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Near-infrared cholangiography with intragallbladder indocyanine green injection in minimally invasive cholecystectomy

Symeonidis S *et al*. Cholangiography using intragallbladder ICG

Abstract

Laparoscopic cholecystectomy (LC) remains one of the most commonly performed procedures in adult and paediatric populations. Despite the advances made in intraoperative biliary anatomy recognition, iatrogenic bile duct injuries during LC represent a fatal complication and consist an economic burden for healthcare systems. A series of methods have been proposed to prevent bile duct injury, among them the use of indocyanine green (ICG) fluorescence. The most commonly reported method of ICG injection is the intravenous administration, while literature is lacking studies investigating the direct intragallbladder ICG injection. This narrative mini-review aims to assess the potential applications, usefulness, and limitations of intragallbladder ICG fluorescence in LC. Authors screened the available international literature to identify the reports of intragallbladder ICG fluorescence imaging in minimally invasive cholecystectomy, as well as special issues regarding its use. Literature search retrieved four prospective cohort studies, three case-control studies, and one case report. In the three case-control studies selected, intragallbladder near-infrared cholangiography (NIRC) was compared with standard LC under white light, with intravenous administration of ICG for NIRC and with standard intraoperative cholangiography (IOC). In total, 133 patients reported in the literature have been administered intragallbladder ICG administration for biliary mapping during LC. Literature includes several reports of intragallbladder ICG administration, but a standardized technique has not been established yet. Published data suggest that NIRC with intragallbladder ICG injection is a promising method to achieve biliary mapping, overwhelming limitations of IOC including intervention and radiation exposure, as well as the high hepatic parenchyma signal and time interval needed in intravenous ICG fluorescence. Evidence-

based guidelines on the role of intragallbladder ICG fluorescence in LC require the assessment of further studies and multicenter data collection into large registries.

Key Words: Minimally invasive cholecystectomy; Laparoscopic cholecystectomy; Biliary tract mapping; Indocyanine green; Near-infrared fluorescent cholangiography; Intracystic indocyanine green; Intragallbladder indocyanine green; Bile duct injury

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INTRODUCTION

Cholelithiasis is the most common indication for laparoscopic cholecystectomy (LC), affecting 10% to 15% of the adult population in developed countries, and is among the most common gastrointestinal indications for hospital admission[1]. LC remains one of the most commonly performed surgical procedures in the United States and across the world[2]. However, it is accompanied by a significant complication incidence of biliary injury of approximately 0.6%, while the respective rate of open cholecystectomy is approximately 0.1%[3]. Iatrogenic biliary tree injuries represent a fatal complication since they are associated with high rates of short-term morbidity and mortality, up to 40%-50% and 2%-4% respectively. In addition, a series of late complications, such as biliary stricture, sepsis, recurrent cholangitis, and biliary cirrhosis, usually accompany even minor biliary injuries[4]. Due to the aforementioned, the culture of safe cholecystectomy has emerged recently, introducing the basic principles for perioperative and postoperative safety[3]. The literature presents misidentification of the bile duct as the cystic duct (CD) in cases of abnormal insertion of the CD into the common hepatic duct (CHD) as the most common cause of iatrogenic bile duct injuries[5]. To eliminate

iatrogenic bile duct injuries, Strasberg established the proposal of Critical View of Safety, in 1965[6].

Numerous techniques have been proposed so far to achieve intraoperative visualization of extrahepatic biliary tree. X-ray intraoperative cholangiography (IOC) is the most widely investigated method of recognition of biliary anatomy, possible choledocholithiasis or abnormal anatomy during LC, as well as early identification of biliary injury. It requires, however, intervention into the biliary tree and is combined with intraoperative radiation exposure of patient and staff and prolonged operative time. In addition, IOC is performed after partial dissection of Calot's triangle, thus it does not eliminate possibility of bile injury[7]. For these reasons, IOC is currently performed selectively or rarely in most centers, based on surgeon's preference[8]. In a systematic review performed by Ford *et al*[9], it is stated that IOC added a mean of 16 min to operating time without offering, however, benefit. Based on the aforementioned limitations, the need for feasible, non-invasive methods of biliary visualization is emerging. In 2009, Ishizawa *et al*[10] were the first who, based on the excretion of indocyanine green (ICG) into bile and the light emission with a peak wavelength of approximately 830 nm under near-infrared light, introduced the technique of fluorescence-based intraoperative near-infrared cholangiography using intravenous administration of ICG (NIRC) for biliary mapping during cholecystectomy. The first results showed that ICG-guided cholangiography led to the successful identification of CD and CHD before the beginning of dissection, thus representing a time and cost-efficient, feasible and safe tool for LC[10]. In addition, a large systematic review including 19 studies concluded that near-infrared imaging with ICG offered equal results, when compared to IOC, regarding biliary tract mapping and thus, could be an efficient non-interventional method of achieving Critical View of Safety[7].

Since the first reports, numerous clinical trials and systematic reviews have been conducted without achieving a consensus regarding dose, timing and optimal way of administration of ICG for optimal visualization of extrahepatic biliary anatomy[11]. In addition, a clinical limitation of NIRC poorly addressed so far is the accumulation of ICG

in hepatic parenchyma shortly after the intravenous administration, which produces a high background signal and obstructs safe biliary tree anatomy recognition. Liu *et al*[12] studied the efficacy of direct intragallbladder ICG injection during LC in cases of severe inflammation, to limit liver parenchyma enhancement and to achieve sufficient biliary identification. However, literature reports regarding the potential intragallbladder ICG administration for biliary anatomy visualization are scarce. Herein, the aim of our study is to critically appraise and present the safety and outcomes of NIRC by intragallbladder ICG injection during minimally invasive cholecystectomy, as well as to present the techniques used and their strong points and weaknesses.

STUDY CHARACTERISTICS

A literature search was conducted in databases PubMed and Scopus, using the search string "Indocyanine Green" [Mesh] AND (intracystic OR intrabiliary OR intracholecystic OR direct) AND "Laparoscopic cholecystectomy". Our literature search retrieved four prospective cohort studies, three case-control studies and one case report. In the three case-control studies selected, intragallbladder near infrared cholangiography (NIRFC) was compared with standard LC under white light, with intravenous administration of ICG for NIRC and with standard IOC. The included studies varied considerably in size and method and there were insufficient numbers of studies for a meta-analysis. In total, 133 patients reported in the literature have undergone intragallbladder ICG administration for biliary mapping during LC. In addition, direct intragallbladder injection is reported in 2 cases uploaded in the online IHU-IRCAD-EAES EURO-FIGS registry[13]. However, these cases were not included in our analysis due to scarce information. Table 1 contains an overview of the studies included.

PRINCIPLES

ICG is a water-soluble, inert anionic dye, which is mainly intravenously[14]. After administration, it mainly binds albumin and β-lipoproteins in the plasma and is selectively captured by the hepatocytes and it is secreted into the bile *via* an ATP-based

transport system[15]. ICG does not undergo metabolism or enterohepatic recirculation. Illumination of the extrahepatic biliary structures containing ICG with the use of a near infra-red (NIR) camera with specific wavelength light in the NIR spectrum (approximately 820 nm) turns ICG into the fluorescent state, leading to visualization of biliary tree and the distal part of the CD due to partial bile reflux[15]. However, intravenous ICG injection is associated with a high hepatic parenchyma signal due to ICG accumulation, and unpredictable reflux of bile and dye into the CD, rendering its visualization insufficient, and has given birth to the idea of exclusion of ICG hepatic absorption, by direct ICG intragallbladder injection[12].

ICG ADMINISTRATION TECHNIQUE AND DOSAGE

Liu *et al*[12] were among the first to introduce intragallbladder ICG administration. In their prospective, cohort study, a combination of the novel and the standard method of ICG injection was used. In 18 cases previously managed for acute cholecystitis (AC) with placement of a percutaneous transhepatic gallbladder drainage catheter, ICG was administered into the gallbladder lumen after bile drainage, while in 28 patients, a 2-0 Prolene purse-string suture was performed at the gallbladder's fundus to facilitate percutaneous insertion of a Veress needle through suture, using the suture edges for countertraction. After bile drainage and ICG administration, the Veress needle was removed and the suture was tightened to avoid dye and bile spillage. The dose administered was a bolus injection of 10 mL ICG with concentration of 0.125 mg/mL. The aforementioned technique led to ICG leakage in 5 among 46 patients, all of whom receiving ICG *via* fine-needle gallbladder puncture. In addition, it requires laparoscopic suturing skills and could be challenging, especially in the hands of novel surgeons[12]. A similar administration route was followed by Jao *et al*[16] in two patients initially treated with percutaneous transhepatic gallbladder drainage (PTGBD) two weeks before interval LC. After direct intracystic administration of ICG through PTGBD tube to visualize extrahepatic bile ducts and to achieve critical view of safety, intravenous administration also followed to visualize the cystic artery. Regarding administered dose, 5 mL of a

solution with a concentration of 2.5 mg/mL were administered *via* PTGBD tube right after entrance into the peritoneal cavity, resulting in a dose of 12.5 mg, while 1 mL of 2.5 mg ICG was administered intravenously after CVS achievement[16].

Cárdenas *et al*[17] described their administration technique, in which, after the gallbladder has been brought close to the abdominal wall in the right subcostal region, percutaneous puncture is performed under direct vision in the fundus using a 22 G epidural needle (Spinocan, Braun). After administration of 2-4 mL of ICG solution with concentration 2.5 mg/mL, laparoscopic forceps are used to close the small puncture hole[17]. Use of a Veress needle was reported by Gené Škrabec *et al*[18] in their case-controlled study, who grasped and punctured the gallbladder fundus before dissection of the triangle of Calot, to aspirate bile and decompress the gallbladder. Afterwards, 1 mL of the 2.5 mg/mL ICG solution was diluted in 9 mL of bile, producing a 10 mL ICG-bile solution with a concentration of 0.25 mg/mL. Following the reverse procedure, 2-3 mL of the final solution was injected and the Veress needle was removed, while the entry site was pinched closed, by using either a grasper, a stitch or a clip[18]. Similarly, Graves *et al*[19] proposed a technique for direct intragallbladder ICG administration, in which the gallbladder is punctured with a cholangiogram catheter or a pigtail catheter before the beginning of dissection and bile is suctioned. More specifically, in their cohort study including pediatric 11 patients, preparation begins after the fundus is grasped and retracted. A needle-tipped Kumar cholangiogram catheter (Nashville Surgical Instruments, Springfield, TN, United States) is introduced into the peritoneal cavity through the 12 mm umbilical port (camera port), and with the use of a grasping or dissecting instrument, the infundibulum of the gallbladder is punctured. For avoidance of dye spillage after catheter removal, the puncture site is closed with a Maryland grasper. An alternative way of administration is also described, with injection of the solution through a pigtail catheter and use of the Seldinger technique. A pleural/pneumopericardial drainage set, including a needle, plastic dilator, wire, and an 8 Fr pigtail drainage catheter (Inc., Bloomington, IN, United States) is used. After cephalad elevation of the gallbladder with a grasper, a needle is inserted percutaneously

into the fundus of the gallbladder, followed by the guidewire, while the dilator is used for subcutaneous muscular tract dilation. The placement of the pigtail catheter over the wire through the gallbladder wall can be assisted using a Maryland grasper. After catheter placement, the wire is removed, while the pigtail is left in place to prevent intraperitoneal leakage of bile. Regarding the solution administered, 9 mL of bile are diluted with 1 mL 0.25 mg/mL ICG solution, creating a 0.025 mg/mL ICG-bile solution[19].

Quaresima *et al*[20] selected intragallbladder ICG administration in cases of two patients admitted on the day of surgery. This team also preferred the use of a Veress needle and administration of 4 mL of 0.5 mg/mL ICG solution, while the entry point in the gallbladder was secured with a simple stitch[20]. Shibata *et al*[21] examined 24 patients who underwent LC under ICG fluorescence guidance, with half receiving intravenous ICG and the other half receiving intrabiliary injection. The latter was achieved either through PTGBD administration in 8 cases, or gallbladder puncture in 3 cases or administration through and endoscopic nasobiliary drainage (ENBD), which was placed in situ during previous ERCP, in one case and injection of a dosage of 0.025 mg[21]. Finally, in the study of Castagneto-Gissey *et al*[22], a 27-gauge needle was selected for percutaneous puncture of the abdominal wall and the fundus of the gallbladder after cephalad retraction of the fundus. ICG solution was produced after dilution of a vial of ICG with a concentration of 25 mg/5 mL in 10 mL of distilled sterile water and an average of 5 mL of solution was administered, taking into consideration gallbladder dimensions and bile density. The puncture point of the needle was grasped after the withdraw of the needle to prevent further dye spillage[22].

BILIARY ANATOMY RECOGNITION

As already stated, iatrogenic bile duct injury is mainly caused by misinterpretation of biliary structures in up to 97% of all cases, especially misidentification of the common bile duct (CBD) as the CD, while technical issues are also associated with increased rate of biliary injury events[23,24]. A series of techniques have been reported in the literature

and have been applied in clinical practice for reducing iatrogenic bile duct injury and its fatal consequences during LC. Hence, apart from establishing Critical view of safety, other technical options include the infundibular technique, the antegrade dissection of the gallbladder from the fundus up to the infundibulum, as well as performance of subtotal cholecystectomy[24]. Use of anatomic landmarks, such as the bile duct, the sulcus of Rouviere, the left hepatic artery, the umbilical fissure, and the duodenum, constitute the B-SAFE method, which aims at eliminating the rate of major biliary or vasculobiliary injury[25]. Regarding methods of intraoperative biliary mapping, IOC remains currently the gold standard technique for intraoperative imaging of the biliary anatomy, despite a series of weaknesses, including exposure of patient and staff to ionising radiation, prolonged operative time and a relatively high failure rate of approximately 3%-17%[9]. Laparoscopic ultrasound (LUS) is also a useful intraoperative tool during LC, with specifical value in delineating biliary anatomy under severe local inflammation, thus contributing in safe completion of LC or an early decision for an alternate operative strategy[26]. In latest years, NIRFC with ICG has been emerged as a powerful new method of dynamic intraoperative extrahepatic bile duct visualization[27]. Intravenous route is the most commonly selected and studied way of dye administration. However, a series of drawbacks, such as high intraoperative background hepatic parenchyma fluorescent signal and need of time interval between dye administration and biliary mapping, have led to investigation of intragallbladder ICG administration as an alternative route for IOC[14].

Current literature contains numerous reports comparing the aforementioned techniques. Regarding use of standard IOC, a recent metanalysis presented that there is variation in terms of clinical practice towards use of IOC. Moreover, while performance of routine IOC led to significantly higher rate of choledocholithiasis detection, when compared to selective IOC, its use led also to lower but not statistically significant lower rates of bile duct injury incidences during cholecystectomy[28]. The role of ICG-FC was also studied by Lie *et al*[29] in their metanalysis including twenty-two studies. Results showed that use of ICG-FC led to higher success in CD and CBD visualization and

significantly reduced the time needed to identify biliary structures, when compared to LC under white light. A large metanalysis by Lim *et al*[30], including seven studies and 481 patients undergoing elective or emergency LC, concluded that there is no statistically significant difference in visualization of CD, CBD and critical junction of CD and CBD, when ICG-FC was compared to IOC. However, authors have proven that ICG-FC was superior to standard IOC in terms of CHD identification. It should be underlined that this metanalysis was subjected to publication bias, as it is stated by authors[30]. Feasibility of two methods in visualization of biliary tree anatomy after complete dissection have been studied by Osayi *et al*[31] in their prospective study including eighty-two patients. The reported rates of visualization of the CD, CBD, and CHD using ICG-FC were 95.1%, 76.8%, and 69.5%, respectively, while for IOC the rates were 72.0%, 75.6%, and 74.3%, respectively. Despite the extensive study of intravenous administration of ICG for intraoperative fluorescent cholangiography, the literature is scarce in general scarce regarding its comparison with the emerging intragallbladder injection method.

In their study comparing NIR imaging with intracystic ICG administration to standard white light, Liu *et al*[12] assessed the efficacy in visualization of extrahepatic biliary before and after dissection and exposure of Calot's triangle. It is highlighted that NIR fluorescence was a useful aid in cases of severe inflammation and in presence of dense fibrotic tissue before dissection, providing a clear visualization of Hartmann's pouch as a safe point to begin dissection. Regarding efficacy in biliary structures identification before dissection, the Hartman pouch was recognized in 86.9%, the CD in 32.6%, the CBD in 58.6%, and the CHD in 45.6% of patients. After dissection of Calot's triangle, the Hartman pouch was easily identified in 89.1%, the CD in 84.7%, the CBD in 78.2%, and the CHD in 73.9% of patients. In mild cases of cholecystitis with absence or presence of mild adhesions, CD was visualized under white light in 11 and 67% before and after dissection, respectively, while there was a statistically significant increase of these rates (77.8% and 100.0%) under ICG fluorescence. When the CD was obstructed by stones or sludge, as noticed in two patients, stone mobilization was necessary to permit the downstream passage of bile and dye. In the contrary, no significant contribution was

reported by the use of NIR cholangiography visualization in cases of cholelithiasis without inflammation, compared to standard white light[12].

Cárdenas *et al*[17], in their prospective cohort study including 23 patients undergoing LC, tried to identify the CD, the CBD and the CHD at three distinct time points during the procedure. At the beginning, the aforementioned structures were assessed as a first step before ICG injection. At this point, in one patient, the CD and CHD were visualized, and in 6 patients the CBD was observed. Assessment of bile structures was undertaken again after percutaneous intragallbladder ICG administration and before dissection and at this point, the CD was successfully identified in 17 cases, the CBD in 15 and CHD in 7 cases. Finally, after initiating dissection, the CD was identified in all cases, the CBD in 21 patients, and the CHD in 11. The critical view of safety was achieved in all cases. Regarding the two patients, in whom the CBD was not visualized after the dissection of Calot's triangle and ICG administration, it was attributed to abundant fatty tissue, despite having normal body mass index (BMI)[17].

Jao *et al*[16], in the report of 2 cases of ICG administration through PTGBD two weeks after an episode of moderate calculous cholecystitis, report dense fibrotic tissue and scarring in the Calot's triangle, as well as dense desmoplastic omental adhesion around the gallbladder. After adhesiolysis, the CD, CBD, and angulated cystobiliary junctions were identified with the use of NIRF cholangiography in both cases. After achieving CVS, an additional bolus dose of 1 mL of ICG was administered intravenously to identify the cystic artery. However, surgeons noticed an additional fluorescent enhancement, apart from biliary structures in the pericystic region, which was attributed to ICG spillage through the lymphatic drainage secondary to the intense inflammatory process after a thorough investigation for bile leakage under white light view[16].

In their case-controlled study, Gené Škrabec *et al*[18] included 20 patients who underwent LC with direct intragallbladder injection of ICG and 20 patients undergoing standard cholecystectomy. In the ICG group, in 80% (16/20) of patients, the gallbladder-CD was identified and among them, 9 out of 16 patients (56%) presented adequate flow of the ICG to visualize the confluence of the CD and CBD. However, fluorescence was

unsuccessful in 3/20 (15%) patients due to no progression of the dye from gallbladder lumen to the CD due stone impaction in the CD, while in one patient (5%) the gallbladder ICG contamination presented due to though penetration of the gallbladder by the Veress needle[18].

In the case-controlled study of Shibata *et al*[21], ICG cholangiography was performed both before CD was dissected and after CD is exposed by dissecting the Calot triangle. In all patients receiving intragallbladder ICG injection, the course of the biliary structures was able to be confirmed with safety, while important biliary anatomy was recognized safely in 10 cases (83.3%) after intravenous injection. In addition, intragallbladder ICG injection helped to successfully recognize two cases of anatomical variations, including a CD originating from the right posterior branch of the hepatic duct and a low junction of CD with CHD. Procedures were completed with no reported adverse events due to ICG administration and without complications, suggesting the feasibility and usefulness of near-infrared fluorescent cholangiography (NIFC) in preventing bile duct injury, especially in cases of anatomical variation or severe inflammation[21].

Graves *et al*[19] studied the efficacy of intragallbladder ICG injection in a paediatric cohort study of 11 patients, with a mean age of 16 years old. In one patient, the impaction of a stone into the CD impaired visualization of the total length of the CD. To solve this problem, cautious milking of the stone towards the gallbladder with a Maryland dissector permitted ICG passage. For all other patients, the entire length of the CD as well as the junction of the CD and CBD were successfully identified, without intraoperative complications. In addition, authors reported that NIR fluorescence with intragallbladddder ICG offered significant guidance during dissection of the gallbladder from the liver bed using cautery, visualizing with efficacy the boundary dissection plane[19]. On the other hand, Quaresima *et al*[20], reporting the results of direct intragallbladder ICG injection, suggest sufficient fluorescence on one case presented with AC, while imaging remained unsatisfying in a case presented with empyema[20].

In a case-control study by Castagneto-Gissey *et al*[22], cholangiography with intravenous ICG led to significantly better visualization of the duodenum wall and the

CHD, compared to the intragallbladder-ICG method (22.2% *vs* 5.9%, $P = 0.009$ and $P = 0.041$, respectively). Before dissection, identification of the CD was achieved in 76.5% and 66.7% ($P = 0.612$) of patients in the intragallbladder-ICG and intravenous-ICG group, respectively, increasing in 88.2% and 83.3% ($P = 0.298$) after Calot's triangle dissection, respectively. The CBD was identified in 76.5% and 77.8% of cases in the intragallbladder-ICG and intravenous-ICG group, respectively ($P = 0.935$). The most important conclusion of the authors, however, is the results regarding liver fluorescence noise, which was noted in only one patient of the intragallbladder-ICG group, but in all patients receiving intravenous ICG (5.9% *vs* 100.0%, $P < 0.0001$), leading to a better signal-to-background ratio and increasing the bile duct-to-liver contrast[22].

From the aforementioned studies, it is easily extracted that direct gallbladder ICG administration is a promising alternative to standard IOC as well as to commonly used near-infrared fluorescent cholangiography with intravenous ICG injection. More specifically, intragallbladder ICG injection is of great aid in presence of inflammation and dense fibrotic tissue in recognizing crucial biliary structures before dissection, while in cases of cholelithiasis without inflammation, intracystic administration of ICG does not success better biliary visualization. This observation is extremely important in clinical practice, since it provides a safe anatomical landmark for initiating dissection. Indeed, the majority of the studies report adequate visualization of the total length of the CD and the confluence of the CD and CBD. Finally, biliary tract visualization was also successfully achieved in cases of biliary anatomical variations. Hence, intragallbladder ICG administration presents equivalent results regarding biliary visualization and could be performed during LC in the same way as the more commonly used intravenous ICG cholangiography. However, biliary visualization was reported to be impaired also in cases of extensive fatty tissue, reducing the feasibility of this method in patients with increased BMI or abundant fatty tissue locally. More clinical studies are necessary, in order to establish with safety a standardized feasible and easily reproducible technique for biliary anatomy visualization with the use of direct gallbladder ICG administration during LC.

NIRFC DEVICE

Equipment required for NIR-ICG fluorescence with intragallbladder ICG administration does not differ from devices used for cholangiography with intravenous ICG administration. Additional equipment was necessary only for the injection procedure, respectively to the technique chosen, as we describe in the following section. A summary of the systems used in different studies, the chosen technique of administration and dosage is presented in Table 2.

COMPLICATIONS

NIR fluorescence with use of ICG is a feasible technique with a high safety profile. Regarding intragallbladder ICG administration, Cárdenas *et al*[17] reported no intraoperative complications related to intragallbladder ICG administration, while postoperative bleeding at a trocar site was noted in one patient. No intraoperative complications were noted in the study of Castagneto-Gissey *et al*[22]. However, bile/ICG spillage was significantly greater in intragallbladder ICG-group compared to intravenous group (64.7% *vs* 5.6%, respectively, $P = 0.001$). Authors correlated spillage of dye and bile with the severe pain noted postoperatively in 23.5% of cases in the intragallbladder-ICG group *vs* none in the intravenous-ICG group ($P = 0.001$). More specifically, leakage may originate from the puncture point at the level of the gallbladder fundus in the intragallbladder-ICG group or due to the perforation of the gallbladder wall during dissection[22].

INTRAOPERATIVE TIME

In addition, in the case report by Jao *et al*[16], trans-PTGBD ICG injection didn't achieve to decrease total operation time in two cases of LC due to extensive inflammatory and fibrotic status. Castagneto-Gissey *et al*[22], comparing the two ways of ICG administration in a case-control study including 35 patients, concluded that the intravenous-ICG group had significantly shorter overall operation duration compared to the intragallbladder-

ICG group (P = 0.017). Regarding the time needed to identify biliary structures after intracystic ICG injection, the CD was visualized after 54.3 s ± 38.5 s, the confluence of CD-CBD after 101.3 s ± 50.6 s and the CBD after 164.2 s ± 53.1 s[22].

LIMITATIONS

In the study of Liu *et al*[12], in 5 out of 18 patients undergoing direct intracystic injection with purse-string suture, dye leakage was noticed, leading to significant contamination of the surgical field, while Jao *et al*[16] reported a case of additional fluorescent enhancement in pericystic area, finally attributed to ICG contamination through the lymphatic system secondary to the inflammatory process. What is more, this technique does not offer visualization of the cystic artery, which can only indirectly be identified by the contrast created with the fluorescent gallbladder wall. If fluorescence identification is needed, an intravenous bolus dose of 2.5 mg of ICG can be administered, leading to fluorescence of the cystic artery approximately 15 s after intravenous injection[19]. Finally, limited imaging and low fluorescence score were achieved after direct ICG administration in a patient of Quaresima *et al*[20], presented with empyema, attributed to elevated cellular concentration in the fluid. Apart from ICG spillage into the peritoneal cavity and impairment of biliary mapping, Castagneto-Gissey *et al*[22], in their case-control study, reported two technical errors regarding intagallbladder ICG administration: injecting the ICG dye into the gallbladder wall instead of the lumen of the gallbladder, leading to high hepatic parenchyma signal and difficulty in identifying biliary structures, and puncturing the gallbladder wall in two sites, leading to intraperitoneal spillage[22].

DISCUSSION

Cholelithiasis and cholecystitis are among the most common gastrointestinal causes of hospital admission in Western countries, accounting for one-third of emergency surgery admissions and occupying a median cost of 11584 USD (€10506.65) per admission in the United States of America[32]. LC is one of the most common abdominal surgical procedures performed, with an annual incidence of over 500000 procedures per year[33].

It remains the gold standard for cholelithiasis, with morbidity among 1.6%-5.3% and mortality among (0.08%-0.14%)[34]. However, the emersion of LC has been associated with an increase in bile duct iatrogenic injuries (BDI) from 0.1% to 0.2% in the era of open cholecystectomy to 0.4% to 0.7% nowadays[35]. The main causes of intraoperative bile duct injury are the result of basic technical failures and misidentification of the biliary system, mistaking the CBD or the CHD for the CD. The main risk factors for BDI are the severity of AC, fibro-sclerosing remodeling associated with chronic inflammation, and anatomical variations of the bile duct[36]. Learning curve, experience volume, technical pitfalls, and anatomical variations hold also a key role in iatrogenic BDI[4]. Iatrogenic bile duct injuries constitute a fatal complication and an economic burden, since they are associated with increased morbidity and mortality rates, lower postoperative quality of life, significant healthcare cost, increased hospital stay and insurance issues[37]. To avoid BDI, the "critical view of safety" should be achieved intraoperatively, including the visualization of the triangle with boundaries the CD, the CHD, and the inferior one third of the liver bed, as well as visualization of only two structures, the CD and the cystic artery, entering the Hartmann's pouch[38].

Intraoperative mapping and recognition of bile duct anatomy as well as anatomical variants is of paramount importance for prevention and early recognition of BDI. Numerous methods have been described in the literature for improving safety during the hepatocystic triangle dissection, achieving to reduce the incidence of BDI to around 0.23% and 0.30%[39]. Among them, IOC is the most commonly described technique and can be conducted *via* the CD, through the gallbladder (cholecystocholangiography) or preoperative endoscopic placement of an ENBD, especially for patients who undergo preoperative ERCP[40,41]. For IOC, the laparoscopic placement of a catheter in the dissected lumen of the CD is necessary. A fluoroscopy C-arm device is placed over the patient and visualization of biliary tree is achieved after administration of radiopaque contrast[42]. It was stated that IOC could limit the rate of BDI IOC. However, it requires additional resources, such as a C-arm fluoroscopy machine and additional human staff for its intraoperative operation, while it is a time-consuming procedure requiring

exposure to ionizing radiation[18]. However, according to a large meta-analysis by Hall *et al*[43], including 440.659 patients, no statistically significant difference was found in BDI detection rates between IOC to no IOC use groups, rendering IOC rather an optional technique. In addition, in order to achieve a significant reduction in BDI percentages, an objective method of biliary visualization before any dissection is needed[20]. LUS has been proposed as an alternative technique to IOC for anatomical delineation of the extrahepatic biliary tract, detection of choledocholithiasis and prevention or early detection of BDI. Literature shows that LUS achieved to provide a highly sensitive mapping of the extra-pancreatic biliary anatomy in 92%-100% of patients, thus providing a useful tool for hilar dissection, both before and after dissection, without needing to cannulate the biliary system[26].

The first report on ICG use in biliary tract visualization goes back to 1992, by Araki *et al*[18], while Ishizawa *et al*[10] in 2009 reported the usefulness of ICG NIRC in liver transplantation by direct intrabilliary injection and in open cholecystectomy by intravenous preoperative administration. ICG is a non-toxic, water-soluble tricarbocyanine product that undergoes hepatic metabolism and is excreted in bile, thus it constitutes an ideal agent for biliary tree visualization. Its angiographic properties are based on its fluorescent character in the near-infrared range between 790 and 805 nm after binding to proteins[44]. It is also a safe technique, with side effects encountered in less than 1 among 40000 cases and including mainly rare cases of allergy in patients with a history of allergy to iodine[45]. In 2020, a single-blind, randomized, 2-arm trial comparing NIFC to white light for detection rate for biliary structures during LC, suggested that the visualization rate of extrahepatic biliary structures was statistically superior in NIFC, even before dissection of triangle of Calot. In addition, 2 BDI were noted in the white-light group *vs* none in the NIFC group. However, no statistical significance was achieved due to sample limitation[46]. In addition, a large systematic review including 19 studies concluded that near-infrared imaging with ICG offered equal results, when compared to IOC, regarding biliary tract mapping and thus, could be an efficient non-interventional method of achieving Critical View of safety[11]. Despite

promising results of ICG fluorescence-guided LC, variability remains in numerous aspects of its use, including optimal dose, route and timing of administration[47].

The first route of ICG described for open cholecystectomy is the intravenous administration reported by Ishizawa *et al*[10], while the same team described the injection of ICG into the bile duct of 13 patients who underwent hepatectomy. Intravenous ICG administration is the most commonly reported way of ICG NIFC, with satisfying results of biliary structure identification. After systemic administration, ICG solution concentrates in the bile and emits light after stimulation by NIR light (700-900 nm)[48]. However, intravenous ICG administration has been correlated with a series of weaknesses in clinical practice.

In the majority of cases, ICG is administered intravenously 15-120 min before anesthesia to achieve optimum visibility of the biliary tree. In this way, hepatic parenchyma fluorescence during LC using a conventional ICG administration method produces a high noise-to-signal ratio and is strong enough to interfere with biliary structures, and thus, reducing safety provided by fluorescence, due to prolonged ICG fluorescence in humans[49]. To address this problem, Verbeek *et al*[50] suggested that prolongation of the time interval between ICG administration and LC would lower the noise-to-signal ratio in NIRF cholangiography, achieving optimal increase bile duct to liver contrast and minimum background liver enhancement when administered 24 h before surgery. It is obvious that methods of achieving lower liver luminance would enhance safety during anatomy recognition within triangle of Calot[49].

Moreover, ICG is excreted exclusively by the liver, rendering fluorescence after intravenous administration impaired on grounds of hepatic dysfunction or biliary excretion problems due to limited flow to the CBD[17]. Last but not least, intravenous administration of ICG provides limited visualization capacity in tissues thicker than 10 mm[51]. This limitation is extremely important in clinical practice, since in patients with abundant adipose tissue or extensive fibrotic tissue, such as obese patients or patients after recurrent episodes of AC or chronic cholecystitis, adequate visualization requires a higher penetration depth of the signal[52].

NIRC with intragallbladder ICG injection is one of the methods proposed to limit background liver enhancement and optimize biliary anatomy recognition during surgery. The first experimental study of direct ICG injection into the gallbladder to address the high affinity of ICG to hepatic parenchyma and the strong background signal was attempted by Liu *et al*[53]. The latter team administered different doses of ICG into the gallbladder after direct puncture by a percutaneous needle in 7 pigs and both normal and cholecystitis models were studied. Results showed that intraoperative fluorescence cholangiography with intracystic administration of ICG provided a clear and adequate visualization of gallbladder neck and CD.

Intragallbladder administration of ICG for biliary anatomy mapping presents a series of advantages over standard IOC and intravenous ICG NIFC. In clinical settings, it is suggested by numerous authors that direct gallbladder injection of ICG allows to minimize the drawback of hepatic parenchyma noise fluorescence by circulating through biliary structures preferentially[13]. In addition, intragallbladder ICG administration provides sufficient intensity of intraductal-only fluorescence, thus rendering dissection safe even for patients with abundant fatty tissue[17]. Moreover, Gené Škrabec *et al*[18] highlight the importance of immediate visualization of the biliary anatomy after intragallbladder ICG administration in real-time, without the time interval needed after intravenous use, and also the high quality of dissection plane between the gallbladder and the liver bed for intraoperative safety. Finally, intragallbladder injection is extremely useful for the identification of accessory bile ducts arising from the gallbladder fossa, since it provides a clear visualization of the dissection plane between the gallbladder wall and the liver parenchyma[19].

What is more, intragallbladder ICG injection permits the administration of a lower dose of ICG compared to the systemic injection. Literature shows that 10 mL of ICG at a concentration of 0.1 mg/mL is adequate for sufficient visualization of the biliary tree[53]. Furthermore, a second advantage of intragallbladder ICG cholangiography is that it provides a reliable image of the gallbladder neck even before dissection, providing a safe

landmark for beginning the dissection without jeopardizing the injury of biliary strictures in cases of intense inflammation[12].

No consensus has been achieved regarding intravenous ICG NIRC regarding dose and timing of administration, since the time needed for ICG excretion into the bile varies among patients. Most studies report a wide range of ICG doses, including 2.5 mg, 5.0 mg, and 10.0 mg, injected from 1 h up to 25 h preoperatively. This limits extremely the usefulness of NIRC in the emergency setting, in which fluorescence is of vital importance due to local inflammation and anatomical plane distortion, as well as in elective cholecystectomies without prior admission. Direct intragallblader ICG administration overwhelms the barrier of time needed between administration and imaging[18]. On the contrary, intragallblader injection requires significantly lower doses compared to intravenous use, approximately 0.025 mg/mL, since the fluorescent dye is confined to the biliary tree[47].

Regarding the technique of intragallbladder ICG administration, Shibata *et al*[21] further classified the routes of intrabiliary injection of ICG, which are divided into gallbladder injection, involving intraoperative gallbladder puncture and ICG injection, and bile duct injection, involving ICG administration into the bile tree through an extra-biliary fistula tube placed preoperatively, such as PTGBD or ENBD. If direct ICG injection *via* direct gallbladder puncture is selected, caution should be taken to avoid extrabiliary dye spillage, because it impairs clear visibility of the operation field. Closure of the puncture site with clips after catheter removal is a feasible way to prevent dye spillage[21]. In addition, a feasible, safe and time-efficient method is reported by Gené Škrabec *et al*[18], which includes puncturing the gallbladder with a Veress needle, suction of bile in cases of distension and simple closing the defect of the puncture site with a suture or clip. In addition, the dilution of ICG solution with bile permits dye binding with bile proteins, resulting in better dissolution and enhanced visualization[18]. Moreover, intracystic ICG administration for near-infrared fluorescent cholangiography in acute calculous cholecystitis is a useful tool in patients initially treated with PTGBD. After recovery from the initial episode, ICG dye is injected through the drain left in place[16]. Caution should

be taken in case of gallbladder hydrop, when the gallbladder content should be aspirated, while in cases of stone impaction at the level of the infundibulum or into the CD, repeated and careful milking of the stone towards the gallbladder is proposed to allow passage of ICG towards the CBD[22].

Shibata *et al*[21] report an extremely high rate (100%) of successful biliary mapping and anatomical variations identification after direct ICG injection, which is better than previous reports, and attribute this difference to the lower concentration of dye used, thus resulting in avoidance of an excessive fluorescent signal. In their cohort study, Liu *et al*[12] concluded that intragallbladder ICG injection followed by NIR imaging offered improved visualization in presence of inflammation, when compared to standard White Light, while it offered no advantage in the absence of inflammation.

Regarding intraoperative time, it is stated that for LC, the total intraoperative time should not be used as a parameter to assess the utility of NIRF technique as total time can be influenced by the severity of inflammation, adhesions, and fibrotic tissue. Literature reports that the mean operation time for NIRF *via* intravenous injection during LC is approximately 70-90 min[31,54,55]. Gené Škrabec *et al*[18] reported that the median time for intragallbladder ICG cholangiography was 65 minutes, with no statistically significant difference compared to standard LC under white light. In addition, no significant differences were reported neither in the operative duration nor in the length of hospital stay (65 min *vs* 55 min, P = 0.113), concluding that this technique does not extend operative time[18]. Moreover, intragallbladder ICG NIFC prevents patients from radiation exposure and is feasible without occupation of additional staff. It is a method that can be performed easily and safely even by trainees, thus it may contribute to the learning curve of LC[15].

However, direct intracystic ICG use is followed by a series of limitations. A significant weakness of intrabiliary administration of ICG is that, in case of bile or ICG spillage and contamination into the extrabiliary peritoneum around the surgical field, ICG binds with proteins and emits strong fluorescence under NIR view[56]. In addition, in cases of dye leakage or gallbladder through puncture intrabdominal ICG spillage cannot be

eradicated immediately with suction or gauze mopping, jeopardizing visualization and recognition of critical structures during LC. Jao *et al*[16] concluded that intracystic ICG injection *via* a mature fistularized drain tubing route may provide a safe option for patients initially treated with PTGBD, to prevent spillage and surgical field contamination. Liu *et al*[12] reported a dye-bile leak in 5 out of 46 patients, while in all these cases ICG was injected *via* a fine-needle gallbladder puncture. On the other hand, no leaks were noticed in patients having a previous percutaneous drainage, rendering them the best candidates for NIR cholecystocholangiography. Furthermore, ectopic fluorescence signal can be reproduced by ICG contamination through the lymphatic drainage secondary to intense inflammatory process. More specifically, ICG may enter into the subcutaneous lymphatic vessels and finally into the lymphatic drainage through ischemic or gangrenous gallbladder mucosa, reproducing fluorescence signal and interfering with biliary structures in severe cases of inflammation[16]. One limitation encountered in 1 out of 20 patients by Gené Škrabec *et al*[18] is the failure of ICG to pass into the CD due to stone impaction, leading to the failure of biliary mapping. What is worth mentioning is the inability to directly visualize the cystic artery by this technique, but only in an indirect way, by the contrast between it and the fluorescent gallbladder wall in the background. However, intravenous ICG administration is required in cases of intraoperative insecurity[18]. Finally, literature reports that near-infrared light can penetrate in a depth of approximately 5-10 mm into tissue, thus it provides limited visualization of intrahepatic biliary anatomy or biliary structure in cases of severe inflammation[57]. No consensus has been reached regarding the role of patient BMI in the efficacy of NIRC, with some authors suggesting no relationship between BMI and biliary mapping success[57], while others highlight high BMI as an obstacle in extrahepatic biliary visualization[31]. Castagneto-Gissey *et al*[22] state also as an absolute contraindication of intragallbladder ICG administration for fluorescence the clinical suspicion of gallbladder malignancy, for preventing bile spillage and following intraperitoneal seeding of cancer cells[22]. Finally, neither intragallbladder nor intravenous ICG injection have sufficient

sensitivity to detect CBD stones intraoperatively, thus are inferior to IOC in case of choledocholithiasis[12].

CONCLUSION

Although rarely used at present, NIRC with direct intragallbladder injection of ICG represents a feasible and safe technique of intraoperative biliary mapping and visualization of the dissection plane between the gallbladder and the liver bed. Among its advantages, one could refer that it is not time-consuming, especially in cases with previous PTGBD placement, and its performance does not require a specific learning curve. In addition, no major complications have been described so far and it is a radiation-free technique, compared to IOC. Furthermore, it is of paramount importance that intracystic ICG administration can significantly reduce liver noise fluorescence and increase operator satisfaction. In conclusion, it is a strong recommendation that further research should be conducted to illuminate the importance of NIRC with direct intragallbladder injection of ICG for surgeon guidance and patient safety during LC.

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Table 1 An overview of included studies

Ref.	Study type	Patients included	Surgery indication	Visualization of biliary structures (%)				
				Hartmann 's pouch	Cystic duct	Common bile duct	Common hepatic duct	Critical junction of cystic duct-common bile duct
Liu *et al*[12], 2018	Prospective, cohort study	46	*n* = 21 symptomatic; *n*=25 cholecystitis	-86.9% before dissection; -89.1% after dissection	-32.6% before dissection; -84.7% after dissection	-58.6% before dissection; -78.2% after dissection	-45.6% before dissection; -73.9% after dissection	Non stated
Graves *et al*[19], 2017	Prospective, cohor	11	*n* = 8 biliary colic; *n* = 1 biliary dyskinesia; *n* = 2 acute cholecystitis	Non stated	0.909	Non stated	Non stated	0.909

	t study							
Quare sima *et al*[20], 2020	Matc hed, case-contr ol study	2 patients received intragallbladder ICG (42 received intravenous ICG administration and 44 patients underwent IOC)	Acute or chronic cholecystitis	Non stated[1]	-95.4% before dissection; -95.4% after dissection[1]	-90.1% before dissection; -97.7% after dissection[1]	-90.1% before dissection; -97.7% after dissection[1]	-79.5% before dissection; -97.7% after dissection[1]
Jao *et al*[16], 2020	Case report s	2	Acute cholecystitis	Non stated	1	1	Non stated	1
Gené Škrabe c *et al*[18], 2020	Case-contr ol study	20 patients received intragallbladder ICG (20 patients underwent standard LC under wight light)	Non stated	80%[2]	80%[2]	56%[2]	Non stated[1]	45%[2]

Cárdenas *et al*[17], 2021	Prospective, cohort study	23	Symptomatic cholelithiasis or acute cholecystitis	Non stated	-16.7% before dissection; -100.0% after dissection	-65.2% before dissection; -91.3% after dissection	-30.4% before dissection; -47.8% after dissection	Non stated
Shibata *et al*[21], 2021	Prospective, cohort study	12	Acute cholecystitis	Non stated	-16.7% before dissection; -100% after dissection	-58.3% before dissection; -100% after dissection	-58.3% before dissection; -100% after dissection	Non stated
Castagneto-Gissey *et al*[22], 2022	Case-control study	17 patients received intragallbladder ICG; and 18 patients intravenous ICG administration	*n* = 14 acute or chronic cholecystitis; *n* = 2 choledocholithiasis	Intragallbladder ICG group Non stated	-76.5% before dissection; -88.2%	76.5%	5.9%	47.1%

; *n* = 1 adenomyomatosis		after dissection			
	Intravenous ICG group				
	Non stated	66.7% before dissection; -83.3% after dissection	77.8%	22.2%	61.1%

[1]Rates of visualization refer to the total of 44 patients undergoing fluorescent cholangiography with intravenous or intragallbladder ICG injection. Data regarding visualization of biliary structures with use of intraoperative cholangiography (IOC) are not provided due to the retrospective character of that group.

[2]Data regarding visualization of biliary structures with use of IOC are not provided due to the retrospective character of that group.

ICG: Indocyanine green; IOC: Intraoperative cholangiography; LC: Laparoscopic cholecystectomy.

Table 2 An overview of systems used in different studies, the chosen technique of Indocyanine Green administration and dosage

Ref.	NIR-ICG fluorescence device	ICG dose/concentration	Technique of administration
Liu *et al*[12], 2018	A specific light source (D-Light P, Karl Storz, GmbH & Co. KG, Tuttlingen, Germany) with a NIR-enabled Hopkins 10-mm, 30° laparoscope (Karl Storz, GmbH & Co. KG, Tuttlingen, Germany); a coupled IMAGE1 S camera head; the IMAGE1 S software enhancement mode	0.125 mg/mL; 10 mL	*n* = 18 PTGBD; *n* = 28 percutaneous punctures of the gallbladder with a Veress needle, using 2-0 Prolene stitch
Graves *et al*[19], 2017	A 30-degree 5 mm laparoscope with NIR imaging capability (Stryker Corporation, Kalamazoo, MI, United States)	0.025 mg/mL ICG-bile solution; 10 mL	Gallbladder puncture with a needle-tipped Kumar cholangiogram catheter or an 8Fr pigtail drainage catheter (Cook, Inc., Bloomington, IN, United States)
Quaresima *et*	-Karl Storz Image 1S D-Light system (Karl Storz Endoscope GmbH & C. K., Tuttlingen Germany) with a 30° forward oblique vision laparoscope; use of adjunctive filters (Spectra A) intraoperatively	0.5 mg/mL; 4.0 mL	Gallbladder puncture with a Veress needle and close of the puncture site with suture material

al[20], 2020			
Jao *et al*[16], 2020	Image 1 High-Definition fluorescence laparoscope (Karl Storz Endoscopes, Germany)	2.5-mg/mL; 5 mL	*Via* PTGBD
Gené Škrabec *et al*[18], 2020	Olympus EndoEye 3D camera	0.25 mg/mL; 2-3 mL	Gallbladder puncture with a Veress needle and closure of the entry point with a grasper, a stitch, or a clip
Cárdenas *et*	Pinpoint fluorescence endoscopic imaging system (Novadaq/Stryker)	2.5 mg/mL; 2-4 mL	Percutaneous gallbladder puncture under direct vision in the fundus using a 22-gauge epidural needle (Spinocan,

al[17], 2021			Braun); puncture site was closed using forceps
Shibata *et al*[21], 2021	Non stated	0.025 mg/mL; 1 mL	*n* = 3 percutaneous gallbladder punctures; *n* = 8 PTGBD; *n* = 1 ENBD
Castagneto-Gissey *et al*[22], 2022	Pinpoint Fluorescence Endoscopic Imaging System (Novadaq/Stryker, Burnaby, Canada)	0.5 mg/mL; 5 mL	Percutaneous gallbladder puncture with a 27-gauge needle

ICG: Indocyanine green; ENBD: Endoscopic nasobiliary drainage; PTGBD: Percutaneous transhepatic gallbladder drainage catheter.

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