Use of Fluorescence Guidance in Cholecystectomy

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Introduction

Laparoscopic cholecystectomy (LC) is widely accepted as the standard of care for cholecystectomy. It is currently the most commonly performed procedure performed by general surgeons in the United States. Bile duct injuries in the era of laparoscopic cholecystectomy range from 0.03% to 0.5% [1–4]. While infrequent, they represent a significant patient and healthcare burden when these injuries occur. Cost of treating bile duct injuries can be 4.5 to 26 times the cost of an uncomplicated procedure with an average 32-day hospitalization and significant mortality rate [5].

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Indocyanine green (ICG) dye is a water-soluble dye with spectral absorption at 800 nm. It has been described visualizing the biliary tree since 2008 [6]. When injected intravenously, ICG binds plasma proteins before being rapidly metabolized by hepatocytes and excreted exclusively into the bile; protein-bound ICG fluoresces green when illuminated with near-infrared (NIR) light [6–9]. The excretion of ICG into the biliary tree peaks at 2–4 h after intravenous injection [10]. Dynamic, real-time NIR light capability is built-in to many modern laparoscopic and robotic cameras. As described elsewhere in this manual, there are also cameras designed to image ICG in open surgery. These cameras are able to toggle between white-light and NIR light with the push of a button, allowing real-time imaging without disrupting surgical workflow, especially in the case of laparoscopic or robotic surgery (Figs. 4.1, 4.2, and 4.3; video clip attached for video chapter). The technology incorporates smoothly into the operation without increased need for staffing or additional supplies in the operative theater.

Through constant reassessment of the anatomy with NIR imaging, surgeons may continuously identify the position of critical biliary structures; these structures are often identifiable prior to dissection of peritoneal layer of the gallbladder, providing a safe dissection starting point as well as areas of critical importance. FC offers the potential detailed anatomical mapping of extrahepatic biliary structures and can be a useful adjunct to the critical view of safety [6–14]. FC allows for surgeons to identify either normal anatomy or anatomic variation prior to dissection

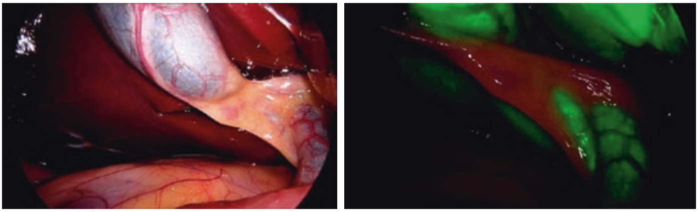

Fig. 4.1 Top panel: white-light laparoscopic view of gallbladder during cholecystectomy. Bottom panel: “overlay mode” ICG view of same patient showing cystic duct and common bile duct junction

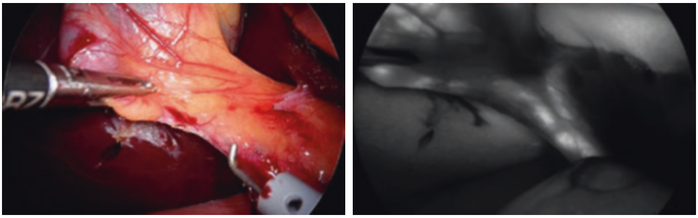

Fig. 4.2 Top panel: white-light laparoscopic view of gallbladder during cholecystectomy prior to peritoneal dissection. Bottom panel: "gray mode" ICG view of same image showing cystic duct, common bile duct, and junction

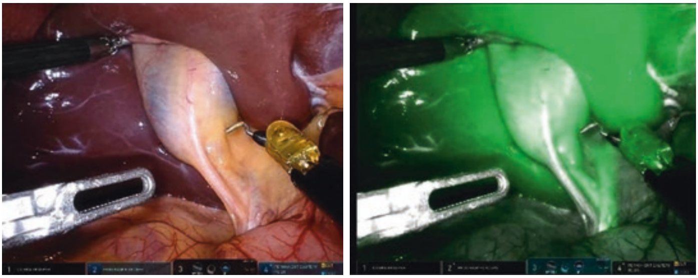

Fig. 4.3 Use of fluorescence cholangiography in robotic surgery. Left panel is traditional bright light view. Right panel is ICG mode highlighting cystic duct, CBD, and CD-CBD junction

and during active dissection. In contrast, IOC can be time consuming and involves exposure of the patient and ancillary staff to radiation, with associated increases in cost [15].

Literature Review

Ishizawa et al. described their laparoscopic experience with preoperative ICG injection for cholangiography during cholecystectomy, demonstrating a 100% visualization of the cystic duct and 96% visualization of the common hepatic duct prior to any dissection, which improved to 100% visualization of both structures with dissection [7]. Several other groups have demonstrated simi-

Table 4.1 Fluorescence cholangiography in laparoscopic cholecystectomy in literature. Reported common bile duct injuries and level of evidence for each study

First author (year)	Total patients	Bile duct injuries	Adverse reactions	Conversions to open	Level of evidence
Ishizawa (2010)	52	0	0	–	IV
Boni (2015)	52	0	0		IV
Dip (2015)	45	0	0		IV
Osayi (2015)	82	0	0		IV
van Dam (2015)	37	0	0		IV
Dip (2016)	70	0	0	0	IV
Dip (2019)	318	0	0	1	II
Hiwatashi (2018)	65	0	0	7	IV
Broderick (2022)	828	0	0	6	III

lar findings during laparoscopic cholecystectomy, as well as during robotic-assisted laparoscopic cholecystectomy, including in obese individuals [6–21]. With a growing body of literature, some surgeons have advocated for FC to become the standard of care in laparoscopic cholecystectomy in both elective and emergent cholecystectomy.

The highest level evidence confirming fluorescent visualization of extrahepatic biliary anatomy was shown in two studies. Dip et al. in 2019 published a single-blind randomized controlled trial comparing FC ($n = 312$) vs LC ($n = 318$) demonstrating that FC was statistically superior in identifying extrahepatic biliary structures [13]. Bile duct injury was zero in FC and two patients in LC; operative times and other complications were not reported. Lim et al. performed a meta-analysis of seven studies comparing biliary anatomy visualization with IOC versus FC. Rates of extrahepatic biliary anatomy identification included cystic duct, common bile duct, CD-CBD junction, and common hepatic duct. FC was safe and effective [14].

Tables 4.1 and 4.2 feature studies evaluating fluorescence cholangiography (FC) during cholecystectomy to evaluate common bile duct injury and operative times. The studies listed are mostly

Table 4.2 Fluorescence use in laparoscopic cholecystectomy with reported decreases in operative times

First author (year)	Number of patients (n)	Operative duration (FC)	Operative duration (LC)	Difference in duration
Ambe (2019)	29	53	54	−1
Bleszynski (2019)	108	70	80	−10
Quaresima (2019)	44	86.9	118	−31.1
Yoshiya (2019)	39	129	150	−21
Esposito (2019)	15	52	69	−17
Broderick (2022)	828	68	99	−31

cohort or case series studies. Currently, there are no reported bile duct injuries for FC in literature.

Broderick et al. performed a clinical review of their institutional experience with adopting ICG as standard of care. FC with ICG reduced operative time by 26.47 min per case compared to traditional LC without IOC ($p < 0.0001$) [16]. For patients with BMI ≥ 30 kg/m^2, operative duration for ICG vs non-ICG groups was 75.57 vs 104.9 min, respectively ($p < 0.0001$). ICG required conversion to open at a rate of 1.5%, while non-ICG converted at a rate of 8.5% ($p < 0.0001$). Conversion rate remained significant with multivariable analysis (OR 0.212, $p = 0.001$). Bile leaks (classified as Strasberg A injuries) were more common in the non-ICG group, with nine patients in the non-ICG group and two in the ICG group. One CBDI occurred in the non-ICG group, although this was not clinically significant. There was no significant difference in 30-day complication rates between groups [16]. Follow-up of this study and expansion on the cohort was published in 2022, confirming the above findings with further reduction in operative times [17].

Osayi et al. reported that significant improvements in patient outcomes are in decreased operative time and reduced rates of conversion to open surgery when comparing FC with white-light cholecystectomy. There is also a significant reduction in operative time when compared to IOC (1.9 ± 1.7 min vs 11.8 ± 5.2 min, $p < 0.001$) [11]. In this study, IOC was unobtainable in 24.4% of patients, while ICG did not visualize biliary structures in 4.9% of patients. After complete dissection, the rates of visualization of the cystic duct, common bile duct, and common hepatic duct using ICG were 95.1, 76.8, and 69.5%, respectively, compared to 72.0, 75.6, and 74.3% for IOC. In patients where IOC could not be obtained, FC successfully identified biliary structures in 80% of the cases. Higher BMI was not a deterrent to visualization of anatomy with ICG.

Reeves et al. utilized a Markov model to shows that use of ICG during cholecystectomy is cost-effective and improves quality of care with $1235 cost reduction per case and 0.09 quality-adjusted life years (QALY) compared to standard white-light cholecystectomy [22]. These improvements were demonstrated due to a reduction in operating time of 20 minutes and decreased conversion to open rate from 6.7% to 1.2% in averaged over available literature [22]. Recommendations in their manuscript are limited by the nature of the predictive model and should be studied prospectively to verify findings. The manuscript also reviewed all published reports of FC in literature to determine the parameters of the predictive model; improvements in operative time and outcomes were in multiple retrospective studies [16–21].

Best evidence is Level III–IV from these studies as well as designed controlled trials or cohorts. No randomized trials evaluating conversion to open surgery, operative times, and common bile duct injuries have been published to date. There is early Level II evidence showing better visualization of extrahepatic biliary structures with FC compared to IOC and white light alone.

Advantages of Indocyanine Green Fluorescence Cholangiography

Fluorescence cholangiography has multiple advantages. Compared to IOC, FC can save time and operative costs associated with traditional radiographic IOC with respect to cannula insertion and contrast injection for biliary imaging [23, 24]. FC is viewed as quite versatile, as a single preoperative injection allows the surgeon to obtain fluorescent imaging at any point during the procedure without the added personnel and equipment needed for

IOC. The fluorescent images can be viewed from several angles, in real time with real-time tissue manipulation, to better understand anatomic relationships. In centers for education, it can be a good adjunct to assist surgical trainees in understanding anatomy and CVS in real time. Additionally, repeated imaging with repeat intravenous ICG injections is possible throughout the surgical procedure to help delineate vascular anatomy. Unlike arguments around routine versus selective IOC, routine use of ICG is supported by the above benefits without additional cost, equipment, or time. Lastly, the use of fluorescence cholangiography is safe and does not involve radiation exposure; it has been used safely in patient with traditional iodine allergies (e.g., rash). Each of these benefits may translate to improved patient outcomes, especially with respect to decreased operative time, overall cost, and conversion to open surgery. [16, 17, 22]

The most significant improvements in patient outcomes are in decreased operative time and reduced rates of conversion to open surgery when comparing FC with white-light cholecystectomy. There is also a significant reduction in operative time when compared to IOC (1.9 ± 1.7 min vs 11.8 ± 5.2 min, $p < 0.001$) [11].

The topic of cost always plays an important role in adopting new technologies or techniques. As described above, comparing FC to traditional white-light LC (without use of IOC), Reeves et al. utilized a Markov model to show that use of ICG during cholecystectomy is cost-effective and improves quality of care with $1235 cost reduction per case and 0.09 quality-adjusted life years (QALY) compared to standard white-light cholecystectomy [22]. Thus, ICG use can be viewed as a cost-effective surgical strategy which improves healthcare outcomes and suggests this should be considered as standard of care for laparoscopic cholecystectomy.

Although current firm recommendations are limited by published sample size, early data suggest both reduced operative time and conversion to open surgery in FC cases for both inflamed and non-inflamed pathology as well as obese patients. Whether FC significantly moves the needle on reducing major common bile duct injury remains to be confirmed with further collation of data and use in practice, although this will take hundreds of thousands of cases due to the low rate of CBD injury.

Limitations of Indocyanine Green Fluorescence Cholangiography

Despite the above advantages, FC with ICG has some limitations. In institutions where there is no NIR camera capability, an up-front cost for purchasing new equipment would be needed to implement FC. There would also be the need to protocol pre-op ordering, reconstitution, and administration of intravenous ICG. Nurse education is often necessary to relay the importance of appropriate dose timing and standardize seamlessly into practice. The cost of ICG alone is inexpensive ($17–130/bottle), and the up-front equipment cost can be recouped if reduced operative time and conversion to open data holds true.

Fluorescence cholangiography cannot visualize deep structures. While Dip et al. note that there is increased visualization of CHD, CBD, and cystic duct in FC, the penetration of the NIR light can still be limited in cases of thick surrounding fat or inflamed tissue in the porta hepatis. The ability to detect bile duct stones with fluorescence cholangiography is also questionable. FC cannot be used as a replacement to IOC in the setting of identifying and treating choledocholithiasis; however, it can be used simultaneously with IOC for identifying overall anatomy and safe cannulation of the cystic duct.

Conclusion

Fluorescence cholangiography with ICG appears to be a promising technology that is safe and cost-effective and improves patient outcomes. The ability to visualize biliary anatomy can have a great benefit to the surgeon and may help prevent complications in the surgical patient.

References

1. Deziel DJ, Millikan KW, Economou SG, Doolas A, Ko ST, Airan MC. Complications of laparoscopic cholecystectomy: a national survey of 4,292 hospitals and an analysis of 77,604 cases. Am J Surg. 1993;165(1):9–14. https://doi.org/10.1016/S0002-9610(05)80397-6.

2. Flum DR, Cheadle A, Prela C, Dellinger EP, Chan L. Bile duct injury during cholecystectomy and survival in Medicare beneficiaries. J Am Med Assoc. 2003;290(16):2168–73. https://doi.org/10.1001/jama.290.16.2168.
3. Dolan JP, Diggs BS, Sheppard BC, Hunter JG. Ten-year trend in the national volume of bile duct injuries requiring operative repair. Surg Endosc Other Interv Tech. 2005;19(7):967–73. https://doi.org/10.1007/s00464-004-8942-6.
4. Halbert C, Pagkratis S, Yang J, et al. Beyond the learning curve: incidence of bile duct injuries following laparoscopic cholecystectomy normalize to open in the modern era. Surg Endosc. 2016;30(6):2239–43. https://doi.org/10.1007/s00464-015-4485-2.
5. Savader SJ, Lillemoe KD, Prescott CA, Winick AB, Venbrux AC, Lund GB, Mitchell SE, Cameron JL, Osterman FA Jr. Laparoscopic cholecystectomy-related bile duct injuries: a health and financial disaster. Ann Surg. 1997;225(3):268–73. https://doi.org/10.1097/00000658-199703000-00005. PMID: 9060582; PMCID: PMC1190676.
6. Ishizawa T, Tamura S, Masuda K, Aoki T, Hasegawa K, Imamura H, Beck Y, Kokudo N. Intraoperative fluorescent cholangiography using indocyanine green: a biliary road map for safe surgery. J Am Coll Surg. 2009;208(1):e1–4. https://doi.org/10.1016/j.jamcollsurg.2008.09.024. Epub 2008 Oct 31. PMID: 19228492.
7. Ishizawa T, Bandai Y, Ijichi M, Kaneko J, Hasegawa K, Kokudo N. Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy. Br J Surg. 2010;97:1369. https://doi.org/10.1002/bjs.7125.
8. Boni L, David G, Mangano A, Dionigi G, Rausei S, Spampatti S, Cassinotti E, Fingerhut A. Clinical applications of indocyanine green (ICG) enhanced fluorescence in laparoscopic surgery. Surg Endosc. 2015;29(7):2046–55. https://doi.org/10.1007/s00464-014-3895-x. Epub 2014 Oct 11. PMID: 25303914; PMCID: PMC4471386.9.
9. Oddi A, Di Nicola V, Panzini A, et al. The intraoperative visualization of the bile ducts by the use of fluorescent substances. A feasibility study. G Chir. 1996;17(11–12):620–3.
10. Sandler BJ. Immunofluorescence in the operating room for biliary visualization and perfusion assessment - a SAGES Technology and Value Assessment [Internet]. SAGES. 2019 [cited 2022 May 1]. Available from: https://www.sages.org/publications/tavac/immunofluorescence-operating-room-biliary-visualization-perfusion-assessment/.
11. Osayi SN, Wendling MR, Drosdeck JM, Chaudhry UI, Perry KA, Noria SF, Mikami DJ, Needleman BJ, Muscarella P 2nd, Abdel-Rasoul M, Renton DB, Melvin WS, Hazey JW, Narula VK. Near-infrared fluorescent cholangiography facilitates identification of biliary anatomy during laparoscopic cholecystectomy. Surg Endosc. 2015;29(2):368–75. https://doi.org/10.1007/s00464-014-3677-5. Epub 2014 Jul 2. PMID: 24986018; PMCID: PMC4415528.

12. Dip F, Nguyen D, Montorfano L, et al. Accuracy of near infrared-guided surgery in morbidly obese subjects undergoing laparoscopic cholecystectomy. Obes Surg. 2016;26(3):525–30. https://doi.org/10.1007/s11695-015-1781-9.
13. Spinoglio G, P.F. Real-time near-infrared (NIR) fluorescent cholangiography in single site robotic cholecystectomy (SSRC): a single institutional study. Surg Endosc. 2013;27:2156–62.
14. Dip F, LoMenzo E, Sarotto L, et al. Randomized trial of near-infrared incisionless fluorescent cholangiography. Ann Surg. 2019;270(6):992–9. https://doi.org/10.1097/SLA.0000000000003178.
15. Lim SH, Tan HTA, Shelat VG. Comparison of indocyanine green dye fluorescent cholangiography with intra-operative cholangiography in laparoscopic cholecystectomy: a meta-analysis. Surg Endosc. 2021;35(4):1511–20. https://doi.org/10.1007/s00464-020-08164-5. Epub 2021 Jan 4. PMID: 33398590.
16. Broderick RC, Lee AM, Cheverie JN, et al. Fluorescent cholangiography significantly improves patient outcomes for laparoscopic cholecystectomy. Surg Endosc. 2021;35(10):5729–39. https://doi.org/10.1007/S00464-020-08045-X.
17. Broderick RC, Li JZ, Huang EY, Blitzer RR, Lee AM, Serra JL, Bouvet M, Sandler BJ, Jacobsen GR, Horgan S. Lighting the way with fluorescent cholangiography in laparoscopic cholecystectomy: reviewing 7 years of experience. J Am Coll Surg. 2022;235(5):713–23. https://doi.org/10.1097/XCS.0000000000000314. Epub 2022 Oct 17. PMID: 36102574.
18. Ambe PC, Plambeck J, Fernandez-Jesberg V, Zarras K. The role of indocyanine green fluoroscopy for intraoperative bile duct visualization during laparoscopic cholecystectomy: an observational cohort study in 70 patients. Patient Saf Surg. 2019;13:2. https://doi.org/10.1186/s13037-019-0182-8. PMID: 30651756; PMCID: PMC6330420.
19. Bleszynski MS, DeGirolamo KM, Meneghetti AT, Chiu CJ, Panton ON. Fluorescent cholangiography in laparoscopic cholecystectomy: an updated Canadian experience. Surg Innov. 2020;27(1):38–43. https://doi.org/10.1177/1553350619885792. Epub 2019 Nov 19. PMID: 31744398.
20. Yoshiya S, Minagawa R, Kamo K, Kasai M, Taketani K, Yukaya T, Kimura Y, Koga T, Kai M, Kajiyama K, Yoshizumi T. Usability of intraoperative fluorescence imaging with indocyanine green during laparoscopic cholecystectomy after percutaneous transhepatic gallbladder drainage. World J Surg. 2019;43(1):127–33. https://doi.org/10.1007/s00268-018-4760-1. PMID: 30105635.
21. Esposito C, Corcione F, Settimi A, Farina A, Centonze A, Esposito G, Spagnuolo MI, Escolino M. Twenty-five year experience with laparoscopic cholecystectomy in the pediatric population-from 10 mm clips to indocyanine green fluorescence technology: long-term results and technical considerations. J Laparoendosc Adv Surg Tech A. 2019;29(9):1185–91. https://doi.org/10.1089/lap.2019.0254. Epub 2019 Jun 14. PMID: 31199700.

22. Reeves JJ, Broderick RC, Lee AM, et al. The price is right: routine fluorescent cholangiography during laparoscopic cholecystectomy. Surgery. 2021;171(5):1168–76. https://doi.org/10.1016/j.surg.2021.09.027.
23. Hiwatashi K, Okumura H, Setoyama T, et al. Evaluation of laparoscopic cholecystectomy using indocyanine green cholangiography including cholecystitis. Medicine. 2018;97(30):e11654. https://doi.org/10.1097/MD.0000000000011654.
24. Dip FD, Asbun D, Rosales-Velderrain A, et al. Cost analysis and effectiveness comparing the routine use of intraoperative fluorescent cholangiography with fluoroscopic cholangiogram in patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2014;28(6):1838–43. https://doi.org/10.1007/s00464-013-3394-5.