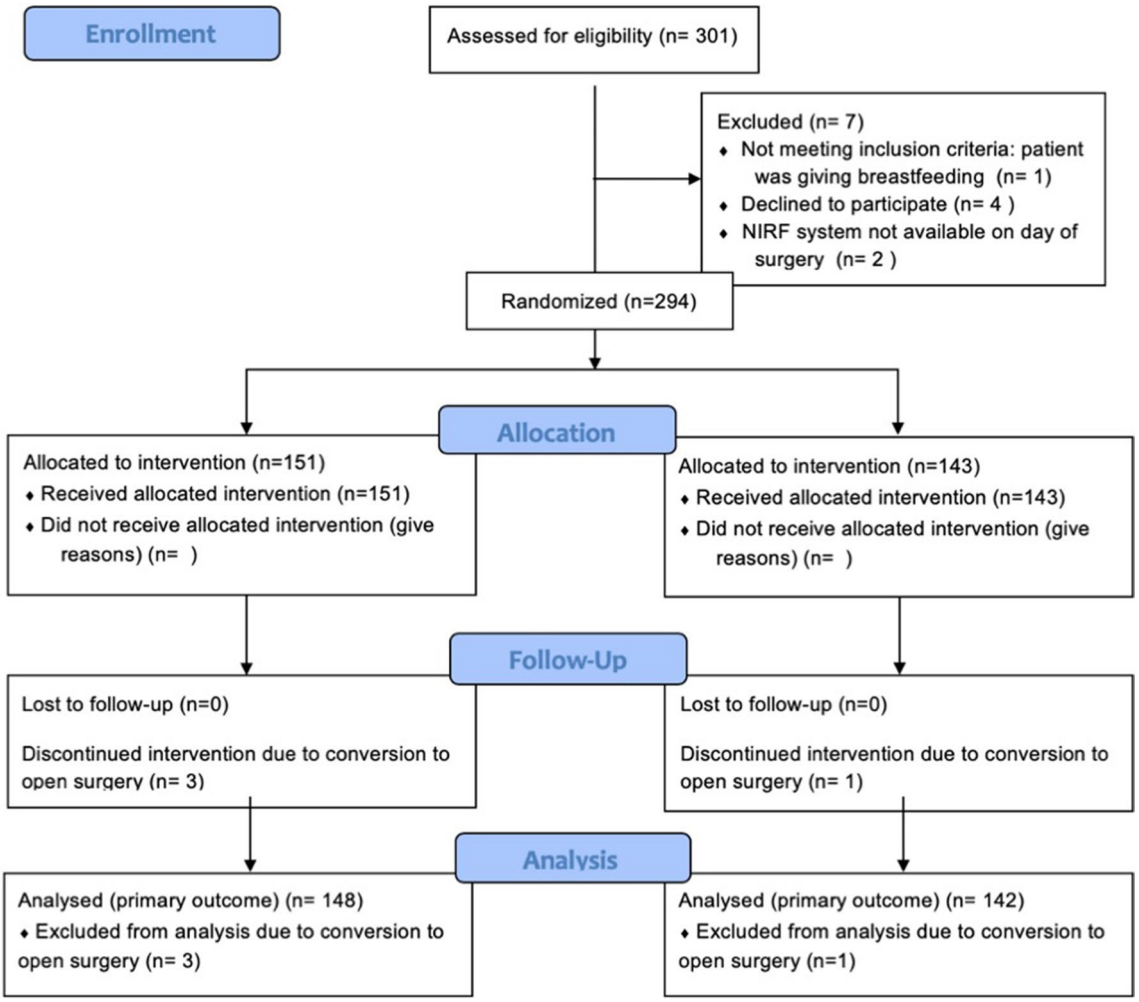

Fig. 2 Flow chart of enrolment of patients

Table 1 Demographic data

	Total	NIRF-LC	CLC
Age (years) (sd)	53.4 (15.1)	53.8 (14.5)	53.1 (15.6)
Weight (sd)	80.4 (17.4)	80.4 (17.9)	80.5 (16.9)
BMI (sd)	27.5 (5.1)	27.6 (5.1)	27.5 (5.1)
Female (%)	184 (63.4%)	87 (61.3%)	97 (65.5%)
Indication for LC			
Symptomatic cholecystolithiasis	260 (88.4%)	123 (85.9%)	137 (90.7%)
Post-cholecystitis	16 (5.4%)	9 (6.3%)	7 (4.6%)
Polyps	8 (2.7%)	4 (2.8%)	4 (2.6%)
Post-biliary pancreatitis	8 (2.7%)	5 (3.5%)	3 (2.0%)
Missing data	2 (0.6%)	2 (1.4%)	0

No significant differences between groups for any variable

Sd standard deviation, *LC* laparoscopic cholecystectomy

patients were operated for symptomatic cholecystolithiasis, with other indications being previous cholecystitis, cholangitis or biliary pancreatitis, or polyps. Only patients undergoing elective cholecystectomy were included, no patients undergoing delayed emergent cholecystectomy or

cholecystectomy after cholecystostomy were included in this study.

Surgical team

Characteristics of the experience level of the surgical team are presented in Table 2. In the NIRF-LC group, the first surgeon was a resident in training in 69.9% of cases, compared to 71.5% in the CLC group. The assisting (second) surgeon was a resident in 51.7% and 53.3% respectively. The surgery was performed by two residents in training in 30.8% of NIRF cases and 23.3% of CLC cases. Experience levels did not differ between both groups. Also, the experience level did not have an influence on the outcomes of this study.

Table 2 Characteristics surgical team

	Total	NIRF-LC	CLC
Experience 1st surgeon			
< 20	70 (23.8%)	33 (23.1%)	37 (24.7%)
20–50	64 (21.8%)	30 (21%)	34 (22.7%)
50–100	63 (21.4%)	29 (20.3%)	34 (22.7%)
> 100	96 (32.6%)	51 (35.7%)	45 (30%)
Missing data	1	0	1
Experience 2nd surgeon			
< 20	76 (25.7%)	35(24.6%)	41 (26.8%)
20–50	25 ((8.5%)	14 (9.8%)	11 (7.2%)
50–100	30 (10.2%)	14 (9.8%)	16 (10.5%)
> 100	158 (53.6%)	77 (53.8%)	81 (56.6%)
Missing / no second surgeon	1/4	1/3	0/1
1st surgeon			
Resident	207 (70.6%)	99 (69.2%)	108 (71.5%)
Attending	86 (29.4%)	44 (30.8%)	42 (27.8%)
Missing	1	0	1
2nd surgeon			
Resident	155 (52.3%)	74 (51.7%)	81 (53.3%)
Attending	135 (46.1%)	66 (46.1%)	69 (46%)
Missing/no second surgeon	0/4	0/3	0/1
Both surgeons are resident	79 (26.9%)	44 (30.8%)	35 (23.3%)

No significant differences between groups for all variables

Intra-operative time analysis

Data concerning the intra-operative visualisation of the essential structures are presented in Table 3. Time between first look at the liver hilum and achievement of CVS was on average 19 min and 14 s in the NIRF-LC group, compared to 23 min and 9 s in the CLC group; resulting in an average decrease of 3 min and 55 s ($p = 0.032$). Time between first look at the liver hilum and identification of the cystic duct was 6 min and 24 s in the NIRF-LC group and 13 min in the CLC group; resulting in an average difference of 6 min and 36 s ($p < 0.001$). The cystic artery was seen 1 min and 53 s earlier, but this difference was not statistically significant ($p = 0.240$). Also, in the group of patients who received a second dose of ICG to visualize the cystic artery, the cystic artery was not seen significantly earlier ($p = 0.726$). The time between first look at the liver hilum and identification of the transition of the cystic duct into the gallbladder was 9 min and 39 s and 18 min 7 s respectively for the NIRF-LC and CLC groups, resulting in an average difference of 8 min and 28 s ($p < 0.001$). The transition of the cystic artery into the gallbladder was identified 4 min and 29 s earlier in the NIRF-LC group ($p = 0.011$). NIRF-assisted laparoscopic cholecystectomy had a mean surgical time of 65 min and 47 s, as compared to 69 min and 52 s for conventional laparoscopic cholecystectomy.

The expert panel registered the identification of the time points, and came to different time points than the exact time points noted by the surgeon during surgery. To

Table 3 Time-measurements during surgery

	NIRF-LC	CLC	P-value	NIRF-LC experts	CLC experts	ICC experts[a]
Time between first look at liver hilum and CVS	19 min 14 s	23 min 9 s	**0.032***	21 min 32 s	23 min 55 s	**0.890**
Time till identification CD	6 min 24 s	13 min	**0.000***	5 min 48 s	11 min 6 s	**0.770**
Time till identification CA	13 min 56 s	15 min 49 s	0.240	12 min 6 s	10 min 53 s	0.435
Time transition CD-gallbladder	9 min 39 s	18 min 7 s	**0.000***	16 min 4 s	21 min 9 s	**0.863**
Time transition CA-gallbladder	15 min 6 s	19 min 35 s	**0.011***	16 min 38 s	21 min 9 s	**0.857**
Total surgical time	65 min 47 s	69 min 52 s	0.198			

[a]*ICC* intraclass correlation coefficient. *NIRF-LC* near infrared fluorescence imaging assisted laparoscopic cholecystectomy. *CLC* conventional laparoscopic cholecystectomy, *CVS* critical view of safety, *CD* cystic duct, *CA* cystic artery

determine whether this difference was relevant, the identification of the different time-points by the expert panel was analysed by calculation of the intraclass correlation coefficient (ICC). The ICC was 0.77, 0.44, 0.86, 0.86 and 0.89 for identification of the CD, CA, transition of CD into the gallbladder, CA into the gallbladder and CVS respectively.

Per- and post-operative outcomes

After the surgeries, each procedure was rated from easy to difficult on a scale from one to five. The mean difficulty did not differ between the two groups and was 1.9 (sd 0.83) in NIRF-LC patients and 2.0 (sd 1.05) in CLC cases ($p=0.318$). No significant effect of difficulty of surgery was seen on the usefulness of NIRF to minimizing time until CVS ($p=0.267$). As shown in Fig. 3, it seemed that in the more difficult cases NIRF was of more added value compared to the easy cases, but the current study was not powered to analyse this outcome. In patients with a higher BMI, the added value of NIRF seemed smaller in minimizing the time until visualisation of the CVS ($p=0.023$).

In four patients, conversion to laparotomy was needed, three times in the NIRF-LC and once in the CLC group. In one of these patients, conversion to open surgery was needed before introduction of the laparoscope because of a difficult introduction due to previous surgery. The other three cases needed conversion to laparotomy because of unclear anatomy due to extensive adhesions after cholecystitis. These patients were excluded from further analysis due to the exclusion criteria.

In one patient, a possible allergic reaction to ICG was seen: the patient had a rash after induction of anaesthesia. 4 mg of dexamethasone was administered resulting in quick disappearance of the rash. As ICG was given 11 min before induction of anaesthesia, and dexamethasone was administered 10 min after induction of anaesthetics (sufentanil, propofol, rocuronium), it is not clear whether the rash could be related to ICG or the anaesthetics.

In 26 of 294 includes patients, a complication occurred. No statistical difference was seen in the complication rate and Clavien-Dindo classification of complications [34] between the NIRF-LC and CLC groups, as shown in Table 4. In both NIRF-LC and CLC group, 5 patients developed a wound infection, which could be treated conservatively. In three patients, postoperative bile leakage was present. All three patients needed re-laparoscopy. In both NIRF-LC patients with bile leakage, the bile leakage came from a duct of Luschka. The leakage in the patient randomized in the CLC group resulted from a small leakage from the cystic duct which was closed by a suture. In three patients, postoperative abdominal pain was a cause for readmission. There was spontaneous resolution of this pain during readmission. No other cause for the abdominal pain was found. A postoperative bleeding occurred in two patients, requiring re-laparoscopy. Two patients developed choledocholithiasis postoperatively. In these patients, stone extraction by ERCP was achieved. In one of these two patients, a conversion to open surgery was needed during the initial laparoscopic cholecystectomy. One patient developed a pneumothorax due to iatrogenic damage caused by insertion of a surgical trocar.

Median length of postoperative hospital stay was 1 night (range 0–14 sd 1.9) in the NIRF-LC group, and also 1 (range 0–13 sd 1.9) night in the CLC group ($p=0.055$). The postoperative hospital stay was mainly determined by the course of postoperative complications.

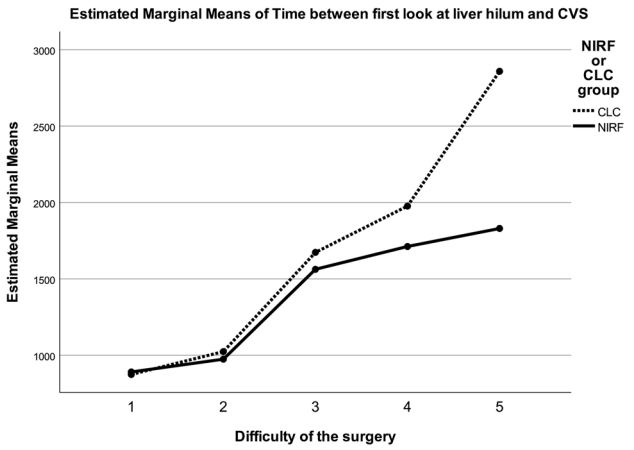

Fig. 3 Relation between difficulty of surgery and time to CVS No significant difference was found between the groups. The current study was not powered for this subgroup analysis

Discussion

The primary objective of this international multicentre randomized clinical study was to evaluate whether earlier establishment of Critical View of Safety (CVS) can be obtained using the NIRF imaging technique during laparoscopic cholecystectomy. In the current study, we found a statistically faster identification of CVS using NIRF imaging compared to conventional white light laparoscopic cholecystectomy. The mean difference was almost four minutes between the two groups. Also, faster recognition of the cystic duct, transition of the cystic duct into the gallbladder and transition of the cystic artery into the gallbladder were achieved using NIRF imaging.

As stated above, the primary endpoint of bile duct injury could not be chosen in a trial like this, because of its low incidence. The chosen endpoint of time saved to identify critical structures is thought to be illustrative of a safe and efficient procedure, thereby likely contributing to the

Table 4 (Post) Operative outcomes

	NIRF-LC	CLC	*p*-value
Difficulty of surgery (scale 1–5)	1.9	2.0	0.653
Intraoperative signs of cholecystitis	30.5%	26.7%	0.222
Conversion to open procedure	3	1	0.285
Length hospital stay (nights, median)	1 (range 0–14)	1 (range 0–13)	0.055
Occurrence of complications	17 (12.8%)	9 (6.4%)	0.126
Wound infection	5	5	
Bile leakage	2	1	
Abdominal pain	2	1	
Postoperative bleeding	2	0	
Thrombus left lower arm	1	0	
ACNES*	1	0	
Choledocholithiasis	1	1	
Pneumothorax	1	0	
Pneumonia	2	0	
Clavien-Dindo Classification			0.409
Grade I	7	6	
Grade II	4	0	
Grade III a	2	1	
Grade III b	4	2	
Grade IV a	0	0	
Grade IV b	0	0	
Grade V	0	0	

**ACNES* anterior cutaneous nerve entrapment syndrome

prevention of bile duct injury. Whether using NIRF, the incidence of BDI will indeed decrease, can only be evaluated through large registry studies, which is beyond the reach of the present study.

The same dilemma of choice of endpoint was recognized in a previous RCT on this topic, by Dip et al. [27]. These authors chose the detection rate of seven biliary structures (cystic duct, right hepatic duct, common hepatic duct, common bile duct, cystic duct-common bile duct junction, cystic duct-gallbladder junction and accessory ducts) before and after surgical dissection. Higher detection rates before dissection for all seven biliary structures were identified using ICG. After dissection, no difference was found in detecting the cystic duct and cystic duct-gallbladder-junction between NIRF and white light, while the other five structures were detected more often with the use of NIRF. Their findings are in line with the current study, namely that during laparoscopic cholecystectomy, near-infrared fluorescent cholangiography improves the visualization of extrahepatic bile duct anatomy over white light imaging alone [27]. Both RCT's support the use of this imaging technique during laparoscopic cholecystectomy.

A second RCT has been published, that included 63 patients to evaluate whether earlier identification of CVS could be obtained using NIRF imaging [32]. No such advantage was determined. The small sample size and lack of adequate power prohibits a definite conclusion based on this trial.

Lehrskov et al. [35] performed a non-inferiority blinded RCT in which NIRF imaging using 0.05 mg/kg indocyanine green was compared with X-ray cholangiography during elective laparoscopic cholecystectomy. Both groups contained 60 patients. No difference was found in visualisation of the anatomical junction between cystic duct, common hepatic duct and common bile duct. This confirms the non-inferiority of fluorescence cholangiography to X-ray cholangiography.

Recently, a RCT was published concerning patients with acute cholecystitis [36], comparing laparoscopic cholecystectomy with or without NIRF imaging. In this non-inferiority trial conversion rate was chosen as the primary endpoint and biliary injury and postoperative complications as secondary endpoints, among others. The authors found no differences in primary and secondary endpoints, concluding that routine use of NIRF imaging in these cases is questionable. Unfortunately, this trial has the limitation to be underpowered to conclude on biliary injury.

In more difficult operations, a technique to aid in performing the procedure, would be valuable. Data in our study suggested that in more difficult cases NIRF was op more added value. However, one should realize that our study was not powered to analyse the impact of the difficulty level of

surgery on the beneficial effect of NIRF imaging. This effect should be investigated in further future studies.

A relatively large retrospective study concerning 1389 patients suggests a protective influence of fluorescence cholangiography on bile duct injury [38], yet for firm conclusions on this endpoint we need larger, preferably population-based, series.

In baseline characteristics our study groups did not differ. Especially indication for surgery, experience of the surgical team and BMI of the patients were comparable in both groups. In a subgroup analysis, NIRF seemed to be less beneficial in patients with a higher BMI. However, this should be interpreted with caution as the current study was not powered on this outcome. Also, the consequences of this outcome for clinical practice are not clear.

In four patients, conversion to open surgery was needed to safely perform the procedure. The reason for conversion to open surgery was inability to introduce laparoscopic instruments, and unclear anatomy due to extensive adhesions. The NIRF technique could not prevent the need for conversion in these cases. Bile leakage occurred in three patients, of which two randomized in the NIRF-LC group. The cause was a duct of Luschka in the two NIRF-LC patients. NIRF imaging had not resulted in its identification during surgery. Both videos have been re-evaluated by one of the experts (LS), and again no leakage in either NIRF or WL mode could be detected during the primary surgery. One point of improvement for future use of NIRF could be continuous application of this visualization mode which was not possible with the equipment used in the present study.

In patients included in two of the participating centres, a second dose of ICG was administered to visualize the cystic artery. This did not result in earlier identification of the cystic artery. A possible explanation is the background fluorescence at the time of administration of a second dose of ICG and low sensitivity of the camera system used in the trial.

In the present study, visualization of the common bile duct was not a secondary endpoint. Dissection of the common bile duct is not part of the CVS technique, and thus the visualization of the common bile duct is not expected to happen during all surgeries. Nevertheless, in some cases in our study, the CBD could be seen fluorescently lightening up even without any specific dissection. This finding should be considered as an additional gain of the technique.

Expert panel

The differences between the current study and the previously published RCT are not only the endpoints chosen, but in the current study the intraoperative data was also analysed by an expert panel for internal validation of the assessment of the time points chosen. This was deemed valuable as it was impossible to blind the intra-operative observers and because surgeons from six participating centres performed the procedures. As shown, an intraclass correlation coefficient of 0.89, 0.77, 0.86, 0.86 and 0.89 was found for time until visualization of CVS, CD, transition of CD in the gallbladder, transition of cystic artery into the gallbladder and achievement of CVS respectively. All these ICCs are above 0.75 and thereby indicate good reliability of the data in the current study.

Limitations

As mentioned above, a limitation of this study is the primary endpoint. The desired endpoint to prove the added value of the use of NIRF imaging in laparoscopic cholecystectomy would be the occurrence of bile duct injury. As discussed before, due to the fact that bile duct injury is a rare event, with an occurrence of about 0.4% [1], this is an unrealistic endpoint for a RCT. Another limitation is the continuous development of equipment for fluorescent imaging. The inclusion of this study was between 2016 and 2019. In the meantime, the technique has evolved and even better image quality is obtained and overlay imaging of NIRF over white light is possible. Presumably, this provides an even better view of the anatomical structures, likely resulting in an even bigger difference between NIRF and conventional imaging. A third limitation of this study is that we only included elective cases for uniformity. A benefit of NIRF imaging has also been shown for more difficult, emergency cases [33].

Our study has added evidence-based support for the use of near-infrared fluorescence imaging to facilitate anatomical identification during laparoscopic cholecystectomy.

Conclusion

The use of NIRF imaging using ICG results in earlier identification of CVS and essential biliary structures during laparoscopic cholecystectomy.

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Declarations

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