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Review Article

An Overview of Near Infrared Fluorescent Cholangiography with Indocyanine Green during Cholecystectomy

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Abstract

Laparoscopic cholecystectomy (LC) is one of the most common surgical procedures performed globally but continues to carry to an unacceptably high risk of iatrogenic bile duct injury (BDI). In recent years several centres have proposed Near Infrared Fluorescent Cholangiography (NIRFC) with Indocyanine Green (ICG) as a potential method of dynamic intraoperative extra hepatic bile duct mapping. We provide an overview of the current problem of BDI during laparoscopic cholecystectomy including the incidence, aetiology and medico legal ramifications. We also provide a short summary of the enduring argument for and against routine intraoperative cholangiogram (IOC) and we discuss the new technology of NIRFC with ICG in detail. We provide an informative summary of the small number of highly heterogeneous clinical trials of NIRFC with ICG currently available and briefly discuss limitations of the technology.

ABBREVIATIONS

BDI: Bile Duct Injury; DLC: Delayed Laparoscopic Cholecystectomy; FL: Fluorescent Light; HCC: Hepatocellular Carcinoma; IALC: Index Admission Laparoscopic Cholecystectomy; ICG: Indocyanine Green; ICGR-15: Indocyanine Green Retention Rate at 15 min; IOUS: Intraoperative Ultrasound; IV: Intravenous; LC: Laparoscopic Cholecystectomy; NICE: National Institute for Health and Care Excellence; NIR: Near Infrared; NIRFC: Near Infrared Fluorescent Cholangiography; OR: Odds Ratio; RCT: Randomized Controlled Trial; RR: Relative Risk; WL: White Light

INTRODUCTION

Laparoscopic cholecystectomy (LC) is one of the most common surgical procedures performed globally, with over 66,000 cases are performed per year in the UK alone. Despite the prevalence of LC, it continues to carry to an unacceptably high risk of iatrogenic bile duct injury (BDI). The cause of BDI is multifactorial, combining a lack technical skill and a sustained perception error from the operating surgeon. Proponents of intraoperative cholangiogram argue cannulation of the cystic duct and fluorescent screening with radiopaque contrast media reduces the incidence of BDI but this is debatable and has not been conclusively proved by the current evidence base. In recent years several centers have proposed Near Infrared Fluorescent Cholangiography (NIRFC) with Indocyanine Green (ICG) as a potential method of dynamic intraoperative extra hepatic bile duct mapping. ICG is exclusively excreted in the bile after intravenous administration. It rapidly accumulates in the extra hepatic biliary anatomy, which can be visualized with several of the commercially available Near Infrared laparoscopes on the market. NIRFC is convenient to use and could potentially negate the radiation dose and rates of cystic duct injury associated with standard Intraoperative Cholangiogram (IOC). However, data is limited; the published studies are all small, with highly variable methodology, outcome measures and interpretation of results, this is insufficient for a systematic review at the current time.

The principles of fluorescence

A fluorophore is defined as a substance capable of absorbing and emitting light energy. In the simplest terms, fluorescence is a three-step process of excitation, "relaxation" and emission. Fluorophores exist in a low energy unexcited "ground state" until excited by light of an appropriate wavelength. Once irradiated to the high energy state the fluorophore rapidly start to relax partially dissipating the absorbed energy as vibration or heat energy. The partially relaxed fluorophore then enters the emission phase of fluorescence, releasing the photon of energy as a detectable fluorescent signal of a longer wavelength. Unless, "photo bleached", irreversible structural damage from high intensity light excitation, or quenched by molecular interaction

in the microenvironment, a fluorophore can be repeatedly excited for sustained detection. It is these essential properties of fluorophores that allows differentiation between absorbed and emitted light and facilitates the multiple diagnostic utilities of fluorophores including perfusion assessment, tumor localization and bile duct mapping [1,2].

Indocyanine green (ICG)

Indocyanine Green (ICG) is a hydrophilic tricarbocyanine dye with fluorescent properties. It was developed by Eastman Kodak® as a sensitising agent in photograph development in the early 1950s and approved for clinical applications by US Food and Drug Authority (FDA) soon after. Early experimental applications of ICG mainly focused on dilutional methods of assessing cardiac perfusion and retinal angiography [3-5]. ICG is safe, with very few adverse reactions reported. Its attractiveness as a fluorescent imaging agent relates to its ready availability, stability, low toxicity and intravascular confinement properties. Once injected intravenously it rapidly and fully binds to serum lipoproteins complexes and plasma proteins [5]. ICG has a very broad optical window, overlapping the edge of the visible light and Near Infrared (NIR) region of the electromagnetic spectrum. The absorption spectrum of ICG is quoted between 695 and 815nm [5-7] with ICG monomers peaking at a lower wavelength than ICG oligomers and albumin bound ICG [5,6,8]. The same is true for the emission properties of ICG with a variable peak emission between 780 and 845nm [5 -7,9,10].

ICG is exclusively excreted in bile and does not undergo any forms of intrahepatic conjugation, metabolism or enterohepatic circulation [4,7]. ICG extraction and biliary excretion is reliant on energy depend trans membrane carrier proteins and it has a biphasic eliminate profile [4,11]. The accepted pharmacokinetics of ICG is based in part, upon the early animal studies of Wheeler [12] and Ketterer [13] and Cherrick's [7] human studies from the same era. ICG is detectable in the bile 15 minutes after administration but concentrations do not peak until two hours later. In the canine model, all ICG was recovered within five hours but in Cherrick's human population levels remained high at trial termination seven hours' post administration indicating a possible longer elimination profile.

ICG shows almost complete intravascular confinement in healthy tissue but delayed washout of up to 72 hours in diseased and malignant tissue [12]. Several factors adversely affect the clearance of ICG. Bilirubin is a competitive inhibitor of ICG uptake by hepatocytes, as is hypo-perfusion and altered hepatic microcirculation. In clinical practice, severe liver disease with severely reduced hepatocyte function, raised serum bilirubin and low albumin states and hypotension all adversely affect ICG and clearance rates. Conversely, calorific restriction increases the rate ICG hepatic clearance [5,13].

Clinical applications of ICG

Since the discovery of ICG, it has been used for a myriad of clinical applications. The majority have utilized the spectral and intravascular confinement properties of ICG for angiographic studies. At the 800nm wavelength, ICG shows peak absorption and this conveniently overlaps with the exact point whereby the optical density of oxygenated hemoglobin is comparable to that of deoxygenated hemoglobin, facilitating methods of NIR imaging in all three fluid mediums, bloods, plasma and serum [14]. ICG is also favoured for fluorescent guided surgery because the tissue penetrance is believed to reach up to 10mm in the correct setting.

There is a wealth of publications describing applications of ICG in surgical practice; we will therefore focus primarily on laparoscopic cholecystectomy and briefly on hepatobiliary surgery only. An accepted application of ICG is retention testing (ICGR-15), as part of functional hepatocyte assessment prior to hepatic resection surgery [15]. The serum concentration of ICG 15 minutes after intravenous administration can act as an accurate surrogate marker of both hepatocyte volume, function and blood flow [16,17].

Recently, ICG with NIR technology has moved in to the operating theatre and has been applied as a dynamic imaging modality for benign and malignant pathologies in both open and laparoscopic surgery. ICG guided navigation in laparoscopic liver resection surgery is of particular interest to hepatobiliary surgeons. The hope is it will compensate, at least in part, for the lack of tactile feedback available in minimally invasive surgery. First trialed by Ishiwara [18], ICG is has proved highly valuable in Hepatocellular Carcinoma (HCC) tumour resection, in part because of its convenient dosing regimen. HCC localization can utilize the residual ICG from preoperative ICGR-15 functional reserve assessments and possibly the leaky basement membrane of tumour capillaries. By administering ICG between three and 28 days prior to surgery groups were able to delineate all tumours within 5mm of the liver capsule and visualize multiple tumours invisible on white light inspection alone. ICG has a HCC sensitivity of 96% [19], produced uniform fluorescence in all lesions and was felt to aide intra operative decision making [20].

Liver metastases are common in the natural history of many cancers, especially colorectal cancer and must be resected if any attempt at long-term survival is to be made. The natural progression for ICG guided NIR surgery was to the field of liver metastases resection. HCC tumours show a characteristic uniform fluorescence with ICG, whereas colorectal liver metastases show ring enhancement with retention of the fluorophore in the tumour stromal and normal liver tissue junction [21]. Kudo's [20] trial of NIR Fluorescence in colorectal liver metastases resection yielded a sensitivity of 69% (detecting 11 out of 16 lesions).

Cholecystectomy

Cholecystectomy is a common procedure, with around 66,660 cases performed each year in the United Kingdom. Of these, only around 5,000 are performed via the traditional open approach [22]. Laparoscopic cholecystectomy (LC) surgery was developed in the late 1980s and entered into standard surgical practice in the early 1990s. Initially, minimally invasive LC took on average, 3 hours to complete and had a conversion to open rate of around 15% [23,24]. Until relatively recently, acute cholecystitis and gallstone induced pancreatitis were a contra-indication to LC. Early adopters of emergency LC in acute cholecystitis reported the procedure feasible but with high rates of morbidity, namely high intra-operative blood loss and BDI incidence in excess of 5% [25]. Many centers therefore continued to endorse open

cholecystectomy or Delayed Laparoscopic Cholecystectomy (DLC) for this patient group.

Emergency or "index admission" LC (IALC) for acute cholecystitis is now the gold standard treatment and recommended by NICE [22]. Multiple comparative studies have confirmed IALC as cost efficient; £4,570 compared to £4,720 for DLC [26] and dismissed concerns around higher rate of BDI and open conversion [27] (Figure 1). Importantly, there is marked patient morbidity in the delayed group with almost 20% of patients waiting for a DLC representing in the interim [28]. Despite this, only 54.8% of patients presenting with acute cholecystitis to UK hospitals receive an IALC and the figure varies widely between UK hospitals [29]. IALC is technically challenging and an adjunct to facilitate dynamic intraoperative bile duct mapping would be of great benefit to laparoscopic surgeons performing these operations.

Bile duct injury (BDI)

The most feared and serious complication of laparoscopic or open cholecystectomy is a bile duct injury (BDI). The implications can be catastrophic, with significant mortality and morbidity for the patient and several medico-legal ramifications for the surgeon and hospital involved. Many years after the BDI patients can continue to suffer physical and psychological complications negatively affecting their quality of life (QoL). The impact of BDI on overall psychological wellness can be severe; BDI patients are "38 times more likely to have a reduced mental health related quality of life" score compared to uneventful LC patients [30] and self-report reduced QOL for many years after the injury [31].

The peak of open cholecystectomy extended from the 1970s up to the introduction of LC in the late 1980s. During this period the overall BDI rate was only 0.2% to 0.32% [32,33]. Since the introduction of LC, the incidence of iatrogenic BDI during LC has varied greatly in the literature. Earlier case series encompassing the LC "learning curve" period, quote significantly higher rates than more recent series from experienced hepatobiliary centers.

The largest early US series retrospectively analyzing

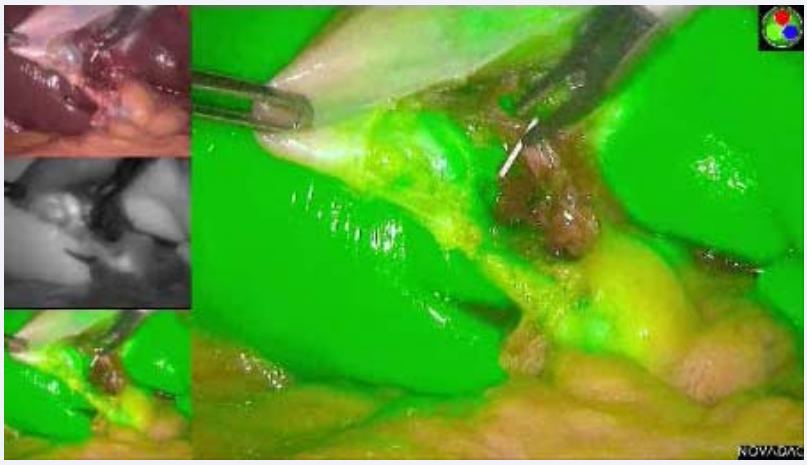

Figure 1 Intraoperative assessment of biliary anatomy with NIRFC after partial dissection of Calot's triangle using the Novadaq™ Pinpoint Endoscopic Fluorescence Imaging System. Courtesy of G Armstrong & G Too good from St James' University Hospital, Leeds (unpublished).

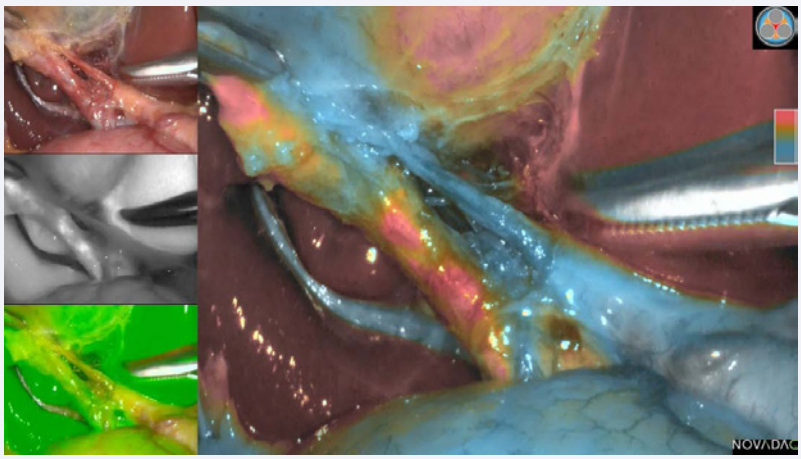

Figure 2 Intraoperative assessment of biliary anatomy with NIRFC after partial dissection of Calot's triangle. Imaging obtained using the Novadaq™ Pinpoint Endoscopic Fluorescence Imaging System in Color-Segmented Fluorescence mode (CSF) a qualitative colour mapping system unique to the Novadaq Pinpoint System. Courtesy of G Armstrong & G Toogood from St James' University Hospital, Leeds (unpublished).

1,570,361 LCs performed between 1992 and 1999 found an overall incidence of BDI of 0.5% [34]. Strasberg's [33] review of BDI during LC published in 1995 also estimates the incidence at 0.52%. In the early years of BDI after LC 26% of patients who sustained a BDI died within one year of the event, compared to only 6.6% of the uncomplicated group. Even when considering independent risk factors the adjusted hazard ratio (HR) for mortality was 2.79 for the BDI cohort [34]. Large European studies from the same period report similar rates of BDI, Italy 0.42% [35], Sweden 0.40% [36], and Switzerland 0.3% [37].

Iatrogenic BDI should be considered preventable. Multiple mechanisms and errors contribute to the occurrence of intra-operative BDI. It remains debatable to what extent lack of technical skill, perception error, or combinations of these factors are the key underlying cause of BDI. Misidentification of the cystic duct is a recurring theme in retrospective analysis of BDI [33]. Way et al., estimate just 3% of BDI are due to a true lack of technical ability [38]. They analyzed 252 BDI cases, regardless of the extent and grade of BDI sustained; the underlying cause in most cases was the surgeon mistaking an extra hepatic duct for the cystic duct. However, previous studies attribute far more blame to the technical skill of the surgeon. Nuzzo et al., attribute "improper use of monopolar coagulation" and an inability to achieve early haemostasis as the primary mechanism of BDI in nearly 20% of reported cases [35].

The safety of LC has dramatically improved since the early days of minimally invasive surgery. UK centers that limit LC surgery to consultants who have declared an interest in upper gastrointestinal surgery and/or minimally invasive hepatobiliary surgery report enviable rates of open conversion and BDI during LC, 3.0-3.8% and 0.1% respectively [39-41]. High volume American centers also report a BDI incidence of around 0.08% [42].

Aside from the mortality and morbidity associated with BDI, there is also a significant medico-legal burden for the surgeon and hospital trust involved. In our litigious society patients are now likely to bring successful legal cases against a trust when they are the victim of any perceived avoidable compilation or medical negligence. Between 1995 and 2009 the NHS Litigation Authority (NHSLA) settled 303 cases emanating from LC surgery, of these, 179 related to BDI. BDI legal cases had the highest success rate (77.9%) of all LC related complications and commanded one of the highest average pay-outs at £114,324 per case [63]. In the United States, the average award for LC related clinical negligence is four times higher than in the UK [64].

The management of the BDI is also vitally important to the likelihood of ligation being brought against a surgeon and the case being upheld. Roy's review of NHSLA BDI cases between 2000 and 2005 found "only half of claims for injuries that had been recognized promptly were successful", compared to 90% of cases recognised late in the clinical course [62]. In the Netherland patients diagnosed with BDI more than 7 days after LC received on average 2.4 times higher pay-out from their ligation case than those diagnosed within one week [58], in the UK, this figure is roughly 3.6 times higher [62].

Intra-operative cholangiogram (IOC)

Since the introduction of LC multiple strategies to reduce BDI have been proposed and Intra-operative cholangiogram (IOC) is one of the most accepted. The advantage of IOC is that it can visualize both the intra and extra hepatic biliary anatomy, the presence of any ductal cholelithiasis and the flow of contrast in to the duodenum can be observed. However, IOC can be problematic and time-consuming to perform, whilst the catheterization process risks injury to the bile ducts. The intervention also carries a radiation dose both to the patient and the operating theatre staff. The most common reason for conducting an IOC is to exclude choleduocholithiasis, but Jamal et al. [43], meta-analysis of IOC yielded a pooled sensitivity and specificity of 87% and 98% for this purpose.

Proponents of IOC argue it improves outcomes, reduces BDI and aides intraoperative decision making processes, a viewpoint not held by all laparoscopic and hepatobiliary surgeons. In the 1990s prior to the "critical view of safety" era as proposed by Strasberg et al., there was a flurry of publications advocating routine IOC. Flum's [44] retrospective review of over one and a half million LCs performed during 1992 and 1999 found regardless of patient and surgeon factors the relative risk of BDI was higher (RR 1.71) when IOC was omitted. Whilst, Fletcher et al. [45], review of BDI in Western Australia from introduction up until 1994 demonstrated the greatest protective effect of IOC in complex biliary pathology, reducing the incidence of BDI from 16.9 to 2.2 per 1000 for both open cholecystectomy and LC. Waage et al. [36], concluded IOC reduced the incidence of BDI by 34% (OR, 0.66; 95% CI, 0.54-0.79) in Sweden between 1987 and 2001. This early period of LC surgery was largely experimental without consensus on timing or indication for LC. It is noteworthy, many centres viewed complex and acute biliary disease as a contraindication to minimally invasive surgery, limiting access to and experience in emergency LC for the majority of surgeons at this time.

Twenty-four percent of laparoscopic surgeons in the UK and about a third in the United States perform routine IOC with every LC [46,47]. In the Netherlands where surgeons adhere to a laparoscopic cholecystectomy protocol incorporating the critical view of safety, only 2.6% perform routine IOC [48]. Preoperative deranged liver function tests and the clinical presentation of cholangitis are independent risk factors for choleduocholithiasis [49]. Therefore, many surgeons use selective IOC when laboratory, radiological or intraoperative findings raise suspicion of intraductal pathology such as stones. IOC significantly increases operative duration [50], the risk of postoperative biliary infection and has an increased financial burden.

It is argued that IOC only increases intraoperative detection but does not reduce the actual incidence of BDI. Extra hepatic bile duct injuries are often missed by the operating surgeon. Just 18% - 32% [51-55] of BDIs are recognised intra-operatively, and an alarmingly high proportion is not recognised until after discharge from hospital [52]. Ludwig et al. [53], report routine IOC both reduced the incidence of and increased the rate of intra-operative BDI identification from 0.43% to 0.21% and from 44.5% to 87% respectively when compared to selective IOC. At casual glance, Sheffield et al. [56], concur with Ludwig et al. [44,53,54], and with earlier published data, reporting a reduction in BDI with IOC from 0.36% to 0.21% between 2000 and 2009. However, after adjustment for immeasurable cofounders and subjecting the data to more rigorous statistical analysis the difference in

outcomes when using routine IOC was not statically significant *(p=0.31).* Khan et al. [50], in a RCT of OTC using identification of CBD stones as the primary endpoint only, argued routine IOC did not reduce BDI and was not clinically indicated. Failure to include biliary anatomy mapping and bile duct injury as primary endpoints somewhat limits the validity of their small RCT with less than 100 patients per arm in a single centre. Ragulin-Coyle's [47] retrospective review of IOC in LC between 2004 and 2009, after the adoption of safe best practice steps in LC including the critical view of safety in many centers, found no difference in rates of BDI between experienced surgeons who routinely use IOC and those who selectively apply it.

Near infrared fluorescent cholangiography with ICG

The stubbornly high rates of BDI, associated morbidity, financial ramification and difficulties associated with performing IOC during LC makes Near Infrared Fluorescent Cholangiography (NIRFC) with ICG an extremely promising potential adjuvant to minimal invasive hepatobiliary surgery. The potential to delineate the extra hepatic biliary anatomy may aid surgeon structure visualization and it is hoped may reduce the rate of serious BDI. Some proponents of the new technology believe, it many even negate the need for traditional intra-operative cholangiogram with radio-opaque contrast media in certain settings. The technique is simple, patients receive a preoperative dose of ICG and the LC surgery is performed with a dedicated NIR laparoscope. The ICG accumulates in the bile ducts to allow dynamic real time NIRFC.

Various teams have performed standard laparoscopic, single incision and robotic cholecystectomy with NIRFC and ICG (Table 1). However, there is no consensus on dose, timing of administration or endpoint measures. The small sample sizes and differing methods used mean there is a distinct lack of comparative data on the emerging field of NIRFC and insufficient data for a systematic review of the literature at this time. Figueiredo et al. [57], explored NIRFC in a mouse model and concluded the peak intraoperative signal to noise ratio was achieved 25 minutes after intravenous administration. The first human application of ICG guided LC was reported by Ishizawa et al., in 2009 using a prototype NIR device [58]. They deemed the administration of a single intravenous dose of 2.5mg ICG two hours prior to surgery a success, reporting ease of visualization of the cystic duct (CD) and the common hepatic duct (CHD) with the technique.

A small number of non-randomized prospective NIRFC trials have followed, using a combination of commercially available and prototype NIR laparoscopic devices. By far, a single preoperative intravenous bolus of 2.5mg of ICG is the most popular dose; every published trial except Boni et al. [59], who used 0.4mg/kg and Zroback et al. [60], who used 3.75mg, has employed this dosing regimen.

Recently, Zarrinpar [61] attempted to define the optimal dose and timing interval and refutes the almost consensus view of a standardized 2.5mg dose in hepatobiliary surgery. Although small, 37 patients in total, and including cholecystectomies and partial hepatectomies, there was a clear improvement in the visualization of important extra hepatic biliary structures with higher doses of ICG administered at a longer pre-operative interval. Using a semi-quantitative scoring system, they suggest "a dose of 0.25mg/kg administered at least 45miniutes prior to visualization facilitates Intraoperative anatomical identification". This is well within the safe adult total daily dose limit of 5mg/kg of ICG. Indeed, with endemic levels of obesity in the Western world a standardized low dose feels counterintuitive. Several trial protocols had scope for additional doses of ICG, but these were rarely required owing to the prolonged fluorescence produced by ICG excreted in to bile. The only exception being whereby a team wished to delineate the vascular anatomy; in this situation, they gave small additional doses of ICG map the cystic and hepatic arteries [59].

The exact timing is also a contentious issue and must take in to consideration the noise to signal ratio created by background liver fluorescence. All studies were guided by the elimination properties of ICG and administered a dose prior to induction of anesthesia, however this ranged from 15 minutes to more than two hours prior to start of surgery time. Verbeek et al. [62], attempted to define the optimal dosing regimen in open hepatic surgery prior to application in LC. Pushing the limits of ICG detectable fluorescence, they proposed 10mg administered 24 hours prior to LC as the optimal dose. They report far less liver background signal and therefore greater contrast between the liver and the common bile duct with easier surgeon visualization with prolonged dosing. However, in a surgical setting, where most LCs is performed on a day-case basis, the feasibility of administering intravenous ICG the day before surgery may be questionable. Zarrinpar [61] observed improved contrast between the liver, ducts and fat with prolonged dosing (3 hours) too, but compromised to a more achievable 45 minutes with the addition of a higher dose to compensate.

A major drawback of NIRFC is its limited depth of tissue penetration, somewhere in the region of 5 to 10mm. In 2013 67% of men and 57% of woman in the England were considered overweight or obese [63] (Figure 2). This figure continues to rise and is far higher than when LC was first introduced in to NHS surgical practice. Operating on patients with a high Body Mass Index (BMI) score and therefore large volumes of intraabdominal adipose tissue in now a common occurrence and poses its own set of challenges to surgical teams. Japanese and American teams piloting NIRFC have attempted to explore the effect of obesity of extra hepatic ductal visualization. Osayi et al., using an ICG dose of 2.5mg total in the USA could only visualize the CBD in 64% of patients with a BMI over 35kg/m^2 and in one super morbidly obese patient with a BMI of 63kg/m^2 the CD was the only structure detected with NIRFC [64-69]. Other teams report similar difficulties with NIRFC in the overweight or obese patient too, including the need for extensive dissection in Calot's triangle to achieve any visualization, [65] and a longer operative time [70-75]. Kono et al. [76], in Japan contradicts this view, "BMI had not predictive value for detection" of the CD and CBD confluence. Although it is important the median BMI was only 23.5kg/m^2 in Kono's study versus a mean 31.49kg/m^2 in Osayi's later publication.

In other fields of NIRF surgery with ICG as the fluorophore, advanced BMI was found to adversely affected structure

Table 1: Summary of NIRFC with ICG cholecystectomy clinical trials published 2009 to 2016.

Author	Country	Year	Number of patients receiving ICG	Procedure	dose	Pre-operative ICG dosing interval (1. as per methodology and 2. Achieved dosing interval)	Mode of admission
Zroback [63]	Canada	2016	12	Laparoscopic cholecystectomy (LC)	3.75mg	1. "pre-op" 2. n/a	Elective
Buchs [70]	USA	2013	23	Robotic single site cholecystectomy	2.5mg	1. "30-45min" pre-op. 2. n/a	Elective
Osayi [68]	USA	2015	82	LC	2.5mg	1. n/a 2. Mean 73.8±26.4m to incision	Elective
Tagaya [73]	Japan	2009	12	8 LC 4 open	2.5mg	1. 1-2 h pre-op 2. n/a	Elective
Boni [59]	Italy	2015	52	LC	0.4mg/kg	1. n/a 2. 15m prior to incision (range14±9m)	Acute & elective
Schols[74]	Netherlands	2013	15	LC	2.5mg	1. n/a 2. Mean 33m (range 19-67m) To 1st visualisation	Elective
Daskalaki [69]	USA	2014	184	Robotic LC (112 multiport & 72 single port)	2.5mg	1. 45m 2. n/a	Elective & acute
Spinoglio [75]	Italy	2013	45	Robotic single port	2.5mg	1. 45m 2. n/a	Elective
Igami [76]	Japan	2016	21	Single incision LC	2.5mg	1. n/a 2. 39m±4 (to 1st incision)	Elective
Ishizawa [77]	Japan	2011	7	Single incision LC	2.5mg	1. 2. 35 – 75m prior (to 1st visualisation)	Elective
Ishizawa [61]	Japan	2009	1	LC	2.5mg	1. 2 h "pre-operatively" 2. n/a	Elective
Kono [71]	Japan	2015	108	LC	2.5mg	1. n/a 2. Median 90m (range 15 -165m)	Elective & Acute
Ishizawa [78]	Japan	2010	52	LC	2.5mg	1. n/a 2. 110m mean (range 35 -165m) to 1st incision	Elective
Zarrinpar [64]	USA	2016	37	LC (13) open cholecystectomy (1) laparoscopic bile duct exploration (2) laparoscopic partial liver resection (6) open partial liver resection (11)	0.02 to 0.25mg/ kg range	1. n/a 2. 3 groups a)10m±3m, b) 45m±15m c) 3h±1h	Elective & acute

Abbreviations: LC: Laparoscopic Cholecystectomy; h: hour; m: minute

visualization [77,78]. To further compound the difficulties of using NIRFC in a population with endemic levels of obesity is the inflammatory process underling cholecystitis and gallstone pancreatitis. The characteristic development of pericholecystic inflammation and tissue oedema, leads to thickening of the gallbladder wall and inflammatory exudates in the surrounding tissues, which all increase the tissue density and depth between duct and camera detector. This is all likely to reduce the diagnostic yield of NIRFC in the obese and in those with the most severe acute biliary pathology who often demonstrate dense adhesions and pericholecystic inflammation. Recent experience at our centre has also found reduced efficacy in high BMI patients

and patients with acute cholecystitis. These cases are the most technically challenging to complete laparoscopically and would show greatest benefit from the adjuvant of NIFRC if it were able to penetrate tissue of this density consistently and show clear delineation of structures.

DISCUSSION

The consequences of BDI during laparoscopic cholecystectomy are catastrophic for the patient and surgeon involved. BDI must be considered preventable but rate remain stubbornly high even in the most experienced of HPB centers. The merits of routine IOC have been debated for nearly twenty years without any sign of a consensus being reached. The literature fails to support the argument for routine IOC and it must be remembered IOC is time consuming to perform, risks injury to the bile ducts and exposes theatre staff and patients to ionizing radiation. There is a clear need for an alternative method of Intraoperative extra hepatic bile duct mapping, a method that is dynamic, easier, quicker and safer to apply intraoperatively.

NIRFC with ICG during LC surgery is an extremely promising adjuvant to minimally invasive surgery and may help to reduce the feared BDI complications associated with LC surgery. ICG is safe, cheap and readily accessible in most hospitals; whilst commercially available NIR laparoscopic systems are now comparable in price to standard white light models.

Our limited experience of NIRFC in a straightforward case has been extremely positive. At our institution we have found the NIRFC technology to be a useful adjunct in elective LCs aiding bile duct mapping without increasing the operative length. Our only caution with NIRFC, is that predictions of NIRFC completing replacing traditional IOC may be premature, for NIRFC is unable in visualize the intrahepatic hepatic ducts or exclude intrahepatic cholelithiasis as IOC can. NIRFC is also limited in its tissue penetrance. With endemic levels of obesity in the Western world and IALC now the norm, surgeons are increasingly encountering difficult cases with dense pericholecystic tissue which is likely to challenge the depth of penetrance achieved with NIRFC.

CONCLUSION

NIRFC is extremely promising but still in its infancy, the technology needs more detailed exploration and evaluation. Currently, there is no consensus on the optimal dose or timing of ICG for NIFRC. Early series favored a single dose of 2.5mg whilst a weight adjusted dose is now more popular and may benefit an increasingly obese patient population. To truly test the hypothesis that NIFRC reduces BDI a large statistically powered international multicentre randomized control trial of NIRFC is required with the potential for meta-analysis a later date.

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