Safety of laparoscopic cholecystectomy performed by trainee surgeons with different cholangiographic techniques (SCOTCH): a prospective non-randomized trial on the impact of fluorescent cholangiography during laparoscopic cholecystectomy performed by trainees

Safety of laparoscopic ChOlecystectomy performed by Trainee surgeons with different CHolangiographic techniques (SCOTCH)

A prospective non-randomized trial on the impact of fluorescent cholangiography during laparoscopic cholecystectomy performed by trainees.

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ABSTRACT

Aims

The identification of the anatomical components of the Calot's Triangle during laparoscopic cholecystectomy (LC) might be challenging and its difficulty may increase when a surgical trainee (ST) is in charge, ultimately allegedly affecting also the incidence of common bile duct injuries (CBDIs). There are various methods to help reach the critical view of safety (CVS): intraoperative cholangiogram (IOC), critical view of safety in white light (CVS-WL) and near-infrared fluorescent cholangiography (NIR-C). The primary objective was to compare the use of these techniques to obtain the CVS during elective LC performed by ST.

Methods

This was a multicentre prospective observational study (Clinicalstrials.gov Registration number: NCT04863482). The enrolled patients were divided into three groups according to the technique used (IOC, CVS-WL, NIR-C). Only surgical trainees who performed less than 30 LC before the beginning of the study participated. All were required to fill in a questionnaire focusing on anatomical identification of the CVS and the NASA task load test at the end of the operation. Surgeon satisfaction was assessed by a Likert scale ranging from 1 to 5.

Results

Thirty centers participated for a total of 338 patients: 260 CVS-WL, 10 IOC and 68 NIR-C groups.

The groups did not differ in the baseline characteristics. CVS was considered achieved in all the included case. Rates were statistically higher in the NIR-C group for common hepatic and common bile duct visualization ($p=0.046$; $p<0.005$, respectively). There were no statistically significant differences in operative time ($p=0.089$) nor in the time to achieve the CVS ($p=0.626$). Three biliary duct injuries were reported: 2 in the CVS-WL and 1 in the NIR-C. Surgical workload scores were statistically lower in every domain in the NIR-C group. Subjective satisfaction was higher in the NIR-C group. There were no other statistically significant differences.

Conclusions

These data showed that using NIR-C did not prolong operative time but positively influenced the surgeon's satisfaction of the performance of LC.

Commentato [MOU1]: Mauro: nel main text c'è scritto 29.

INTRODUCTION

Laparoscopic cholecystectomy (LC) gained popularity among general surgeons in the 1990s. It rapidly became one of the most performed procedures in digestive surgery [**1, 2**], with more than one million cholecystectomies being performed annually in the United States [**3**]. Currently, LC is one of the most common procedures general surgeons perform throughout their careers. It is likely one of the first laparoscopic procedures performed as a first operator during training [**4, 5**].

Given its uniform spread among the departments and its peculiar characteristic as the introductory playground to the laparoscopic world, LC is often regarded as the testing field for many new technologies.

In previous reports, LC cases performed by surgical trainees (ST) are not associated with higher operative morbidity [**6**]. However, the length of operative time was described as potentially significantly increased when compared with LC cases performed by attending surgeons, due, in the most part, to difficulties in identifying anatomical structures [**7, 8**], which, often leads to an attending surgeon taking over the operative case.

Furthermore, even though LC has proven to be a safe procedure, the rate of common bile duct (CBD) injuries (CBDI) remains unacceptably high even in the hands of minimally invasive trained surgeons [**9**], ranging from 0.2 to 1.5% in individual reports [**10, 11-15**]. CBDIs are associated with significant morbidity and mortality, poor quality of life and increased costs related to additional health care measures, loss of work days, and insurance claims [**2,10, 16, 17**]. Way *et al.* reported that in 97% of CBDIs non-technical errors predominantly relating to perceptual errors in which the operator was led to make false assumptions regarding the position of the CBD were at the root cause of the injury [**18**].

From this observation, many existing recommendations to avoid CBDI insist on establishing a critical view and understanding the relevant anatomy, aided by adequate retraction and visualization [**19**].

The correct identification of Calot's triangle, sometimes hard even in expert hands, may be particularly challenging for ST, leading to such misidentifications of the structures, which are the most frequent causes of CBDI during LC. Once anatomic confusion has led the surgeon astray, injury occurs in relatively predictable locations along the biliary tree [**4**]. The most frequent site of CBDI is below the bifurcation of the right and left hepatic ducts (65%) [**20**].

In laparoscopic surgery, there is also a loss of haptic input and stereoscopic depth perception, predisposing to a misperception leading to CBDI [**20, 21**]. Various methods have been described to help the identification of the structures in Calot's triangle; these include intraoperative cholangiogram (IOC) [**22**], critical view of safety (CVS) [**23**], and the near-infrared fluorescent cholangiography (NIRF-C) [**24**].

Each of these techniques has proven to be helpful and, at the same time, to have some intrinsic drawbacks that could be amplified when in inexperienced hands.

Since, to date, there is no consensus on the best technique to correctly identify the anatomy of the Calot's triangle during LC performed by ST, this prospective non-randomized trial aimed to identify which of the current available techniques allowed the most effective and safe visualization of the single components of the triangle for trainee surgeons to finally propose a standard technique for this particular setting [**25-28**].

MATERIALS and METHODS

This multicenter prospective non-randomized study was promoted by the Italian Society of Endoscopic Surgery and new technologies (SICE https://siceitalia.com/). Ethical approval was granted by the Institutional Review Board of the University of Ancona (Italy) (PROT.2021-196) and local boards of the participating centres. This study was conducted under the principles of the Declaration of Helsinki. It was developed and presented according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE, ClinicalTrials. Gov NCT04863482) [**29**]. **Supplementary Table 1.**

The included patients were divided into three groups according to the technique used to achieve the CVS during LC:

- **CVS-WL group**: The CVS was achieved in white light (WL) without an intraoperative imaging technique. CVS in white light was selected as the control group since it is the recognized standard in clinical practice.
- **IOC group**: The CVS was achieved with the help of intraoperative cholangiography (IOC). IOC was performed after dissection of the cystic duct in a standardised manner, by cannulation of the cystic duct with a catheter using either a Kumar or Olsen grasper. Leakage was controlled by injecting saline prior to injection of iodine contrast means, according to the centre usual habits. A mobile X-ray C-arm system was used, and the monochrome X-ray image was shown on a separate screen.
- **NIRF-C group**: The CVS was achieved with the help of near-infrared fluorescence cholangiography (NIRF-C). NIRF-C was performed injecting intravenously, 2.5-7.5 mg of indocyanine green (0.2 mg/kg) at the admission of the patients into the hospital, in patients admitted the same day of surgery, and at least 45 mins before the acquisition of the images.

The choice of the procedure was left to the operating surgeon, following standard care, department policies, availability of the instrumentation, and personal preferences; however, to reduce selection biases, the allocation in each arm was decided prior to the beginning of the surgical intervention by the first operator.

Patients received written information regarding the index procedure. The included variables regarded patients' baseline characteristics (age, gender, ASA score, pre-operative diagnosis), intra-operative data (operative time, duration of cholangiography, time needed to achieve the CVS, intraoperative complications), CBDI (according to the ATOM, Strasberg's and LAU classifications [**30-32**] as reported in **Supplementary Table 2**, and how the CBDI was diagnosed intraoperatively). Post-operative outcomes (early post-operative complications, late complications, need for readmission, length of hospital stay), and surgeons' ease at performing the procedure were also

investigated. The latest information was achieved by asking the operating surgeon to complete three different questionnaires soon after the completion of the procedure [**33-34**].

As per protocol sample size estimation we previously calculated the need to include 60 patients per group to reach a power of 90%, assuming a success rate of 80% for the conventional intraoperative cholangiography, 90% for the intraoperative fluorescent cholangiography and CVS-WL and after the analysis of dataset to test whether intraoperative fluorescent cholangiography was no more than 10% inferior to conventional intraoperative cholangiography in a one-sided test applying a 5% level of significance.

Inclusion and exclusion criteria

The study's local lead surgeon considered consecutive eligible patients aged ≥ 18 years**,** scheduled for elective LC, and able to consent to the procedure at the outpatient clinic.

Elective LC in this study was defined as any planned intervention to be performed during the ordinary scheduled operatory list for asymptomatic or mildly symptomatic patients with a known history of cholelithiasis not requiring an urgent intervention.

Previous choledocholithiasis undergone CPRE before the intervention and previous pancreatitis were not an exclusion criterion.

All the patients received surgery according to the existing guidelines for the underlined gallbladder disease indicating the intervention.

All patients fulfilling the criteria mentioned above were informed about the study. After consent, central data acquisition occurred web-based, and patients were treated according to the study protocol.

Open cholecystectomy, emergency laparoscopic cholecystectomy (defined as LC performed in patients with severe symptoms related to the presence of gallstones disease, severe inflammation of the gallbladder and their complications eg. gallbladder perforation, fistula, septic shock etc), untreated and known choledocholithiasis, acute and chronic cholecystitis, allergy towards iodine or indocyanine green, liver or renal insufficiency, thyrotoxicosis, pregnancy or lactation, legal incompetence for any reason, withdrawal of inclusion consent at any time, and age outside inclusion range were considered as exclusion criteria.

Primary outcomes

The primary objective was to compare NIRF-C, IOC, and CVS-WL to identify the junction between the cystic duct (CD), the common hepatic duct (CHD), and the CBD during LC entirely performed by a general surgery

Commentato [MOU2]: Mauro:
Così però sembra che siano stati operati pazienti senza indicazione all'intervento.

trainee under the supervision of an expert surgeon. The technique was considered successful when the CVS was achieved. The CVS was defined as the complete fulfillment of the biliary three criteria described originally by Strasberg [**23**]. In addition, the correct achievement of the CVS and the time to accomplish it were assessed and recorded by an independent and expert surgeon (by definition a surgeon who had fulfilled the learning curve considered for the procedure) in the operative room during the procedure.

The definition of trainee was based on the number of procedures performed prior to the start of the study. Surgeons who had completed less than 30 procedures before the beginning of the study were considered trainee surgeons, since learning curve studies have determined the steepest area of the learning curve to be between 10 and 35 operations [**33-36**].

The surgeon was asked to complete an *ad hoc* structured questionnaire on anatomical identification of the biliary anatomy and a more general questionnaire on task load immediately after the procedure (**Supplementary Box 1**) [**37**], (**Supplementary Box 2**) [**38**]. The surgeon's satisfaction score was given on a subjective visual analogue scale ranging from 1 to 5 (1 = not satisfied, 5 = extremely satisfied) (**Supplementary Box 3**).

Secondary Outcomes

Secondary objectives were the ability to visualize the CHD (from the junction to the bifurcation), the CBD (from the junction to the upper-duodenal part), and the CD (from the junction to the infundibulum of the gallbladder).

Other secondary objectives included short-term outcomes, procedural characteristics (operating time, intraoperative complications, need for conversion), rate and type of CBDI, and post-operative care characteristics (type of post-operative admission, length of post-operative stay).

Intraoperative, unpredicted events were recorded and classified according to a grade of adverse intraprocedural events in keeping with the EAES (European Association for Endoscopic Surgery and other interventional techniques) classification of intraoperative events [**39**] (**Supplementary Table 2**). Short-term was defined as within 30 days after surgery.

Statistical analysis

Descriptive statistics were provided for all discrete variables with absolute numbers, rates, and proportions with 95% confidence intervals (95%CI). Continuous variables were described by the mean and standard deviation (SD ±). Exploratory comparisons of discrete variables were performed using the Chi-squared test, with continuity correction or Fisher's exact test when necessary. Continuous variables were compared using

Commentato [MOU3]: Mauro:
resto sempre scettico su questo perché solo due delle tre tecniche te lo permettono (quella convenzionale braccio di controllo non può farlo). Ma hai beccato reviewers poco sul pezzo secondo me.

the Student's t-test or a non-parametric equivalent (Wilcoxon). All tests were two-sided, with a p-value of less than 0.05 considered to indicate statistical significance. Data were analyzed according to intention-to-treat principles.

Logistic regression analyses were performed to estimate the effect of the patient's characteristics and the used procedure used for the identification of the biliary anatomy as described previously and the performance workload (dichotomized at > 10 points for each subscale). Body mass index (BMI) (dichotomized at 65 years), previous abdominal surgery, operative time (dichotomized at 60 minutes), and cholangiography time (dichotomized at 15 minutes) were considered independent factors. Models' goodness of fit was evaluated using the Likelihood Ratio (LR) and Hosmer-Lemeshow tests. Results were expressed as points and 95%CI estimation of the odds ratios (OR).

The statistical analyses were performed using MedCalc, version 19.4 (MedCalc Software, Ostend, Belgium).

RESULTS

Data from a total of 342 patients from 29 centers were collected between September 1, 2021, and September 31, 2022. Four of them were excluded: 2 did not met the inclusion criteria since they were 15 and 17 years old whereas, for two patients, incomplete data were provided.

After the initial screening process a total of 338 patients met the eligibility criteria and were included for further analysis, all of them gave consent to participate to the study. Of these, 260 (76.9%) were included in the CVS-WL group, 10 (3%) in the IOC group, and 68 (20.1%) in the NIRF-C group. The groups did not differ in demographic and baseline characteristics, as reported in **Table 1**.

There were no cases of intraoperative cross-over from one to another visualization technique. No retained stone was observed. CVS was considered achieved in all the included patients.

Operative time did not differ among the three groups (p= 0.089), and mean cholangiography time was 24 ± 15.6 minutes and 22.6 ± 22.5 minutes, respectively, in the IOC and NIRF-C groups.

Three CBDIs were reported, two (0.8%) in the CVS-WL group and one (1.5%) in the NIRF-C group (p= 0.546) (**Table 2, Supplementary Table 1).**

Conversion to open surgery was needed in four patients of the CVS-WL group (p= 0.631) (**Table 2**). The causes of conversion included difficult dissection due to adhesions from previous surgery or local inflammation.

The post-operative course was mainly uneventful, and the length of hospital stay did not differ among the three groups (p= 0.076) (**Table 3**).

There were four hospital readmissions in the CVS-WL group due to post-operative intra-abdominal infected fluid and not biliary collections treated with radiologically-guided percutaneous drainage, post-operative jaundice caused by CD junction stenosis that was treated endoscopically with Endoscopic Retrograde Cholangiopancreatography (ERCP) and the positioning of a stent, late post-operative bleeding from the cystic artery causing hemoperitoneum that was conservatively treated with the positioning of a percutaneous drain, and a reintervention performed due to the incidental finding of cancer of the gallbladder in the definitive pathology report.

Surgical performance

The NASA-TLX Assessment of Surgeon Workload statistically differed in all the explored domains.
Mental demand (13.7±3.4), physical demand (14.4±4.0), and temporal demand (12.6±2.8) represented the highest workload subscales in the IOC group and the lowest in the NIRF-C group (8.9±4.6, 8.3±4.3, 8.1±4.3). Performance (measured from 0=perfect to 20=failure) and effort required, had the highest values in the CVS-WL group (11.7±5.2 and 11.3±4.8, respectively), while effort had the lowest mean value in the NIRF-C group (9.5 ± 4.4). Frustration was the lowest subscale, with the lowest mean value reported in the NIRF-C group (5.7±4.2, p<0.005) (**Table 4**).

Surgeons surpassed the midpoint on the NASA-TLX scale (indicating an unsustainably high workload) in more than 50% of cases. The reasons were mental demand (58.58%), temporal demand (55.03), and physical demand (52.07%). Effort exceeded the midpoint for physical workload in 66.43 of cases (**Figure 1**).
There was a significant difference in the number of cases exceeding the midpoint for performance and temporal demand across the type of visualization used (**Table 5**). The number of cases exceeding the midpoint was higher than 70% of surgeons in most of the subscales of the NASA-TLX scale in the IOC group, except for frustration. In comparison, the CVS-WL group exceeded 60% for performance, effort, and frustration and 50% for mental, physical, and temporal demands. In the NIRF-C group, only for effort, more than 50% of the surgeons reported values exceeding the midpoint. Subjective reported surgeon satisfaction significantly differed with the lowest mean value registered in the CVS-WL group (**Table 4**).
The univariable analysis showed a correlation between performance, frustration, and CVS-WL (OR= 2.36, 95%CI 1.41;3.94, *p*= 0.001; OR= 3.22, 95%CI 1.74;5.96, *p*= 0.0002, respectively) (**Table 6**). On multivariable analysis, IOC was associated with an increased physical (OR= 5.23, 95%CI 1.01;27.07, *p*= 0.048 and OR=

4.94, 95%CI 1.01;24.04, *p*= 0.047) and temporal demand (OR= 12.26, 95%CI 1.43;104.6, *p*= 0.021 and OR= 5.33, 95%CI 1.10;25.8, *p*= 0.037) compared to NIRF-C and CVS-WL, respectively (**Table 7**).

Visualization of the biliary anatomy

The CVS was reported to have been achieved in all the patients in the IOC and NIRF-C groups and 97.7% of cases in the CVS-WL group (*p*= 0.459).

The subjective quality of visualization of the biliary anatomy was statistically different (*p*< 0.005) among the groups with the highest mean value in the NIRF-C group (8.8±1.4).

The CHD and the CBD were reported to be visualized in 206 and 270 patients, respectively (*p*< 0.005 and *p*= 0.046).

The surgeons felt confident in dissecting the CD in all the IOC and NIRF-C groups cases and 98.8% of cases in the CVS-WL group (**Table 7**).

The use of NIRF-C correlated with the higher possibility of visualizing the CHD and CBD in univariable and multivariable analyses (**Table 8**).

DISCUSSION

This prospective multicenter study aimed to highlight the impact of using three different intraoperative visualization techniques of the biliary anatomy during LC on the performance of surgical trainees, defined as surgeons having performed less than 30 LC before the beginning of the study. Despite equivalent overall operative times, time to achieve the CVS, the incidence of CBDI, and other intraoperative and post-operative complications among the three techniques, NIRF-C correlated with a higher possibility of visualizing the CHD and CBD. Moreover, mental, physical, and temporal demands were the lowest in the NIRF-C group compared with the others. As a confirmation of the advantages of the NIRF-C technique, the lowest mean value in the frustration scale was reported in the NIRF-C group.

Our results show a low rate of intraoperative and post-operative adverse events, which justifies the definition of LC as a safe procedure, even when performed by trainees. This is a significant finding for two main reasons. The first is that the rapidly increasing complexity of many surgical procedures from the technical and technological point of view has required equally rapid adjustments in all aspects of surgical performance [**6, 40-46**]. Secondly, the widespread adoption of LC in the 1990s due to the several advantages connected to the

minimally invasive nature of the procedure was associated with a sharp increase in the incidence of CBDI, which continue to occur two-three times more frequently compared to open surgery [**47-49**].

Because of its simplicity compared with other laparoscopic procedures, LC is performed by surgical residents in most training hospitals. More than other procedures, LC is considered the mainstay to achieve technical proficiency during the early stage of surgical training. However, it does not have to compromise the procedure's safety profile [**39**]. Demonstrating that there are no additional risks if the procedure is performed by surgeons in their learning curve could be life-changing in how teaching delivery and training are perceived. To date, several studies have assessed LC surgical proficiency, most of them focusing on the occurrence of complications, such as CBDI, conversion rates to open surgery, mortality, and readmission [**44-47**].

In our study, the elective setting was chosen to avoid the biases to the expected superior technical difficulties and higher occurrence of complications that characterize emergency surgery for acute cholecystitis [**44**]. Prevention of CBDI, major morbidity, prolonged hospitalization, and increasing costs [**43, 50**] are paramount in LC. This has drawn the surgical community to address this topic repeatedly throughout the years, reflecting the advancement of the available technologies. Therefore, the description of the CVS and the use of intraoperative imaging techniques (IOC or NIRF-C) were all introduced with the same purpose [**25-27**]. CVS-WL is now considered the gold standard to perform what has been recognized worldwide as a "safe cholecystectomy" [**26, 27, 51**]. Given this, it is unsurprising that our study's most represented group was CVS-WL. However, despite its solid theoretical foundation, CVS adoption has yet to be universal, even in countries where it was included in the national guidelines [**52-54**]. Nevertheless, obtaining a proper CVS requires more extensive clearance of the hepatocystic triangle compared to the more popular infundibular technique, which may be attempted in mild or no inflammation cases [**7, 51**].

Another observation that could be made from our series is the clear and striking unbalanced enrolment in the cholangiography groups. IOC was used only in ten cases, despite being a well-established procedure with the ability to allow the intra-operative detection of CBD stones, the visualization of the biliary tree anatomy, and the early recognition of CBDIs [**51,55-59**]. This reflects the general attitude towards this procedure. The literature regarding the benefit of IOC is inconclusive [**7, 51**], with some studies suggesting that it adds significant operating time and costs without reducing the risk of detection of retained CBD stones or CBDIs [**60-63**]. On the counterpart, the use of IOC was independently related to lower CBDI unregarding the experience of the surgeons and this only should have been sufficient to justify its massive routine utilization. [**64**]. From this point of view, the rate of IOC use in our study could be considered unjustifiably and dangerously

low. It could be argued, however, that to perform IOC, it is necessary to incise what is presumed to be the CD, which itself may be the cause of a lateral injury of the CBD (or CHD) in case of poorly understood anatomy [**60**] and that, considering the training set of the study, IOC can be difficult to teach. Indeed, residents do not gain enough experience as not all surgeons perform it routinely [**1**]. Besides, even the most recent Guidelines limit the routine use of IOC to a setting where the operating surgeon is familiar with it [**25**]. The reported duration of IOC ranges from 4.3-18 minutes [**25**]. The longer duration of the procedure is associated with limited availability of fluoroscopy, inadequate surgical skill, and infrequent use of the procedure [**65**]. Reportedly needs of specific expertise and allegedly longer operative times give this technique an excellent theoretical and practical value in expert hands but questionable importance in a routine and training setting. [**66**] Given these premises, the more enthusiastic acceptance of introducing a novel, accessible to perform and interpret, and the less time-consuming technique sounds easy to understand. Since the intraoperative real-time visualization of the biliary tree is a crucial feature to lower CBDI rate, this could pose towards the introduction in the routine practice of other less technically demanding techniques to obtain it. The NIRF-C technique was described by Ishizawa *et al.* in 2009 [**6**] to improve the outcome of LC [**67-69**] by the real-time enhanced visualization of the extrahepatic biliary tree. The technique uses fluorescence due to the administration of a fluorophore, the indocyanine green (ICG), which is excreted in the biliary system, and the use of a near-infrared light source, exciting the fluorophore and enabling visualization. NIRF-C offers some clear advantages compared with conventional cholangiography (real-time visualization of the biliary tree, reduced costs, easy learning curve, lack of X-ray exposure, safer dissection of Calot's triangle, and possibility to associate fluorescent angiography for highlight vessels) [**70, 71**] and its feasibility and safety were already described [**71**].

To better clarify the study design, the dissection of CHD and CBD was not requested as a procedure since an extensive dissection in that area is undoubtedly linked to a major risk of CBDIs [**2**]. However, we aimed to assess the possibility to visualize them intraoperatively respecting the basic principles for a “safe cholecystectomy” and the impact that their visualization could have on the general surgical performance. As expected, CHD and CBD can be visualized without the need of further dissection if one of the two intra-operative visualization techniques object of the study is used. Regarding the identification of the hepatocystic triangle, in our study, NIRF-C proved to be superior to the other techniques in terms of visualization quality and identification of the CBD and CHD.

Additionally, the performance of the additional step of the cholangiography did not affect the length of the procedure in this study. A previous prospective study comparing IOC and NIRF-C showed that the latter was

associated with a shorter duration of the operation [**70**] and confirmed its non-inferiority to IOC with X-ray cholangiography in visualizing the biliary junction during LC [**66, 73**]. No differences between the techniques were found in this study supporting the belief that the routine of NIRF-C could be an added value to the safety profile of LC [**74, 75**] without unbalancing the

Commentato [MOU4]: Mauro:
si tronca così?

These results are even more valuable because our multivariable analysis showed that physical demand, temporal demand, operating time greater than 60 minutes, and a cholangiography time greater than 15 minutes were associated with an increased workload for the surgeon. In this sense, using NIRF-C has proven helpful in reducing stressing variables for the surgeon. However, as demonstrated by the EURO-FIGS registry on fluorescence-guided surgery, there is a wide disparity in terms of protocols for NIRF-C across several European surgical centers, particularly in terms of ICG dose and timing of administration [**39, 66**].

The study provides information also on another debated topic regarding the frequency of obtaining a correct CVS during LC, because despite the promising results from consistent use of CVS, it has been previously reported how the use of this technique remains inconsistent [**47, 52, 54**].

In our series, only three lesions of the biliary tree occurred in the CVS-WL group. However, the low occurrence of intra-operative and post-operative complications makes it difficult to draw conclusive observations on the impact of the visualization technique on such outcomes [**74-76**]. Therefore, other variables must be used to indicate surgical performance and efficiency. For example, operative time is the most immediate and intuitive indicator of surgical efficiency. Prolonged surgery time means increased operating room occupation and operating costs with prolonged anaesthesia and a risk factor for complications such as surgical site infections [**77-79**]. However, in our study, operative time did not statistically differ among the considered groups. Alternatively, the utilization of additional intraoperative imaging to support the decisional aspect did not result in prolonged operative time, and their routine implementation in a peculiar setting, such as the training one, could be justified.

Commentato [MOU5]: Mauro:
e questo è il motivo per cui non lo abbiamo inserito tra gli outcomes primari

The potential benefit as an educational tool of additional intra-operative imaging techniques has already been explored, and NIRF-C has shown good potential as a teaching tool for trainees [**1, 39**]. However, in the latest published consensus about the clinical use of ICG, the participating surgeons in the survey did not agree that surgeons in training should be skilled in fluorescence imaging techniques [**1, 28**]. To be able to draw more conclusive observations on the potential impact of the implementation of intraoperative imaging techniques to achieve the CVS, we decided to include other evaluations strictly concerning the ability to visualize the different

components of the biliary tree and the subjective assessment of the surgical workload and global satisfaction of the first operator.

Our results showed that the minimum impact of intraoperative techniques on the procedure's safety profile was counterbalanced by striking differences in the visualization of the CHD and CBD in favour of the NIRF-C group regarding global surgical workload and satisfaction levels. With the results of this study, we demonstrated that the exposure of trainees to ICG technology at an early stage of their surgical training before reaching the recognized peak of the learning curve has a positive impact on the surgeon's confidence, with possible further implications on the reduction of the learning curve and improvement of the safety profile of LC.

We could also hypothesize that a higher satisfaction level may contribute to a shorter learning curve, but this cannot be determined from the results of the current study.

The study's main limitations include its non-randomized design and the different enrolment rates in the three groups. In addition, the imbalanced availability of the studied technologies across the participating departments represents a further limitation.

As per protocol sample size estimation we previously calculated the need to include 60 patients per group to reach a power of 90%, assuming a success rate of 80% for the conventional intraoperative cholangiography, 90% for the intraoperative fluorescent cholangiography and CVS-WL and after the analysis of dataset to test whether intraoperative fluorescent cholangiography was no more than 10% inferior to conventional intraoperative cholangiography in a one-sided test applying a 5% level of significance. This criterion was met in two of the considered groups. However, we strongly believe that the allocation trend mirrors the trend in the actual clinical practice, and leaving to the surgeons the possibility to choose according to their preferences and not to a concealed allocation we already expected to observe this kind of discrepancy.

In particular, this study aims to address which of the available techniques could be the best option in a training setting to enhance the learning curve and, ideally, build a safe LC training program.

Commentato [MOU6]: Mauro: usa gli acronimi prestabiliti.

Commentato [MOU7]: Mauro: Non capisco. Perché è qui?

CONCLUSIONS

Our study showed that using NIRF-C did not prolong operative time but positively influenced the trainee surgeon's perception of the performance in LC.

In teaching hospitals and, more generally, in a training setting, overcoming the problem of providing high surgical quality while educating trainee surgeons can be challenging. This may change in the future if residents can better identify the anatomical structures with NIRF-C, shortening the learning curve and improving the safety profile of LC. Better identification of the biliary anatomy could translate into a shorter learning curve, an improved safety profile, and, ultimately, shorter operative time and reduced potential risks for CBDI.

Figure 1. Percentage of surgeons that surpassed the midpoint on the several subscales of the NASA-TLX scale according to the type of procedure

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