Assessment of the biliary tree

Buddingh, Karel Tim

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K. T. Buddingh

Assessment of the biliary tree

during gallbladder surgery

Stellingen

behorende bij het proefschrift 'Assessment of the biliary tree during gallbladder surgery' door K.T. Buddingh

1. Het intraoperatief cholangiogram wordt geacht te behoren tot het arsenaal van iedere chirurg.

2. Intraoperatieve cholangiografie dreigt in Nederland verloren te gaan als maatregel om galwegletsel te voorkómen en choledocholithiasis op te sporen. *(dit proefschrift)*

3. Implementatie van routinematige intraoperatieve cholangiografie leidde in een universitair medisch centrum tot een daling van het aantal galwegletsels en peri-operatieve ERCPs. *(dit proefschrift)*

4. De Kumar cannulatietechniek voor intraoperatieve cholangiografie is niet sneller en ook niet gemakkelijker dan de Olsen techniek. *(dit proefschrift)*

5. Het Best Practice Initiatief Laparoscopische Cholecystectomie heeft er toe geleid dat de 'critical view of safety' techniek door 98% van de Nederlandse chirurgen wordt gehanteerd. *(dit proefschrift)*

6. Statische beelden en teksten zijn suboptimaal om de biliaire anatomie voor medicolegale doeleinden vast te leggen. *(dit proefschrift en Wauben et al 2011)*

7. Alleen met een 'black box recorder', zoals die in de luchtvaart wordt gebruikt, kan maximale transparantie worden bereikt over wat zich afspeelt in de operatiekamer.

8. Perorale cholangioscopie heeft meerwaarde boven conventioneel onderzoek van onbegrepen galwegafwijkingen. *(dit proefschrift)*

9. Fluorescentiecholangiografie is een veelbelovende manier om de galboom peroperatief in beeld te brengen.

10. Gallbladder surgery is not exactly brain surgery. (vrij naar *That Mitchell and Webb look, Series 3, BBC Two*)

11. Het Soedanees gezegde 'yōm 'asal, yōm baṣal' (dagen van honing en dagen van uien) is van toepassing op het doen van wetenschappelijk onderzoek.

12. Zowel in het dagelijks leven als in wielerkoersen kan men beter in 'een treintje' zitten dan in 'de bus.'

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Promotor:	Prof. dr. R.J. Ploeg
Copromotores:	Dr. V.B. Nieuwenhuijs
	Dr. G.M. van Dam
Beoordelingscommissie:	Prof. dr. E.J. van der Jagt
	Prof. dr. R.J. Porte
	Prof. dr. L.P.S. Stassen

Paranimfen: Drs. Jeroen G. Veldhuis

Drs. Ben M. Bosma

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Chapter 1

Introduction, aim and outline of the thesis

Surgical removal of the gallbladder, or cholecystectomy, is one of the most frequently performed operations in the Western world. Important topics in gallbladder surgery are the prevention of bile duct injury (BDI) and the detection of common bile duct (CBD) stones. Intraoperative assessment of the biliary tree plays a crucial role in both of these issues.

A short history of gallbladder surgery

Although descriptions of both gallstones and biliary colics date from the first centuries AD, the causal link between the two was not established until 1609 AD by Johann Schenk[1]. Recent population-based studies reveal that gallstones are present in 5 to 25% of the population in the Western world, varying with risk factors as ethnicity, gender, and age[2-4]. A substantial proportion of these stones will at some point become symptomatic. This may present as uncomplicated gallstone disease (biliary colic), or complicated gallstone disease (choledocholithiasis, cholecystitis, cholangitis or pancreatitis). The latter group forms serious conditions with significant morbidity and mortality.

The mainstay of therapy for any form of symptomatic gallstone disease is surgical removal of the gallbladder. Carl August Langenbuch was the first to perform the procedure in 1882 (figure 1). Prior to this, removal of gallstones from the gallbladder (or cholecystostomy) had been reported as early as 1743[1]. To date, cholecystectomy is one of the most frequently performed operations in the western world, with 750,000 annual procedures in the United States[5] and 24'000 per year in the Netherlands[6].

An important development in gallbladder surgery was the advent of laparoscopy. Eric Muhe is recognized to have performed the first laparoscopic cholecystectomy in 1985[7]. There is quite some evidence that demonstrates a marked reduction in recovery time using the laparoscopic technique compared to the conventional open technique using a subcostal incision[8]. Hence, the 'lap chole' is currently used for more than 95% of cholecystectomies and has become an integral part of modern surgical practice.

Bile duct injury

The procedure of cholecystectomy includes transecting the cystic duct. Other parts of the biliary tree (i.e. the common bile duct (CBD) and the left and right hepatic ducts) are to be left intact. Injury of these ducts (bile duct injury, (BDI)) is a feared complication of cholecystectomy, and is as old as the procedure itself[9]. The BDI rate of traditional open cholecystectomy was around 0.2%. When laparoscopic technique was widely implemented in the nineties, a marked increase in the number of major BDI was noted to approximately 0.5%[10] (figure 2) .

Figure 1: Carl August Langenbuch (1846 – 1901)

Several classification systems for BDI have been proposed. The most straightforward system is that of the Amsterdam criteria[11]. This classification will be used throughout this thesis. In short, the Amsterdam criteria classify cystic stump leaks and leaks form accessory (Luschkan) bile ducts as type A. Common bile duct leakage, with or without stricture, is type B injury. Pure CBD strictures are classified as type C. Complete transections of the CBD or hepatic bile ducts are the most severe injuries and are classified as type D.

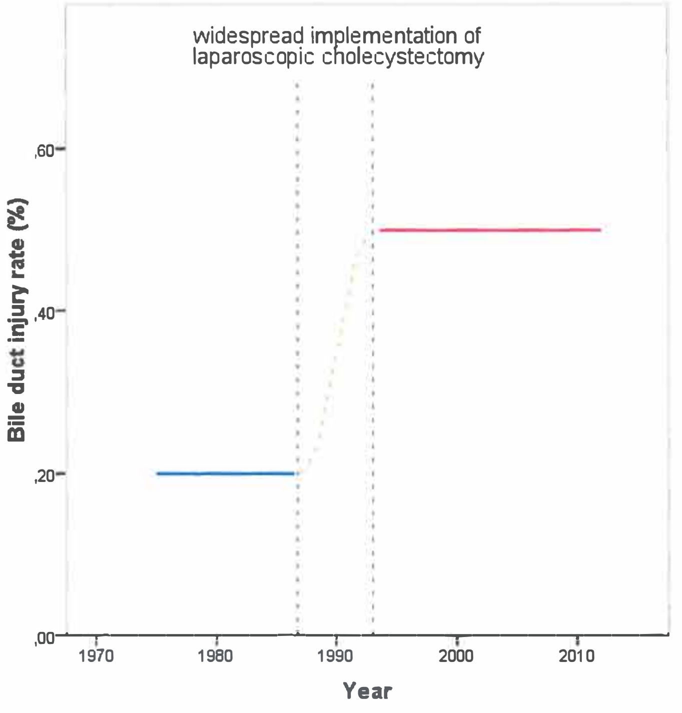

Figure 2: graphical representation of trends observed in the incidence of bile duct injury as laparoscopic cholecystectomy was introduced[10]

The thesis of Philip de Reuver (2008, University of Amsterdam) describes a large Dutch population of BDI patients referred to the Academic Medical Centre (Amsterdam). His work provides insight in the consequences for patients in terms of morbidity and necessary re-interventions using surgical, endoscopic or radiologic procedures[12]. He defines important parameters that deteriorate patient outcome, such as delay in referral to a specialist centre[13]. Patients with BDI retain poorer quality of life years after the event[14]. From time to time, BDI leads leads to malpractice litigation in the Netherlands[15]. Based on the number of patients referred with BDI it has been suggested that the incidence of BDI in the Netherlands is relatively high. The thesis of de Reuver does not assess the role of safety measures in the prevention of bile duct injury.

The severity of the injuries and the increased incidence of BDI in laparoscopic cholecystectomy have sparked renewed interest in safety measures to prevent BDI.

Intraoperative assessment of the biliary tree for prevention of bile duct injury

The main cause of major BDI (types B-D, involving CBD), is misperception of the biliary anatomy[16,17]. Factors that impede visual assessment and increase the risk of BDI include previous or ongoing inflammation[10,18,19], variation in ductal anatomy[20] and limited surgical experience[10,21]. Safety precautions are geared towards improving intraoperative assessment of biliary anatomy. The most frequently used safety precautions are the 'critical view of safety' (CVS) surgical approach, and intraoperative cholangiography (IOC). The CVS is a particular view of the operating field that must be obtained before clipping and transecting any structures. IOC is an imaging technique that consists of cannulating the cystic duct, injecting radiopaque contrast and obtaining x-ray images of the biliary tree. IOC demonstrates whether the cystic duct has been correctly identified, whether there are anatomic variations and whether there are gallstones in the CBD. Besides the CVS technique and IOC, several other safety interventions have been assessed in the past decades.

The low absolute risk of BDI poses a challenge assessing the efficacy of preventive measures. Sufficiently powered randomized controlled trials would need to include thousands of patients and such trials are almost impossible from a logistic point of view. The evidence for the different safety measures therefore consists mainly of retrospective population-based studies. One of the frequently heard criticisms on currently available studies is that these were performed in the era before completion of the global learning curve for laparoscopic cholecystectomy. Cohort studies investigating the prevention of bile duct injuries in the modern surgical era are therefore warranted.

Intraoperative assessment of the biliary tree for detection of common bile duct stones

Another purpose of intraoperative assessment of the biliary tree is the detection of concomitant CBD stones. CBD stones, if left untreated, may cause cholestasis, cholangitis and pancreatitis. There are different methods for detection of CBD stones. Preoperatively, several patient characteristics increase the odds of concomitant CBD stones. Age above 55 years, elevated bilirubin levels and a dilated CBD upon transabdominal ultrasound, especially, seem to predict the presence of CBD stones. Figure 3 demonstrates how low and high risk patients may be identified in this manner. Yet the algorithm provides only general guidance and limited sensitivity and specificity in most patients[22].

Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) are very accurate, but are quite expensive. Endoscopic retrograde cholangiopancreatography (ERCP) is also accurate and immediate treatment of CBD stones is possible. However, ERCP is associated with potentially hazardous complications such as post-ERCP pancreatitis and post-papillotomy hemorrhage. Therefore, ERCP is not recommended unless the presence of CBD stones is highly likely[22].

Intraoperative imaging by IOC is safe and accurate for detection of CBD stones. In skilled hands, stones may be extracted transcystically during the same procedure.

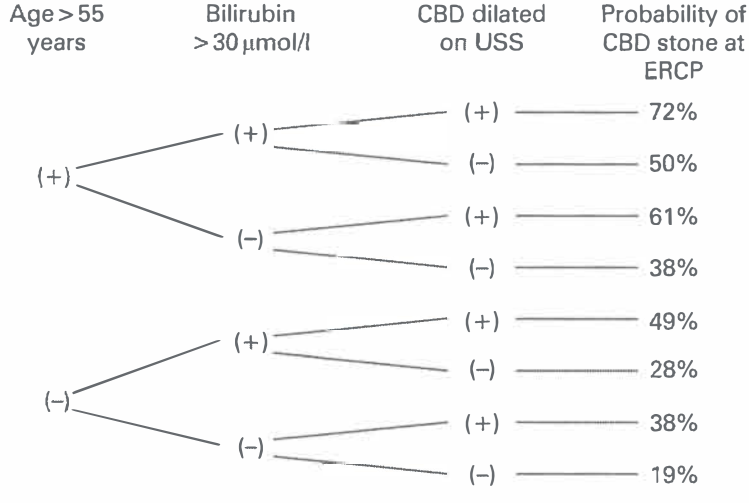

Figure 3: algorithm for prediction of common bile duct stones[22]

Medico-legal aspects of correct assessment of the biliary anatomy

Bile duct injury is a frequent reason for malpractice claims. In the United States, settlements and liability payments are often above 100,000 dollars)[23,24]. In the United Kingdom costs are slightly lower at an average of 54,000 pounds[25]. Although there is a limited tradition of medical claims in the Netherlands, BDI remains a recurring cause of malpractice complaints.

For this reason, as well as part of increasing transparency of surgical practice, explicit guidelines were issued by the Dutch Society of Surgery (Nederlandse Vereniging voor Heelkunde) regarding the documentation that the biliary anatomy had correctly been assessed.

The guidelines dating from 2007 specify that the CVS ought to be recorded in the operative notes. Furthermore, they suggest that the CVS is captured as a still image or a short videoclip. Besides images of the CVS, IOC also serves as documentation of correct assessment of biliary anatomy. There has been very little research exploring the value of the abovementioned methods for documentation of the biliary anatomy.

Assessing the endoluminal surface of the biliary tree

In the previous section, we have focused upon 'benign' conditions of the biliary tree: bile duct injury and common bile duct stones. In certain cases, however, the bile ducts need to be assessed because of suspected bile duct cancer (cholangiocarcinoma). This relatively infrequent cancer type has one of the least favourable prognoses of all gastrointestinal cancers[26]. Prognosis depends largely upon a radical surgical resection, and thus a timely diagnosis of the lesion.

Common investigations when a malignant lesion of the bile duct is suspected are CT-scan, MRCP, EUS and ERCP with brush cytology. However, in a proportion of patients the suspicion of cholangiocarcinoma persists despite negative conventional investigations. Peroral cholangioscopy is a technique by which the endoluminal surface of the biliary tree may be directly visualized. For this purpose, a thin endoscope is advanced from the duodenum through the papilla of Vater into the biliary tree. The technique has been around for a few decades but was always very unwieldy, requiring two experienced endoscopists and yielding mediocre images. The apparatus was expensive, fragile and high-maintenance. In the past few years, thinner flexible fibre endoscopes have been developed that allow for single-operator peroral cholangioscopy[27]. As a result, experience is growing with this diagnostic modality. Currently, the literature is still insufficient to determine the precise role of cholangioscopy in the work-up of patients with indeterminate bile duct lesions.

Novel technique for intraoperative assessment of the biliary tree

New experimental techniques are being developed for intraoperative visualization of bile ducts. One promising new modality is intraoperative fluorescence imaging. This technique is based upon the principle that fluorescent agents, when excited by a laser at a specific wavelength, subsequently release a light of a slightly longer wavelength. For visualization of bile ducts fluorescent agents may be administered directly into the biliary tract. Alternatively, if an agent is used that is excreted into the bile, it may be administered systemically (i.e. intravenously).

Light in the near-infrared spectrum (NIR, 750-1000nm) has the best properties for in vivo intraoperative imaging. Imaging at shorter wavelengths (400-750 nm) is impeded to some extent by autofluorescence of human tissue, lowering the signal-to-background ratio, and by poor penetrance of through human tissue at this wavelength. Light of longer wavelengths than NIR (i.e. 1000 nm-0.5 cm) is absorbed by water, and is thus unsuitable for in-vivo imaging. Also, scattering of the signal is minimal in NIR range.

There is currently one agent that is fluorescent in the NIR range that has been approved for use in clinical patients: indocyanine green (ICG). ICG is excreted in the bile and may therefore be administered directly in the biliary tract or intravenously for NIR fluorescence cholangiography[28].

Light in the NIR spectrum is not visible for the naked eye and needs to be detected by an intraoperative camera system. In collaboration with the Technical University Munich, such a camera system was developed for intraoperative use[29]. The system consists of a white light source for illumination of the surgical field, a laser beam for excitation of the fluorescent dye, dichroic mirrors which separate the signal into visible light, fluorescence and intrinsic fluorescence, and sensitive charge-coupled device (CCD) cameras which transfer the signal into a color image and a fluorescence image (figure 4).

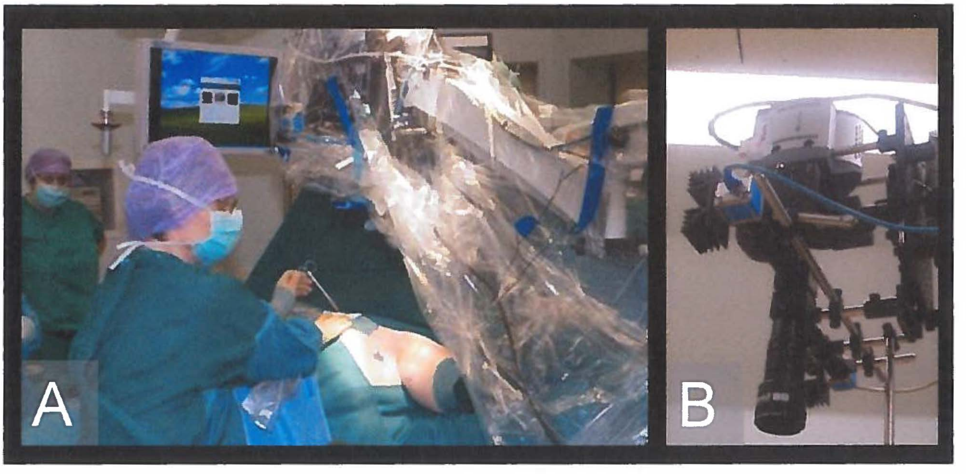

Figure 4: Intraoperative fluorescence camera (A) and close-up (B)

Aim and outline

From the previous section it is apparent that intraoperative assessment of the biliary tree remains an important issue in modern surgery. There is concern that the tradidtional technique of intraoperative cholangiography is no longer of value in the laparoscopic era. Innovative techniques for bile duct imaging are only just beginning to emerge. The goal of this thesis was to evaluate established and experimental techniques for intraoperative assessment of the biliary tree. The main outcome parameters that will be assessed are prevention of BDI, detection of CBD stones, documentation for medico-legal purposes and identification of malignant lesions of bile ducts.

We have attempted to carefully examine and analyse the currently available literature concerning the different techniques for bile duct imaging. Subsequently, we hypothesized that IOC is infrequently used in the Netherlands and assessed this with a nation-wide survey. We suspected that the bile duct injury rate at our own University Medical Centre had decreased after implementation of a routine IOC policy. This hypothesis was tested with a retrospective cohort study, which also examined whether the need for ERCP decreased as a result of this policy. In addition, we aimed to increase the speed and ease at which IOC is performed testing an alternative instrument for IOC. Where documentation of biliary anatomy is concerned, we felt that still photographs are probably not sufficient, and proposed that stored IOC images may be more adequate.

Moving from benign to malignant biliary disease and from the exterior of the bile ducts to the endoluminal surface, we aimed to assess the diagnostic accuracy of peroral cholangioscopy in patients with indeterminate biliary irregularites. We continue to describe the technique of intraoperative fluorescence imaging, a novel technique that may prove useful in delineating the biliary tree, both for benign conditions and malignant lesions.

Finally, the results of this thesis are summarized. Recommendations and possible future developments in patient safety during laparoscopic cholecystectomy are discussed. In the appendices, a few practical and theoretical aspects of gallbladder surgery are discussed in form of a number of submitted letters. This thesis concludes with a short tale with a light-hearted reference to the daily worries in clinical research.

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Chapter

2

Intraoperative assessment of biliary anatomy for prevention of bile duct injury: a review of current and future patient safety interventions

KT Buddingh, VB Nieuwenhuijs, L van Buuren, JBF Hulscher, JS de Jong, GM van Dam

ABSTRACT

Background: Bile duct injury (BDI) is a dreaded complication of cholecystectomy, often caused by misinterpretation of biliary anatomy. To prevent BDI, techniques have been developed for intraoperative assessment of biliary anatomy. This paper reviews the evidence for the different techniques and discusses their strengths and weaknesses in terms of efficacy, ease and cost-effectiveness.

Method: PubMed was searched from January 1980 through December 2009 for articles concerning bile duct visualization techniques for prevention of BDI during laparoscopic cholecystectomy.

Results: Nine techniques were identified. The critical view of safety approach, indirectly establishing biliary anatomy, is accepted by most guidelines and commentaries as the surgical technique of choice to minimize BDI risk. Intraoperative cholangiography is associated with lower BDI risk (OR 0.67, CI 0.61-0.75). However, it carries extra costs, prolongs the operative procedure and may be experienced as cumbersome. An established reliable alternative is laparoscopic ultrasound, but its long learning curve limits widespread implementation.

Easier to perform are cholecystocholangiography and dye cholangiography but these yield poor quality images. Light cholangiography, requiring retrograde insertion of an optical fibre into the common bile duct, is too unwieldy for routine use. Experimental techniques are passive infrared cholangiography, hyperspectral cholangiography and near-infrared fluorescence cholangiography. The latter two are performed non-invasively and provide real-time images. Quantitative data in patients is necessary to further evaluate these techniques.

Conclusions: The critical view of safety approach should be used during laparoscopic cholecystectomy. Intraoperative cholangiography or laparoscopic ultrasound is recommended to be performed routinely. Hyperspectral cholangiography and near-infrared fluorescence cholangiography are promising novel techniques to prevent BDI and thus increase patient safety.

INTRODUCTION

Cholecystectomy is one of the most frequently performed operations in the Western world, at over 750,000 yearly in the United States alone[1]. Bile duct injury (BDI) is a dreaded complication of cholecystectomy. When the laparoscopic technique was introduced in the early nineties an increase of BDI was noted from ~0.2% to ~0.5%[2].

The burden of BDI on patients is considerable. Re-interventions through surgical, endoscopic or radiologic procedures in specialist centers are frequently necessary[3-5]. BDI has a low but finite short and long term mortality rate[6,7]. A recent study reported that BDI had a significant negative effect on quality of life even ten years after the event[8]. BDI is also associated with substantial financial burden for the health care system: a British study calculated an average cost of 108,000 pounds (~175,000 dollars) for major BDI (hospital and society costs). In addition, BDI is a frequent ground for malpractice litigation[7,9,10].

During laparoscopic cholecystectomy the primary cause of BDI is an error of visual perception (in 71-97% of cases), and not insufficient technical skill of the surgeon[11,12]. Factors that impede visual assessment and increase the risk of BDI include past or ongoing inflammation, variant ductal anatomy and limited surgical experience[2,13].

To prevent BDI, systematic safety interventions have been developed to provide insight into the biliary anatomy during cholecystectomy. For such an intervention to be effective, firstly, it needs to be safe for patients and personnel. Secondly, it needs to be simple to use and easy to interpret as a wide range of surgeons and residents perform cholecystectomies. Thirdly, considering the large volume of cholecystectomies and the continuous pressure to keep health care expenditures under control, extra operating time, material expenses and personnel expenses need to be kept to a minimum.

This review aims to provide an overview of the different modalities for intraoperative assessment of biliary anatomy during cholecystectomy and discuss their strengths and weaknesses.

METHODS

The electronic database PubMed and Web of Science were searched from January 1980 through November 2010 for English language articles concerning techniques of intraoperative assessment of biliary anatomy for prevention of BDI. The following search terms were used: "bile duct injury", "cholecystectomy", "intraoperative cholangiography",

“cholangiography”, “bile duct visualization”, bile duct imaging and “bile duct mapping”. The reference lists of the selected articles were also searched.

To portray the protective effect of conventional intraoperative cholangiography (IOC) on BDI in a forest plot, all studies of more than 10,000 patients were selected that explicitly compared the incidence of BDI in (laparoscopic) cholecystectomy with IOC to that without IOC. Studies that only compared the routine use of IOC with selective use were not included in the forest plot. Microsoft Office Excel 2003 (Microsoft, Seattle, USA) and SPSS 16.0 for Windows (SPSS Inc, Chicago) were used for statistical analysis and to create the forest plot.

RESULTS

Critical view of safety (CVS)

Although CVS is not an imaging modality per se, the operative technique plays a major role in establishing the anatomical orientation of the bile ducts and therefore needs to be discussed in this review.

Already in 1995, Strasberg et al described the “critical view of safety” (CVS) approach[14]. Calot’s triangle is dissected to achieve the following. First, one third of the gallbladder must be dissected free from the liver bed. Second, the triangle of Calot must be cleared (with liver segment V visible through the window). Third, the cystic artery and cystic duct must be the only two tubular structures remaining between the gallbladder and the hepatoduodenal ligament. In some cases, the cystic artery is diathermically dissected close to the gallbladder, in which case only the cystic duct remains to form the CVS. It is not necessary or recommended that the CBD is visualized. In this manner, the bile duct remaining can be none other than the cystic duct.

Achievement of the CVS is recorded in the operation report, preferably augmented by laparoscopic video or photographic images[15]. Failure to achieve the CVS is an absolute indication for conversion or additional bile duct imaging.

Four series, totaling ~4,500 patients, have been published in which cholecystectomies have explicitly been performed using the CVS technique[16-19]}. All these series showed very low BDI rates (0-0.03%). A Japanese review article notes a decrease in self-reported BDI during laparoscopic cholecystectomy from 0.77% in 2005 to 0.58% in 2007 and suggests that the increased implementation of the CVS technique plays a role in this decrease[20]. Strasberg mentions the lack of level 1 evidence that the CVS prevents bile duct injury in his recent commentary[21].

Although undoubtedly a great step towards safer cholecystectomy, it is unclear whether the CVS alone is sufficient as a technique to minimize the risk of BDI. Our own data show occurrence of major BDI even after the CVS approach was adopted (manuscript under review). Also, major BDI continues to occur in the Netherlands despite increasing adoption of the CVS technique[4]. In spite of the lack of level 1 evidence, virtually all recent reviews, guidelines and commentaries advocate the CVS technique[22-24]. Without an eligible alternative, the CVS should be regarded the gold standard among *operative* techniques for assessment of biliary anatomy during laparoscopic cholecystectomy.

Intraoperative cholangiography

Intraoperative cholangiography (IOC) is the most frequently applied technique for intraoperative assessment of the biliary anatomy. After dissection in Calot's triangle, the surgeon identifies and cannulates the cystic duct at the junction with the gallbladder. Radiographic contrast is then injected into the cystic duct and (subtracted) X-ray fluoroscopy images are obtained. The advent of dynamic fluoroscopy has improved the speed with which IOC can be performed and yields series of high resolution images which more accurately depict the biliary anatomy[25,26]. IOC identifies whether the cannulated duct is indeed the cystic duct or mistakenly the CBD. In the latter case, the ductotomy may be repaired by inserting a T-tube and complete transsection of the CBD is prevented. IOC may also identify abnormal biliary anatomy such as an accessory cystic duct or an aberrant right hepatic duct. IOC allows early detection of BDI, in which case a blush of contrast originating from the biliary tract or clips placed over the common or hepatic bile ducts may be seen. Quoted success percentages are generally around or upwards of 90%[27,28]

It has been calculated that a sufficiently powered randomized controlled trial assessing the impact of IOC on BDI would need to include >30,000 patients[29]. As a result, the evidence for IOC in prevention of BDI consists mainly of population-based studies (Table 1).

Figure 1 shows a forest plot of the six largest population-based studies (each >10,000 patients)[30-35] that compare the incidence of BDI in cholecystectomies explicitly performed using IOC to that in cholecystectomies explicitly performed without IOC. From this meta-analysis, the OR for BDI when using IOC was 0.67 (0.61-0.75). When the studies were weighted according to actual size, rather than square root of the size, the OR was 0.60 (0.52-0.70). Although the strongest evidence available, these studies are prone to bias and confounders as they rely heavily on administrative data of heterogeneous groups. For example, in these studies IOCs that are performed only because BDI is already suspected or observed, are included in the 'IOC group'. For this reason, the number of BDIs occurring when IOC is used could be presented to be substantially higher than the true incidence.

Perhaps even more relevant than whether IOC in itself is useful, might be whether it should be performed routinely or selectively. Metcalfe et al[36] review eight retrospective series of laparoscopic cholecystectomies (totaling 6,024 patients) with routine IOC and nine series (3,268 patients) with selective IOC policy. In this underpowered study, the rates of complete CBD transsection were not significantly different, although a larger proportion of BDI was identified intraoperatively when routine IOC was used. Flum et al, in their analysis of 1.5 million patients found lower incidence of BDI in surgeons who used IOC routinely: 0.43% versus 0.51-0.54% ($p<0.001$)[31].

An important limitation of all the mentioned studies is that the cholecystectomies described mostly took place in the 1990's. During this era, the CVS technique was not yet widely implemented and therefore the studies can provide no information on the added value of IOC when the CVS technique is used. In our university hospital we retrospectively evaluated the implementation of a routine IOC policy in a population in which CVS was already the standard of care. We found 8/421 (1.9%) major BDI before implementation of routine IOC versus 0/435 cholecystectomies after implementation of routine IOC ($p = 0.004$) (personal data). Although the CVS was standard of care for all these patients, these data are limited in its retrospective nature.

In an editorial, Talamini rightly pointed out that if the association between IOC and BDI is accepted to be causal, this will "radically alter the current practice of cholecystectomy"[37].

Notwithstanding the association of IOC with lower BDI rates, it has several disadvantages which impede routine implementation. Cystic duct cannulation can be challenging, especially when it concerns a short, thin or brittle cystic duct and the reported extra time needed for IOC is 10 to 27 minutes[38-40]. Special attention should be paid to the learning curve of interpretation of IOC, as some studies report high proportions of incorrectly interpreted cholangiograms. For example, Way and colleagues demonstrated that 34/43(79%) routine

*Table 1: Evidence on the different modalities for intraoperative assessment of the biliary tree. LC = laparoscopic cholecystectomy; CVS = critical view of safety; BDI = bile duct injury; IOC = intraoperative cholangiography; LUS = laparoscopic ultrasound; CCC = cholecysto-cholangiography; NIRF-C = near-infrared fluorescence cholangiography; CBD = common bile duct; ICG = indocyanine green; OR = odds ratio; * includes dataset of Fletcher et al[84]; ** includes dataset of Krahenbuhl et al[85].*

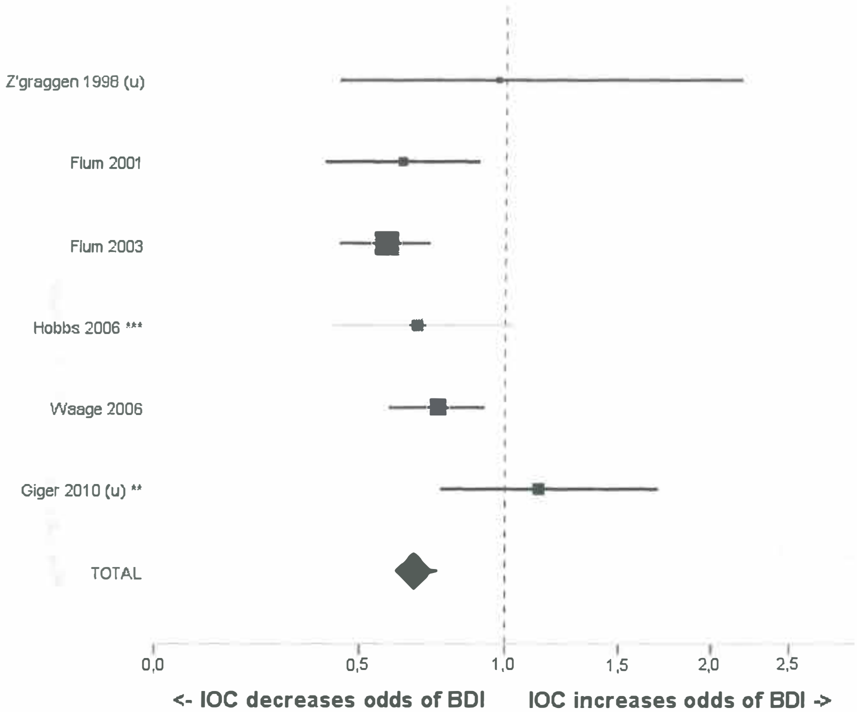
Primary author	No. of patients	Study description	Outcome
CVS – patient series of LCs using the CVS			
Rawlings [19]	54	All patients (suffering from biliary colic) underwent single port LC using the CVS technique.	CVS in all patients; 0 BDI, 0 bile leaks
Sanjay[18]	447	All patients (acute pathology) underwent LC using the CVS technique.	CVS achieved in 388 (87%); 0 BDI, 0 bile leaks
Avgerinos [16]	1,046	All patients underwent LC using the CVS technique.	CVS achieved in 998 (95%); 0 BDI, 5 bile leaks (0.5%)
Yegiyants [17]	3,046	Administrative data of an institution in which CVS was standard. Injuries requiring surgical repair were identified.	CVS percentage not assessed; 1 BDI (0.03%), bile leaks not assessed
IOC – studies >10,000 patients on the association between IOC and BDI			
Z'graggen [34]	10,174	'92-'95; Analysis of LCs in a prospective database for which numerous Swiss institutions provide data (SALTS).	OR for BDI using IOC = 0.97 (95%-CI 0.44-2.18), unadjusted for confounders
Flum[32]	30,630	'91-'98; Washington State Hospital Discharge Database searched for CBD repair codes <90 days after LC.	OR for BDI using IOC = 0.63 (95%-CI 0.40-0.90), adjusted for confounders
Hobbs[30] *	33,309	'88-'98; Western Australia Data Linkage System was searched in different ways for patients with complications. Medical files of these patients were assessed in detail.	OR for BDI using IOC = 0.68 (95%-CI 0.42-1.03), adjusted for confounders
Flum[31]	1,570,361	'92-'99; US Medicare data was searched for codes for CBD repair within one year after cholecystectomy.	OR for BDI using IOC = 0.58 (95%-CI 0.44-0.72), adjusted for confounders
Waage[33]	152,776	'87-'01; Swedish Inpatient Registry searched for codes for CBD repair within 1 year after cholecystectomy.	OR for BDI using IOC = 0.75 (95%-CI 0.59-0.92), adjusted for confounders
Giger[35] **	31,838	'95-'05; Analysis of LCs in a prospective database for which numerous Swiss institutions provide data (SALTS).	OR for BDI using IOC = 1.14 (95%-CI 0.76-1.70), unadjusted for confounders

Primary author	No. of patients	Study description	Outcome
LUS – patient studies on LUS during LC			
Machi[44]	2,159	Review of twelve studies (from before 1999) comparing LUS to IOC during LC.	Success of LUS and IOC 88-100%; BDI not assessed
Catheline[45]	600	All patients underwent LCs with LUS, 498 also underwent IOC.	LUS and IOC equal success; LUS faster; (10 vs 18 min, p=0.001) BDI not reported
Kimura[49]	183	All patients underwent LCs with LUS and IOC.	LUS success 95%; IOC success 96%; 0 BDI; 1 bile leak after choledochotomy
Tranter[54]	367	All Patients underwent LC with LUS.	LUS success 99%; BDI not reported
Biffl[46]	844	Non-randomized comparison between LC with LUS (n=248) and without LUS (594).	Without LUS: 11 BDI (1.9%); routine LUS: 0 BDI (p=0.04)
Catheline[47]	900	All patients underwent LCs with LUS and IOC.	LUS success 100%; IOC success 85%; BDI not reported
Tranter[55]	135	All patients underwent LCs with LUS and IOC.	LUS success 97%, IOC success 90%; BDI not reported
Onders[52]	256	Description of one surgeon's experience with LUS.	Increase in use of LUS from 29% in 2001 to 77% in 2004; 0 BDI
Machi[50]	200	All patients underwent LC with LUS.	LUS success in 97%; 0 BDI, 0 bile leaks
Perry[53]	236	All patients underwent LC with LUS.	LUS success in 95%; 0 BDI; 0 bile leaks
Hakamada[48]	644	Comparison of outcome before (n=368) and after (n=276) introduction of routine LUS.	Without LUS: 4 BDI (1.1%); routine LUS: 0 BDI (p=0.08)
Machi[51]	1,381	Prospective multicenter series of LC with LUS.	LUS success 98%; 0 BDI; 3 leaks (0.2%)

Primary author	No. of patients	Study description	Outcome
CCC – patient studies on CCC during LC			
Wills[58]	76	Randomized controlled trial between IOC (n=36) and CCC (n=40) during LC.	IOC success in 100%, CCC in 72% (p<0.001); CCC images of poor quality
Daoud[59]	325	Non-randomized comparison between IOC (n=35) and CCC (n=290).	IOC success 83%, CCC success 86%
Glattli[60]	69	Non-randomized comparison between IOC (n=38) and CCC (n=31).	IOC success 92%, CCC success 48%; CCC images of inferior quality
Fox[61]	113	All patients underwent LC with CCC.	CCC was successful in 81%
Koksal[62]	40	All patients underwent LC with CCC.	CCC was successful in 90%
Moont[63]	97	All patients underwent LC with CCC.	CCC was successful in 85%
Young[64]	194	All patients underwent LC with CCC.	CCC was successful in 81%
Holzman[65]	60	Patients underwent 'partial CCC' with the Kumar clamp.	Kumar CCC was successful in 83%
Kumar[66]	50	Patients underwent 'partial CCC' with the Kumar clamp.	Kumar CCC was successful in 98%
Dye cholangiography – patient series on dye cholangiography during LC			
Pertsem-lidis[67]	18	Indocyanine green (ICG) was intravenously administered to patients undergoing LC.	Cystic duct and CBD colored green in all patients. No images provided
Sari[68]	46	Blue dye was injected into the gallbladder during LC.	Cystic duct and CBD colored blue in 43/46 patients
Xu[69]	20	Blue dye was injected into the gallbladder during LC.	Extrahepatic bile ducts colored blue in 18/20 patients. No images provided
Light cholangiography – patient series			
Xu[69]	16	Optical fiber led into the CBD with a duodenoscope during LC. CBD cannulation successful in 13/16 patients.	CBD visualized in 13 cases, cystic duct only in 4 cases. No images provided

Primary author	No. of patients	Study description	Outcome
Passive infrared cholangiography – animal study			
Liu[70]	6 pigs	Room temperature saline was infused into the biliary tract. Images were taken with an infrared camera.	Infrared images correlated well with IOC. Artificial stones and BDI detected
Near-infrared cholangiography (NIRF-C) – patient studies on NIRF-C			
Mitsuhashi[73]	5	Open cholecystectomy after intravenous infusion of ICG. A NIRF camera system was used to capture images.	Fluorescence was observed in the liver, gallbladder and bile ducts of all patients
Ishizawa [71]	1	First laparoscopic experience with NIRF-C during cholecystectomy.	Fluorescence observed in cystic duct and CBD
Ishizawa [74]	10	Open cholecystectomy after intravenous infusion of ICG. A NIRF camera system was used to capture images.	Cystic duct and CBD were identified in 9/10 patients using NIRF-C
Aoki[75]	14	LC after intravenous administration of ICG.	CBD-cystic duct junction identified in 10/14 patients
Tagaya[76]	12	LC after intravenous ICG. Hepatoduodenal ligament was compressed with plastic device for improved exposure.	The CBD-cystic duct junction was identified in all patients
Ishizawa [86]	52	LC after intravenous ICG.	CBD-cystic duct junction identified in 50/52 patiens
Hyperspectral cholangiography – animal studies			
Zuzak[82]	1 pig	A laparoscopic near-infrared, hyperspectral imaging system was used to assess bile duct anatomy in a pig.	Bile ducts, arteries and veins all have unique reflectance spectra
Livingston [81]	8 pigs	Characteristics of different types of tissue were assessed using a laparoscopic hyperspectral imaging system.	Bile ducts, arteries and veins all have unique reflectance spectra

*Figure 1: Forest plot of protective effect of IOC on BDI during cholecystectomy[30-35]. OR = odds ratio, BDI = bile duct injury, IOC = intraoperative cholangiography. (u) unadjusted OR; ** the dataset of Fletcher et al[84] is included in the study by Hobbs et al[30].; *** the dataset of Krahenbuhl et al[85] is included in the study by Giger et al[35]. Studies were weighted by the square root of the study size. Results are plotted on a natural logarithmic scale.*



cholangiograms showing BDI were incorrectly interpreted[11]. The radiation received during IOC is only around 0.18 mSv and represents a <0.001% lifetime added risk of developing cancer[41]. Radiation exposure is therefore no argument against routine use of IOC in the adult population. Another advantage of IOC is that the learning curve is generally short: a success rate of 95% was reached in an institution of eight supervising surgeons after 46 [42]. Our own data, too, indicate a short learning curve: a success rate of 90% was reached in the first three months after implementation of routine IOC (personal data).

Whether routine IOC is cost-effective depends on the estimated cost of IOC, the reduction of BDI-rate and the cost of repair of BDI, patient death and malpractice litigation. Flum et al entered varying estimates into cost-effectiveness models and concluded that if the relationship between IOC and lower BDI is indeed causal, routine application of IOC is cost-effective[43].

In summary, there is a well-established relationship between IOC and lower incidence and increased early detection of BDI. It should be taken into account that these data are from before the CVS era, and might not be extrapolated. Also the sometimes cumbersome and time-consuming procedure limits the routine use of IOC in clinical practice.

Laparoscopic ultrasound

An alternative to radiography for intraoperative assessment of biliary anatomy is laparoscopic ultrasonography (LUS)47. Laparoscopic flexible multifrequency ultrasound transducers with a Doppler flow detection system visualize tissue 4 cm in length and 6 cm in depth. The extrahepatic bile ducts may be scanned in the transverse and longitudinal planes. LUS can identify the CBD, the bifurcation cystic duct-CBD, hepatic artery, portal vein, inferior vena cava, and ampulla.

In 1999 Machi et al reviewed 2,059 patients that underwent both LUS and IOC[44] finding success rates of over 90% for both modalities. In the subsequent years extra evidence has amassed on the value of LUS[45-55] (Table 1). Virtually all these studies report success rates of more than 95%, comparable to or higher than in IOC. The intrapancreatic and intrahepatic parts of the biliary system are not always accurately depicted. The time needed for LUS ranges between 5 and 10 minutes.

One retrospective cohort study achieved significance in the main endpoint of BDI: 11/594 without LUS versus 0/248 with LUS (p=0.04)[46]. A prospective multicentre cohort study by Machi et al reported no BDI and only three bile leaks in 1381 patients. The ability of LUS to detect BDI intraoperatively is limited to two studies in pigs, in which it successfully identified wrongfully placed clips and complete transsections[56,57].

All evidence shows excellent results of LUS in delineating biliary anatomy. The advantages of LUS over IOC are the shorter procedure time, the non-invasive nature and avoiding the use of radiation. Furthermore, it may be performed prior to dissection in Calot's triangle and repeated in uncertain cases. One of the main drawbacks of LUS is the reported long learning curve. Strangely, little data is available on this learning curve. Machi et al suggest that it takes 50-100 operations before one can successfully apply LUS[51]. Although no efficient technique should be discarded simply because it takes time to learn, this does pose a limitation for the widespread implementation of LUS.

Cholecystocholangiography

Cholecystocholangiography (CCC) is performed by injecting radiographic contrast directly into the gallbladder. An alternative instrument for "partial" CCC is the so-called 'Kumar clamp', which is placed across the base of the gallbladder, after which radiographic contrast is injected into Hartmann's pouch.

The only randomized controlled trial found a lower success rate of CCC compared to IOC (72% versus 100%, p=0,0005)[58]. Also, CCC yielded inferior image quality and a 2.3 times longer radiation exposure. In comparative studies, Daoud et al report comparable success rates for CCC and IOC[59] whilst Glattli et al found a very low success rate of 36% in CCC versus 90% in IOC[60]. Mostly, success rates in series of CCC vary between 72% and 90%[61-64]. CCC reduces operative time compared to IOC[58], times quoted as necessary for CCC are between 2 and 14 minutes[59,61,64]. The Kumar clamp for "partial" CCC was only used in two series, with success rates of 98% and 83%[65,66]. Abovementioned studies are further described in Table 1.

CCC is a simple technique with a steep learning curve[61], requires no cystic duct cannulation and is faster than IOC. However, the success rate is low (~80%), and even when successful, the image quality is often poor. Of extra concern is the report of hypotension and gallbladder perforation when the gallbladder is distended[58]. Based on these arguments CCC is not recommended as a standard procedure for cholangiography. An exception may be partial CCC using the Kumar clamp, as this instrument allows the injection of contrast under higher pressure and only needs to fill part of the gallbladder. However, this instrument has yet to prove its non-inferiority to standard IOC.

Dye cholangiography

Intravenous injection of high doses of indocyanine green (ICG) in patients undergoing LC has been reported to color the extrahepatic bile ducts dark blue for two hours[67]. Sari et al injected methylene blue directly into the gallbladder and were able to identify the gallbladder, cystic duct and CBD in 43/46 cases (93%)[68]. Xu et al[69] report a success rate of 90% (18/20) (see also Table 1).

Dye cholangiography has the advantage of visualizing the bile ducts prior to dissection. The technique is reasonably safe, although extravasation of the dye is not easily washed away and may obscure the view of the surgeon. The evidence for its effectiveness is limited. Xu et al indicate that the images obtained had a low resolution[69] None of the mentioned studies provide convincing images or quantitative data in support of dye cholangiography. From a technical perspective, dyes in the visible light spectrum (380 – 600 nm) may not exhibit the necessary penetration necessary for a successful cholangiography, especially when Calot's triangle is filled and surrounded by fatty tissue or fibrosis resulting from a surpassed inflammatory process. This presents a serious limitation, as it is in these particular cases that cholangiography has the greatest value.

Light cholangiography

Xu et al describe an experimental technique denominated as light cholangiography[69]. An optic fiber is endoscopically passed up through the papilla of Vater and illuminates the extrahepatic duct system. Unfortunately, no images are provided, limiting the readers' ability to judge it on its clear merits.

Even if shown to be effective, light cholangiography in this manner may find difficulties to be introduced as a routine procedure during laparoscopic cholecystectomy as it requires endoscopy with retrograde maneuvering of the optical fiber. Besides being time-consuming this procedure is potentially hazardous, considering the reported morbidity and mortality associated with ERCP.

Passive infrared cholangiography

Liu et al experimented with a passive infrared camera[70]. In nine pigs they infused room temperature saline or warm saline into the biliary tract, which contrasted with body temperature so that the biliary tract could be delineated (Figure 2). Also, artificially created BDI and stones could be identified with this technique.

This method, using the brilliantly simple principle of small temperature differences, bypasses the ionizing radiation of IOC and can therefore take place repeatedly and real-time. However, it only works by direct infusion into the biliary system, as intravenous infusion would result in regression to body temperature within seconds. Moreover, the temperature of the saline within the bile duct may regress along the procedure necessitating repetitive injections. Therefore, infrared cholangiography is regarded as suboptimal technique in the operating theatre.

Near-Infrared fluorescence cholangiography

In the past few years a new imaging modality has been tested for bile duct visualization: near-infrared fluorescence cholangiography (NIRF-C)[71]. This technique uses a laser to excite fluorescent agents and an imaging filter to register the light (of a slightly higher wavelength) which is subsequently emitted. Light in the NIRF spectrum (~800nm) has optimal penetration and minimal absorbance and scattering in human tissue. Fluorophores cleared by the liver, such as indocyanine green (ICG) and IRDye® 800CW (LI-COR Biosciences), may be administered intravenously or directly into the biliary system for imaging purposes.

After preliminary animal studies[72], NIRF-C was applied in a small number of patients since 2008 in open and laparoscopic (Figure 3) cholecystectomy[71,73-76]. Fluorescent signal was detected in the bile ducts of most patients but the images were not very clear and had with limited resolution. These studies are listed in Table 1. Figueiredo et al published high quality images of detection of BDI in a mouse model[77], although their relevance was limited through the absence of peri-ductal fat in the mouse.

Very recently, Ishizawa et al published a larger series of 52 patients in whom laparoscopic near-infrared fluorescence images were achieved of a higher resolution than in previous series[78]. Eight preoperatively diagnosed accessory bile ducts were also visualized by NIRF-C. Although the authors, in a letter to the editor, state that ICG is an excellent fluorophore, novel improved fluorophores will probably further increase the quality and the resolution of the images. This is necessary to decrease the potential for misinterpretation of the fluorescence images, which is vital for widespread implementation of safety measures.

A multispectral NIRF imaging system as recently described by Themelis et al[79] simultaneously acquires real-time color and NIRF images of the operative field. A possible draw back of fluorescence imaging is the limited penetration depth. However, up to three centimeters penetration through medium resembling human adipose tissue has been described[80], which is sufficient to visualize structures in Calot's triangle. NIRF-C is still in its experimental stage and images acquired are not as informative as IOC. However, properly developed using high quality cameras and bile-cleared fluorophores, NIRF-C has the potential to be a simple-to-perform, easy-to-interpret, radiation-free and personnel sparing bile duct visualization technique.

Hyperspectral cholangiography

The group of Livingston and Zuzak investigated the use of hyperspectral cholangiography in pigs[81,82]. This method relies on different absorption and reflection patterns of different tissue (not upon excitation and emission as in fluorescence). The authors differentiate between gallbladder tissue and vascular tissue in pigs with a sensitivity and specificity of 98%[81]. Also, they processed the data into images that delineate the cystic duct in the hepatoduodenal ligament (Figure 4)[82].

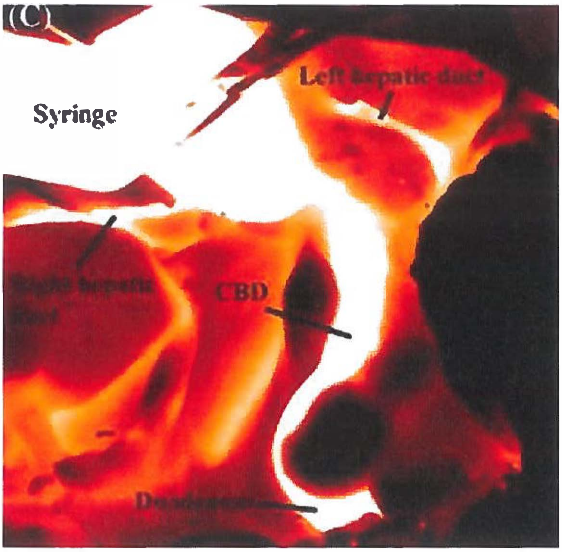
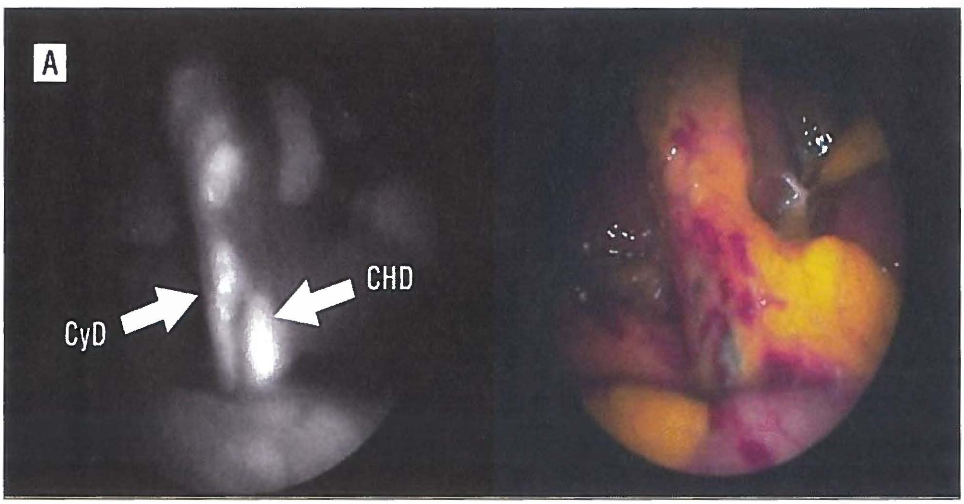


Figure 2: Passive infrared cholangiography in a porcine model depicting the common bile duct (CBD), left and right hepatic ducts and the duodenum[70]. With kind permission from Springer Science + Business Media, copyright © (2008).

Figure 3: Fig. 3 Near infrared fluorescen cholangiography during laparoscopic cholecystectom[86]. A Cystic duct running parallel to common hepatic duct, B isolation of cystic duct from anterior side of Calot's triangle, C isolation of cystic duct from posterior side of Calot's triangle, D closure of cystic duct (with kind permission from John Wiley and Sons Ltd 2010, all rights reserved).



Hyperspectral cholangiography is appealing as it requires no exogenous contrast agent at all. Preliminary studies in pigs may be misleading as the porcine biliary system is often less obscured by fibrosis than is the human system. Validation studies in humans will need to take place before hyperspectral cholangiography may be considered a potential modality for intraoperative visualization of bile ducts.

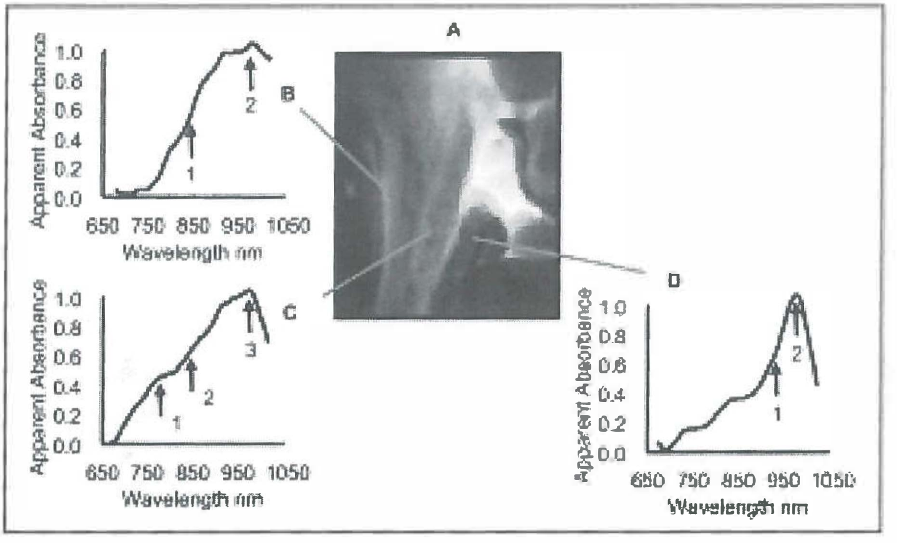


Figure 4: Hyperspectral cholangiography. Near infrared (NIR) laparoscopic hyperspectral image of the hepatoduodenal ligament in live anesthetized pigs (A). An artery indicated by spectra with broad oxyhemoglobin peak and a small water peak at 970 nm (B). A vein is identified by spectra containing a deoxyhemoglobin shoulder, a broad oxyhemoglobin peak and a small water peak (C). The common bile duct is associated with spectra containing a lipid shoulder and a prominent water peak (D)[82]. With kind permission from Elsevier Inc., copyright © (2008) Elsevier Limited.

DISCUSSION

This paper has provided an overview of the different modalities for intraoperative assessment of biliary anatomy, summarized in table 2. The CVS approach is considered the gold standard surgical technique to prevent BDI. As of yet, only a few series were found in which achievement of CVS was specifically appraised. Although these studies suggest protective effect of the CVS, future studies are necessary appraising the effect of the CVS technique on BDI. Without an eligible alternative, and based on worldwide consensus, the CVS should be regarded the gold standard among *operative* techniques for assessment of biliary anatomy during laparoscopic cholecystectomy.

Level 1 studies on conventional IOC have not been published (Oxford Centre for Evidence Based Medicine[83]), but the consistent large cohort studies warrant a grade B recommendation. Further research will need to show the added value of IOC as the CVS technique gains acceptance. The inherent disadvantages of IOC cannot be denied: sometimes technically challenging cystic duct cannulation, need for X-ray equipment, prolonged operation time and additional costs. Any developments in reducing these challenges, i.e. improvement in technology for the cannulation technique, would aid in increasing acceptance by the general surgeon of routine IOC during cholecystectomy. Also, an appropriate financial incentive to perform IOC needs to be provided by the healthcare insurance system to ensure regular use of this technique.

Many "outcome" studies (level 2c evidence[83]) support laparoscopic ultrasound (LUS) for prevention of BDI. The outcome is generally excellent, thus warranting grade B recommendation. It should be kept in mind that the reported studies were executed in dedicated centers with experienced surgeons. As a consequence, their results cannot be automatically extrapolated to general surgical practices worldwide. However, in trained hands, LUS is at least as effective as IOC in defining biliary anatomy, and does so in less time and radiation-free. Failure of LUS to achieve wider acceptance probably lies within the presumed long learning curve.

Cholecystocholangiography, dye cholangiography and light cholangiography may be dismissed as valid modalities for bile duct visualization. They either have too low a success rate, yield inferior images, or are too unwieldy for routine implementation. Passive infrared cholangiography may also prove too unpractical for large scale utilization.

The most promising novel developments in the field of bile duct visualization are NIRF-C and hyperspectral cholangiography. The main points to be proven in the future are whether they can provide sufficient anatomical resolution through the fatty fibrous tissue in Calot's triangle. With the development of more sensitive charge-coupled device camera systems and superior clinical-grade NIR-fluorophores, these imaging modalities may provide the ideal tool for intraoperative bile duct imaging.

Table 2: Summary of techniques and modalities for intraoperative visualization of bile ducts. BDI = bile duct injury. CBD = common bile duct.

Modality	Application	Evidence	Safety	Ease	Success rate	Time
Critical view of safety (CVS)	-	Worldwide consensus that the CVS technique is the golden standard for performing laparoscopic cholecystectomy, but limited evidence.	-	-	90-95%	-
Intraoperative cholangiography (IOC)	After dissection in Calot's triangle	Several very large retrospective datasets report association of IOC with lower rates of BDI.	Safe (Minimally invasive)	At times cumbersome	90-95%	15 min
Laparoscopic ultrasound (LUS)	Repetitively	One retrospective study reported lower rates of BDI with LUS compared to no imaging modality. Many prospective studies report higher success rates of LUS than of IOC.	Very safe (Non-invasive)	Requires considerable experience	>95%	5-10 min
Cholecysto-cholangiography (CCC)	Before dissection in Calot's triangle	One randomized controlled trial and several retrospective studies all show inferiority of images compared to IOC.	Reasonably safe (Possible added risk of gallbladder rupture)	Easy	~80%	5-10 min
Dye cholangiography	Real time	Several series describe visualizing the biliary tract but convincing images and quantitative data are lacking.	Reasonably safe (Risk of dye extravasation)	Easy	~90%	5-10 min
Light cholangiography	Real time	One series in patients is reported but no images are provided.	Potentially hazardous (Retrograde maneuvering of an optical fiber into CBD)	Requires endoscopy skills	Unknown	Unknown
Passive infrared cholangiography	Real time	One study in pigs yielding excellent images.	Safe (Minimally invasive)	Unknown	Unknown	Unknown
Near-Infrared fluorescence cholangio-graphy (NIRF-C)	Real time	Several animal studies yielding high quality images of the biliary tract and BDI. A few small studies in patients yielding images of limited quality. One study of 52 patients with fair results.	Safe (Non-invasive when intravenous agents are used)	Easy	Unknown	Unknown
Hyperspectral cholangiography	Real time	Two studies in pigs report positive differentiation between gallbladder tissue and blood vessel tissue.	Very safe (Non-invasive)	Easy	Unknown	Unknown

This review has focused solely on bile duct visualization for prevention and early detection of BDI. A second function of bile duct visualization is the detection of CBD stones during surgery. IOC and LUS are currently the only proven modalities for clinical purpose. Some surgeons assess for stones only if there are clinical symptoms of cholestasis or abnormal liver function tests indicative of cholestasis, in which case a routine bile duct visualization modality does not necessarily need to convey information on the presence of stones.

In summary, the search is still ongoing for an optimal bile technique for intraoperative assessment of biliary anatomy that is safe, easy-to-perform, simple-to-interpret, personnel-sparing, cheap and radiation-free. For now, we recommend that all surgeons should use the critical view of safety approach. Based on the available literature, intraoperative cholangiography or laparoscopic ultrasound of the biliary tree is recommended to be performed routinely (grade B recommendation). In the future, hyperspectral cholangiography and near-infrared fluorescence cholangiography may prove superior techniques for intraoperative visualization of the biliary anatomy.

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Chapter

3

Safety measures during cholecystectomy: results of a nationwide survey

KT Buddingh, HS Hofker, HO ten Cate Hoedemaker, GM van Dam, RJ Ploeg, VB Nieuwenhuijs

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ABSTRACT

Background: This study aimed to identify safety measures practiced by Dutch surgeons during laparoscopic cholecystectomy.

Method: An electronic questionnaire was sent to all members of the Dutch Society of Surgery with a registered e-mail address.

Results: The response rate was 40.4% and 453 responses were analyzed. The distribution of the respondents with regard to types of hospitals was similar to that in the general population of Dutch surgeons.

The CVS technique is used by 97.6% of the surgeons. It is documented by 92.6%, mostly in the operation report (80.0%), but often augmented by photography (42.7%) or video (30.2%). If the CVS is not obtained 50.9% convert to open approach, 39.1% continues laparoscopically and 10.0% performs additional imaging studies.

Of the Dutch surgeons, 53.2% never perform IOC, 41.3% perform it incidentally and only 2.6% of the surgeons perform it routinely.

A total of 105 BDI were reported in around 14387 cholecystectomies (0.73%). The self-reported major BDI rate (involving the common bile duct) was 0.13% but these figures need to be confirmed in other studies.

Conclusions: The CVS approach in laparoscopic cholecystectomy is embraced by virtually all Dutch surgeons. The course of action when CVS is not obtained varies. IOC seems to be an endangered skill as over half the Dutch surgeons never perform it and the rest performs it only incidentally.

INTRODUCTION

After laparoscopic cholecystectomy was introduced in the early nineties an increase in the number of bile duct injuries (BDI) was noted[1]. BDI has serious medical, financial and medico-legal consequences for patients and health care professionals[2-4]. Subsequently, additional patient safety interventions were implemented.

A major step towards safe cholecystectomy was the description of the 'critical view of safety' (CVS) technique by Strasberg in 1995[5]. The CVS technique is advocated by virtually all recent guidelines and expert commentaries[6-9]. The Dutch Society of Surgery issued a best practice guideline in 2005 endorsing the CVS technique[10]. According to the guideline, CVS is achieved once one third of the gallbladder is dissected off the liver, and the presumed cystic duct and artery are the only structures running from the gallbladder to the hepatoduodenal ligament. The guidelines were promoted through publication and presentation at national conferences; all Dutch surgeons are expected to follow them.

Another safety intervention is intraoperative cholangiography (IOC). Population-based analyses have shown a reduction in major BDI by 25 - 39% when IOC is performed[11-13]. The guidelines of the Dutch Society of Surgery currently do not recommend routine IOC.

It has been suggested that the incidence of BDI in the Netherlands is higher than in other countries[2]. Numerous papers have been published on preventive measures during cholecystectomy, but it remains unclear which safety measures are actually being employed by Dutch surgeons. This study aimed to identify practice as well as opinions on CVS technique and IOC.

METHODS

An electronic questionnaire was composed by a panel of five abdominal surgeons and a medical psychologist (Appendix A). The survey was completely anonymous. E-mail addresses were obtained of all members of the Dutch Society of Surgery, including surgical trainees The electronic questionnaire was sent to all addresses. Two weeks after the first e-mail, one reminder was sent. The study closed for recruitment two weeks later.

Hospitals in the Netherlands may be classified as 'university teaching' (tertiary referral, specialist training and medical research), 'non-university teaching' (general hospitals licensed to train surgical trainees) or 'non-teaching' (general hospitals that do not train surgical trainees). Once deemed sufficiently qualified, surgical trainees may perform cholecystectomies without supervision of a consultant present in operating theatre.

Statistical analysis was performed with SPPS 16.0 for Windows (SPPS Inc, Chicago, Illinois). Descriptive statistics were used to portray the responses. The accumulated number of cholecystectomies performed by groups of surgeons was calculated using the median of the self-reported range of cholecystectomies (i.e. 17 for the range 10-25). In case of >50 cholecystectomies per year, the arbitrarily chosen number of 60 was used. Chi-squared tests were used to compare the incidence of BDI in different groups. A $P < 0.05$ was considered significant.

RESULTS

The electronic survey was successfully delivered to 1206 addresses. There was a 40.4% (487/1206) response rate. Thirty-four surgeons indicated that they no longer performed cholecystectomies. Thus, 453 questionnaires were included for analysis.

Clinical profile

The clinical profile of the respondents is shown in table 1. Most respondents were abdominal or hepatobiliary surgeons (31.3%), surgeons of other subspecialties (28.9%) and surgical trainees (23.8%). The majority of respondents worked in non-university teaching hospitals (56.7%), followed by university hospitals (22.7%) and non-teaching hospitals (20.5%). This closely resembles the general distribution in the Netherlands[14]. The total number of estimated cholecystectomies in the last 12 months accumulated to approximately 14,387.

Operative technique

The CVS technique was used by 97.6% of the respondents (table 2). It was documented by 91.6%, usually in the operation notes. Photographs of the CVS were stored by 42.7% of surgeons and video images by 30.1%. If the CVS cannot be obtained, 50.9% opt for conversion to open surgery, 39.1% continue laparoscopically and 10.0% perform additional imaging studies.

Table 1. Clinical profile of the respondents.

	N
Differentiation	
Surgeon, abdominal or hepatobiliary	142 (31.3%)
Surgeon, other subspecialty	131 (28.9%)
General surgeon / Fellow	49 (15.9%)
Surgical trainee	108 (23.8%)
Type of hospital	
University hospital	103 (22.7%)
Teaching hospital	257 (56.7%)
Non-teaching hospital	91 (20.5%)
No of cholecystectomies in past 12 months	
< 10	60 (13.2%)
10 – 25	117 (25.8%)
26 – 50	194 (42.8%)
> 50	82 (18.1%)

Intraoperative imaging studies

More than half of the surgeons (53.2%) never perform IOC. The remaining group uses it incidentally (<5%). Only 2.6% of the surgeons perform IOC routinely, (>80% of cholecystectomies). Indications for IOC according to the surgeons were suspected BDI (53.0%), unclear anatomy (46.6%) and suspected common bile duct (CBD) stones (38.0%), as portrayed in table 3. Laparoscopic ultrasound was used by 2.1% of the surgeons.

Opinions on IOC

IOC was regarded as cumbersome by 39.0% of the surgeons (table 3). Most surgeons (77.5%) assume IOC to take 10 – 30 minutes. Around one third of the surgeons think IOC reduces the risk of major BDI, one third does not, and one third does not know. 92.9% of the surgeons feel that IOC should not be performed routinely..

Trainees

All trainees reported use of the CVS versus 96.8% of other surgeons (p=0.074). There were more trainees who never performed IOC than other surgeons (72.2% versus 47.2%, p=0.002 in linear-by-linear association).

Table 2. Operative technique and imaging

*CVS = critical view of safety; IOC = intraoperative cholangiography; CBD = common bile duct; BDI = bile duct injury; N/A = not applicable; * multiple answers were possible*

	N
CVS technique used	442 (97,6%)
CVS documented	
Yes	405 (91.6%)
No	37 (8.4%)
N/A	11
CVS documented by*	
Operation notes	324 (80.0%)
Photograph	173 (42.7%)
Video	122 (30.1%)
N/A	48
What course when CVS is not obtained	
Usually continue laparoscopically	165 (39.1%)
Usually convert to open	225 (50.9%)
Usually additional imaging studies	44 (10.0%)
N/A	11
IOC performed	
Never	241 (53.2%)
< 5%	187 (41.3%)
5 – 20%	8 (1.8%)
21 – 80%	5 (1.1%)
> 80%	12 (2.6%)
Indications for IOC*	
Routine	17 (3.8%)
Suspected CBD stones	172 (38.0%)
Unclear anatomy	211 (46.6%)
Suspected BDI	240 (53.0%)
Other	54 (11.9%)
Laparoscopic ultrasound performed	
Never	443 (97.8%)
< 5%	7 (1.5%)
5 – 20%	2 (0.4%)
21 – 80%	0
> 80%	1 (0.2%)
BDI in the past 12 months	
None	361 (79.7%)
1	79 (17.4%)
2	13 (2.9%)
>2	0
Types of BDI	
Cystic stump leak	53
Luschkan duct leak	28
CBD leak	9
CBD transsection	10
Other	5

Table 3. Opinions on IOC; IOC = intraoperative cholangiography; BDI = bile duct injury; IOC = intraoperative cholangiography

	N
Performing IOC is cumbersome	
Usually	74 (16.3%)
More often than not	103 (22.7%)
Sometimes	127 (28.0%)
Usually not	114 (25.2%)
Missing	35 (7.7%)
How long does IOC take	
< 10 minutes	30 (6.7%)
10 – 20 minutes	179 (39.5%)
20 – 30 minutes	170 (37.5%)
30 – 40 minutes	50 (11.0%)
> 40 minutes	24 (5.3%)
IOC reduces the risk of major BDI	
Yes	134 (29.6%)
No	153 (33.8%)
Don't know	136 (36.6%)
IOC should be performed routinely	
Not	421 (92.9%)
In all teaching hospitals	21 (4.6%)
In all hospitals	11 (2.4%)

Bile duct injuries

Of the respondents, 20.3% had experienced one ore more cases of BDI in the past 12 months. These injuries involved the cystic and Luschkan ducts (type A injuries according to the Amsterdam criteria[15]) in 77.2% of cases and the CBD (nine cases of type B and ten type D) in 18.1% (table 2). The self-reported BDI rate was 105/14,387 = 0.73%. The self-reported rate of major BDI (i.e. involving the CBD) was 19/14,387 = 0.13%.

The rate of self-reported major BDI was not correlated with the level of training of the surgeon, the course of action if CVS could not be obtained or the use of IOC (table 4). There was a non-signicant lower rate of major BDI in university hospitals ($p = 0.098$) and higher rate in surgeons who perform <10 cholecystectomies per year ($p = 0.082$). These figures are based upon self-reporting and were not corrected for the indication for the cholecystectomy, i.e. cholecystitis or biliary colic.

Table 4. Factors associated with major BDI (i.e. involving the CBD)

** calculated by multiplying the number of surgeons by the median of the reported range of cholecystectomies performed yearly, and by 60 for those who reported to perform more than 50 per year; † these constituted nine type B injuries and ten type D injuries(15); ‡ for the surgeons who indicated to use the CVS technique; BDI = bile duct injury; IOC = intraoperative cholangiography; CVS = critical view of safety*

	No. of surgeons	**Accumulated no. of cholecystectomies***	**Major BDI†**	**p**
Differentiation				0.621
Abdominal/HPB surgeon,	142	5267	6 (0.11%)	
Other subspecialty	131	3786	7 (0.18%)	
General surgeon / fellow	49	2580	4 (0.16%)	
Surgical trainee	108	2754	2 (0.07%)	
Type of hospital				0.098
University teaching	103	2005	0	
Non-university teaching	257	8679	11 (0.13%)	
Non-teaching	91	3703	8 (0.22%)	
No of cholecystectomies in past 12 months				0.082
< 10	60	300	2 (0.67%)	
10 – 25	117	1989	2 (0.10%)	
26 – 50	194	7178	9 (0.13%)	
> 50	82	4920	6 (0.12%)	
What course when CVS is not obtained‡				0.350
Usually continue laparoscopically	165	5139	8 (0.16%)	
Usually convert to open	225	7291	11 (0.15%)	
Usually additional imaging	44	1369	0	
IOC performed				0.505
Never	241	7495	12 (0.16%)	
< 5%	187	6342	6 (0.09%)	
5 – 20%	8	218	1 (0.46%)	
21 – 80%	5	136	0	
> 80%	12	196	0	

DISCUSSION

The current study is an inventory of safety measures during cholecystectomy in a broad population of general surgeons and trainees in the Netherlands. The response rate was fair with 40.4%, allowing a comparison with a similar survey in the United States[16] and a survey among British and Irish upper GI surgeons[17]. The distribution of the respondents with regard to types of hospitals resembled the general distribution in the Netherlands. The self-reported number of cholecystectomies performed yearly represents about 60% of the 24,000 performed yearly[18]. The survey therefore provides a reliable representation of the general Dutch practice.

The critical view of safety (CVS) was found to be widely accepted in Dutch practice: 97.6% of the respondents use this technique. Reviewing 13 Dutch cholecystectomy protocols in 2008, Wauben et al found that only one of them explicitly incorporated the use of CVS[19]. It seems that although protocols need to be updated in some hospitals, the CVS is widely accepted in the Netherlands as the gold standard. The implementation of the most important safety measure to prevent bile duct injury (BDI) can thus be considered highly successful, and is praiseworthy. In a similar survey by Sanjay et al, 82% of the British and Irish upper GI surgeons advocated the CVS technique[17]. It is unknown how often this technique is actually practiced by British general surgeons or how well institutionalized the CVS technique is in other countries.

Documentation of CVS in the operation notes is done by 80.0% of surgeons, and augmented by a majority by video or photographs. The course of action when CVS is not obtained varies. Although the nature of the question does not address some of the nuances in difficult cholecystectomies, a divergent strategic approach of the surgeons is illustrated. Timely conversion in case of uncertain anatomy is seen by many surgeons as an important safety measure. However, as the open approach is increasingly reserved for "difficult cases" and the experience with the open technique diminishes, there are increasing reports of BDI occurring *after* conversion[20;21]. Depending on the experience of the surgeon, other alternatives such as laparoscopic subtotal cholecystectomy may in some cases be safer than conversion. In a Dutch series of 1509 patients, experienced laparoscopic surgeons were four times less likely to convert than less experienced laparoscopy surgeons (3.6% versus 15.6%)[22]. Conversion rates in the Netherlands vary; up to 18% has been reported[23]. These papers, like most, do not assess whether CVS was achieved.

Intraoperative cholangiography (IOC) is very seldomly performed in the Netherlands; 53.1% of surgeons never use it and 41.3% perform it incidentally (<5% of cholecystectomies). This contrasts with the practice in the United States and the United Kingdom, where over 25% of surgeons routinely perform IOC and there are few surgeons who never apply it[16;17]. In Australia IOC is performed in over 60% of cholecystectomies[12]. Despite the fact that many Dutch surgeons feel that suspected CBD stones, unclear anatomy and suspected bile duct injury (BDI) are indications for IOC, in clinical practice they only rarely apply it.

Around one third of the surgeons believe that IOC reduces the risk of BDI, one third did not and one third indicated that they did not know. Opinions were divided on whether IOC is a cumbersome procedure and how much time it consumes. The great majority of surgeons (93%) believe that IOC should not be routinely practiced. This is remarkable as many of these surgeons believed that IOC reduces the risk of BDI. Apparently, the arguments against routine IOC are thought to outweigh the benefits. Additionally, Dutch insurance companies currently do not reimburse the surgeon for performing IOC. The guidelines currently do not advise selective or routine IOC, and this is reflected in the daily practice of Dutch surgeons. Although the discussion on whether to perform IOC routinely or selectively is far from closed, it seems undesirable that surgeons would lose the skill of IOC altogether. We advocate a low threshold for IOC, especially in complicated biliary disease such as cholangitis and pancreatitis, and certainly in cases of unclear anatomy. An attitude change may be necessary in order for Dutch surgeons to apply IOC more frequently as an investment in patient safety.

The self-reported major BDI rate (i.e. involving the CBD) of 0.13%. This is much lower than the figures mentioned in literature and similar to the rate observed before the laparoscopic era[11;24]. Caution is necessary interpreting these figures as a survey such as this is not the optimal tool to assess the occurrence of complications. No evidence could be found in the literature on the validity of self-reported complications by surgeons. Further research is needed to confirm this low complication rate The most important limitation of this study is that it relies on self-reporting. It cannot be confirmed that the surgeons use the techniques that they report to use, and to what extent. However, the results are certainly of interest as they reflect opinions on and the acceptance of safety measures during cholecystectomy.

In summary, our survey provides insight into safety precautions taken by Dutch surgeons to prevent BDI during cholecystectomy. The CVS approach is embraced by virtually all Dutch surgeons. When CVS is not obtained, differnet approach are used with half of the surgeons choosing to convert. IOC seems to be an endangered skill as over half the Dutch surgeons never performs it, and the rest only does so incidentally. Although one may argue as to whether IOC should be performed routinely or selectively, it seems an undesirable development that surgeons would loose the skill of IOC altogether.

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Surgeon survey (translated from Dutch)

Part A: Profile

1. What is your differentiation?
   a. Abdominal or hepatobiliary surgeon
   b. Otherwise differentiated surgeon
   c. General surgeon
   d. Fellow
   e. Surgical trainee
2. What type of hospital do you work in?
   a. University medical centre
   b. Teaching hospital
   c. Non-teaching hospital
3. How many cholecystectomies have you performed or supervised in the past 12 months?
   a. < 10
   b. 10-25
   c. 25-50
   d. > 50

Part B: Operative technique

4. Do you use the "Critical View of Safety" technique?
   a. Yes
   b. No
5. Do you document the "Critical View of Safety"?
   a. Yes
   b. No
   c. Not applicable
6. How do you usually register the "Critical View of Safety"? (Multiple answers possible)
   a. Not
   b. Operation report
   c. Photograph
   d. Video
7. What do you do when you cannot achieve the "Critical View of Safety"?
   a. Usually continue laparoscopically
   b. Usually convert
   c. Usually perform additional imaging studies
8. How often do you perform intraoperative cholangiography during cholecystectomy?
   a. Never
   b. 1-5%
   c. 5-20%
   d. 20-80%
   e. > 80%
9. What are indications for you to perform intraoperative cholangiography?
   a. Routinely during every cholecystectomy

b. Suspected common bile duct stones
c. Unclear anatomy
d. Suspected bile duct injury
e. Othe

10. How often do you perform laparoscopic ultrasound for intraoperative visualization of bile ducts?
    a. Never
    b. 1-5%
    c. 5-20%
    d. 20-80%
    e. > 80%
11. How often, in the past 12 months, was one of your cholecystectomies complicated by bile duct injury?
    a. 0
    b. 1
    c. 2
    d. 3
    e. > 3
12. If there was a bile duct injury, what type was it?
    a. Cystic stump leakage
    b. Luschkan duct
    c. Common bile duct leakage
    d. Common bile duct transsection
    e. Other injuries

Part C: Opinions on intraoperative cholangiography

13. Performing intraoperative cholangiography is a cumbersome procedure
    a. Usually
    b. More often than not
    c. Sometimes
    d. Usually not
14. By how much time does intraoperative cholangiography prolong the procedure?
    a. 1-10 minutes
    b. 10-20 minutes
    c. 20-30 minutes
    d. 30-40 minutes
    e. >40 minutes
15. Intraoperative cholangiography reduces the risk of major bile duct injury.
    a. Agree
    b. Disagree
    c. Don't know
16. Intraoperative cholangiography should be performed routinely.
    a. Not
    b. In all teaching hospitals
    c. In all hospitals

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Chapter

4

Lower rate of major bile duct injury and increased intraoperative management of common bile duct stones after implementation of routine intraoperative cholangiography

KT Buddingh, RK Weersma, RAJ Savenije, GM van Dam, VB Nieuwenhuijs

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ABSTRACT

Background: Our university medical center is the only center in the Netherlands that has adopted a policy of routine IOC during cholecystectomy. This study aimed to describe the rate of bile duct injury (BDI) and the management of common bile duct (CBD) stones before and after implementation of a routine intraoperative cholangiography (IOC) policy.

Study design: Medical records were reviewed of all patients undergoing cholecystectomy in three years prior to implementation of routine IOC and three years thereafter. Dissection with the goal to achieve the critical view of safety was the standard operative technique during the entire study period.

Results: Four hundred and twenty-one patients underwent cholecystectomy with selective IOC, 435 patients with routine IOC. The groups were similar in age, gender, co-morbidity, indication for surgery and surgical approach. IOC was attempted in 5.9% in the selective IOC group and 59.8% in the routine IOC group (p<0.001).

The rate of major BDI was 1.9% in the selective IOC group and 0% in the routine IOC group (p=0.004). The injuries comprised five type B and three type D injuries according to the Amsterdam classification. The rate of minor BDI did not differ significantly between the groups.

More CBD stones were detected in the routine IOC group (4.8% versus 1.0%, p=0.001) and they were managed intraoperatively more frequently (2.8% versus 0.7%, p=0.023). There was a trend towards fewer preoperative and postoperative ERCPs and other interventions for CBD stones (19.1% versus 24.2%, p=0.067).

Conclusions: Implementation of routine IOC policy was followed by fewer major BDI and higher rates of intraoperative CBD stone management.

INTRODUCTION

Cholecystectomy is a frequently performed operation in the Western world, at over 750,000 per year in the United States alone[1] and over 20,000 per year in the Netherlands(2). A dreaded complication of cholecystectomy is iatrogenic bile duct injury (BDI) and an increase in the rate of BDI was noted after the introduction of laparoscopic cholecystectomy in the early nineties[3,4]. Previous studies have shown that BDI is a major health care problem in the Netherlands[3,5] and the incidence is believed to be higher than the 0.3% to 0.5% that is often described in literature[6].

To minimize the risk of BDI, careful dissection in the triangle of Calot is essential. Additionally, intraoperative cholangiography (IOC) may be performed. Performing IOC has been associated with significantly lower incidence of major BDI in large population-based studies[7,8]. It is also a prelude to intraoperative bile duct exploration, thus allowing a single stage procedure for the management of gallstones in the gallbladder and bile ducts. Whether to perform IOC selectively or routinely is still a matter of debate and practice varies between and within countries[9,10,4,11].

The Dutch Society of Surgery currently does not recommend routine IOC, stating that "the value of IOC with regards to identification of the anatomical structures and prevention of BDI is unclear"[12]. In spite of these guidelines our university medical center adopted a policy of routine IOC in 2007, to the best of our knowledge the first and only center in the Netherlands to do so. The aim of this study was to describe the outcome of cholecystectomies before and after the implementation of routine IOC in terms of (a) major bile duct injuries and (b) interventions for CBD stones.

METHODS

Setting

In the University Medical Center Groningen most cholecystectomies are performed by surgical trainees and are supervised by a consultant surgeon or fellow of the abdominal surgery unit. During the study period, the abdominal surgery unit comprised seven experienced abdominal surgeons. One consultant surgeon left the group and was replaced by a different surgeon who introduced the policy of routine intraoperative cholangiography (IOC). At any given time there were one or two fellows in the abdominal surgery unit, who spent either one or two years with the unit.

The 'Critical View of Safety' (CVS) technique as described by Strasberg et al[13], i.e. careful dissection in the triangle of Calot before clipping any tubular structures has been the standard operative technique for laparoscopic cholecystectomy in our center since 2003. This is several years before the Best Practice Guidelines were published in which the CVS was established as gold standard for all laparoscopic cholecystectomies in the Netherlands. If the CVS cannot be obtained, conversion is considered. Also, IOC may be performed at this stage to reach certainty about the biliary anatomy.

Selective or routine IOC

Before implementation of routine IOC in January 2007, IOC was performed selectively. Indications for selective IOC were liver function test abnormalities, dilated bile ducts upon abdominal ultrasonography and failed pre-operative endoscopic retrograde cholangiopancreatography (ERCP).

In 2007, all residents and consultant surgeons were trained to perform IOC. After completion of training in the skills lab, residents and consultant surgeons started to adopt the policy of routine IOC. Since the implementation of routine IOC, it is hospital policy to attempt IOC in all adult patients undergoing cholecystectomy except pregnant women. The policy of routine IOC was deliberately not strictly enforced upon surgeons at first. Instead, a period of gradual introduction allowed the surgical team to become familiar with the technique.

Generally, IOC is attempted when the CVS has been achieved, but in case of difficult dissection it may be performed at an earlier stage of the operation. IOC was by performed by cystic duct cannulation. The standard instrument used for IOC was the Olsen cholangiogram fixation clamp (Karl Storz Endoscopy-America, Inc., Culver City, CA) in combination with cholangiography catheters by Cook® Medical, Bloomington, IN. Images were obtained by dynamic fluoroscopy. No changes were made in operative technique during the study period, and no other major changes were made in the laparoscopy equipment.

Successful IOC was defined as passage of contrast into the CBD visualized during fluoroscopy. If intent to perform cholangiography was expressed in the operation report but a duct image was not obtained, cholangiography was classified as 'unsuccessful'. If no intent to perform cholangiography was expressed, cholangiography was classified as 'not attempted'.

Patients and data

Medical charts were retrospectively reviewed of all patients > 18 years old that underwent open or laparoscopic cholecystectomy between January 2004 and December 2009. The patients were divided into a selective IOC group (2004-2006) and a routine IOC group (2007-2009). Patients that underwent cholecystectomy as part of a different surgical procedure (i.e. hemihepatectomy or pancreaticoduodenectomy) were not included. Also, patients in whom a choledochotomy was planned beforehand were not included. The following data was extracted from the medical records: epidemiologic characteristics, American Society for Anesthesiology (ASA) score, indication for surgery, whether IOC was attempted and successful, and perioperative complications. Also, data was collected on the preoperative, intraoperative and postoperative management of CBD stones. Patients' medical records were reviewed after July 2010 so that at least six months of follow-up was available for all patients.

Bile duct injury

Bile duct injuries were classified according to the Amsterdam criteria(14). In short, cystic stump leaks and leaks of accessory branches of the right hepatic duct or Luschkan ducts are type A injuries. Type B injuries comprise common bile duct (CBD) leaks with or without strictures. Type C injuries are biliary strictures without leakage and type D injuries are complete transsections of the common or hepatic bile ducts. Injuries of type B, C and D were considered major BDI, type A injuries were regarded as minor BDI. Bile duct injuries were registered if they were confirmed by re-operation, bile duct imaging or prolonged drain output of fluid with a high bilirubin content (> 3 times serum bilirubin).

Management of CBD stones

Intraoperative management of CBD stones was classified as 'milking' (massaging the stone to the cystic duct and thus extraction), 'flushing' (detection of a CBD-stone which is subsequently flushed into the duodenum) and common bile duct exploration (CBDE). CBDE comprises transcystic exploration of the CBD or choledochotomy.

Perioperative management of CBD stones included preoperative ERCP (up to six months before cholecystectomy), postoperative ERCP (up to six months after cholecystectomy) and re-operation with CBDE (also up to six months after cholecystectomy). Postoperative ERCP for treatment of BDI rather than for suspected stones was not included in the analysis of perioperative management of CBD stones.

Statistical analysis

Statistical analysis was performed with SPPS 16.0 for Windows (SPPS Inc, Chicago, Illinois). Two-sided tests were used to compare patients in the selective IOC group (2004-2006) to patients in routine IOC group (2007-2009). The Pearsson chi-square test was used to compare proportions where all values in the table were >5. The Fisher Exact test was used to compare proportions where one or more values in the table were <5. The independent Student's t-test was used to compare the mean age and mean operating time between groups. The Mann-Whiney U test was used to compare the ASA-scores between groups. The Wilcoxon signed ranks test was used to compare the median time till postoperative ERCP for remnant stones between the two groups. A p-value < 0.05 was considered significant.

RESULTS

Patients

A total of 835 patients were identified; 421 patients underwent cholecystectomy between 2004 and 2006 (selective intraoperative cholangiography (IOC)) and 435 patients underwent cholecystectomy between 2007 and 2009 (routine IOC). The two groups are portrayed in Table 1. Patients in both groups were similar in age, gender and ASA-score. The indication for cholecystectomy was uncomplicated cholecystolithiasis in just over half of the patients in both groups. The remaining patients had complicated biliary disease including cholecystitis, choledocholithiasis and pancreatitis. In both groups the procedure was started laparoscopically in around 90% of patients. IOC was attempted in 5.9% of the patients in the selective IOC group and in 59.8% of the patients in the routine IOC group ($p < 0.001$). The proportion of patients in which IOC was attempted increased gradually from 38.1% in the first six months after implementation to 76.8% in the second half of 2009.

The outcome of the cholecystectomies in terms of perioperative complications is shown in Table 2. The conversion rate was 15.0% in the selective IOC group and 16.7% in the routine IOC group ($p = 0.527$). The complication rate was 15.9% using selective IOC and 13.3% using routine IOC ($p = 0.285$). The distribution of surgical and non-surgical complications was similar in both groups. There were no IOC-related complications

Table 1: Baseline characteristics of patients in the selective and the routine IOC group

** p < 0.05; † i.e. cholecystitis, choledocholithiasis, pancreatitis; SD = standard deviation; IOC = intraoperative cholangiography;;*

	Selective IOC (2004-2006) n = 421	Routine IOC (2007-2009) n = 435	P
Age (mean ± SD in years)	53±16	53±17	0.930
Female gender	271 (64.4%)	278 (63.9%)	0.888
Median ASA-score (range)	2 (1-5)	2 (1-4)	0.903
Complicated biliary disease†	181 (43.0%)	214 (49.2%)	0.069
Laparoscopic intent	379 (90.0%)	389 (89.4%)	0.773
IOC attempted	25 (5.9%)	260 (59.8%)	**<0.001***
Operating time (mean ± SD in minutes)	100±47	110±44	**0.001***

Bile duct injury

The rate of major bile duct injury (BDI) was significantly lower after implementation of routine IOC (1.9% versus 0%, p = 0.004). The characteristics and management of the major bile duct injuries are shown in Table 3. In the selective IOC group there were three type D injuries and five type B injuries. The type D injuries were all managed during primary surgery by hepatojejunostomy or choledochojejunostomy. Four type B injuries were managed during primary surgery, the fifth required re-operation. There was no mortality in this group of patients

The cholecystectomies in the eight patients with major BDI were supervised by seven different surgeons. Therefore, apart from one surgeon who experienced two injuries, there was no clustering of major BDI per surgeon. There were no cases of accidental CBD cannulation for which placement of a T-tube was necessary.

The rate of minor BDI was not significantly different after implementation of routine IOC. In total there were six cystic stump leaks, nine Luschkan duct leaks and three bile leaks of unknown origin or from the gallbladder bed. Most cases of minor BDI (16/18) were detected postoperatively. Of the BDI that was detected postoperatively seven patients required re-operation (mainly drainage of biloma), seven could be managed by ERCP with stent and two patients were managed conservatively. One of the patients with minor BDI died as a result of intestinal ischemia.

Table 2: Complications and bile duct injuries before and after introduction of routine intraoperative cholangiography

** p < 0.05; ‡ Amsterdam classification; IOC = intraoperative cholangiography;*

	Selective IOC (2004-2006) n = 421	**Routine IOC (2007-2009) n = 435**	**p**
Conversion to open	57 (15.0%)	65 (16.7%)	0.527
Complications			
Surgical complications	29 (6.7%)	27 (6.2%)	0.687
Other complications	31 (7.4%)	32 (7.4%)	0.997
Total complications	67 (15.9%)	58 (13.3%)	0.285
Bile duct injury			
Major leaks and injuries (type B-D‡)	8 (1.9%)	0 (0%)	**0.004***
Minor bile leaks (type A‡)	7 (1.7%)	11 (2.5%)	0.377
Total	15 (3.6%)	11 (2.5%)	0.378

Management of CBD stones

The detection and management of common bile duct (CBD) stones is shown in Table 4. CBD stones were detected intraoperatively in four patients (1.0%) using selective IOC versus 21 patients (4.8%) using routine IOC (p = 0.001). Successful intraoperative management of CBD stones took place in three patients (0.7%) in the selective IOC group versus twelve patients (2.8%) in the routine IOC group (p = 0.026).

The number of patients that underwent preoperative ERCP was 95 (22.6%) in the selective IOC group versus 72 (16.6%) in the routine group (p = 0.026). The number of postoperative ERCPs (excluding ERCP for BDI) and secondary CBD exploration was not significantly different between the two groups 11 (2.6%) versus 18 (4.1%, p = 0.218). There was a trend towards fewer total perioperative interventions for CBD stones in the routine IOC group: 102 (24.2%) versus 83 (19.1%, p = 0.067).

Also, the time between the cholecystectomy and the postoperative ERCP was shorter in the routine IOC group: median 6 days versus 42 days (p = 0.044).

Table 3 - Detection and management of major bile duct leaks and injuries

‡ Amsterdam classification; CBD = common bile duct; LHD = left hepatic duct;

RHD = right hepatic duct

Operative approach	Description	Type ‡	Detection	Treatment	IOC attempted
Primary laparoscopic, BDI after conversion	Near complete CBD transsection	D	Visual inspection during primary procedure	Primary reconstruction by choledocho-jejunostomy	No
Primary open	Near complete CBD transsection	D	Visual inspection during primary procedure	Primary reconstruction by hepaticojejunostomy	After BDI was noted
Primary laparoscopic, BDI after conversion	LHD transsection, aberrant anatomy of the RHD	D	Visual inspection during primary procedure	Primary reconstruction by choledocho-jejunostomy	After BDI was noted
Primary laparoscopic, BDI after conversion	CBD-leak	B	Visual inspection during primary procedure	Primary surgical repair by suturing the CBD	No
Laparoscopic	CBD-leak close to the confluence of cystic duct and CBD	B	Postoperative detection	Secondary surgical drain placement and endoscopic stenting	No
Primary laparoscopic, conversion after BDI	CBD-leak close to the confluence of cystic duct and CBD	B	Visual inspection during primary procedure	Primary surgical repair by suturing the CBD	After BDI was noted
Primary open	CBD-injury	B	Visual inspection during primary procedure	Primary surgical repair by suturing the CBD over a biliary splint	No
Primary laparoscopic, BDI after conversion	CBD-leak	B	Visual inspection during primary procedure	Primary surgical repair	No

Table 4: Management of common bile duct stones before and after introduction of routine intraoperative cholangiography

** indicates p < 0.05; IOC = intraoperative cholangiography; ERCP = endoscopic retrograde cholangiopancreatography; CBD = common bile duct; CBDE = common bile duct exploration*

	Selective IOC (2004-2006) n = 421	**Routine IOC (2007-2009) n = 435**	**p**
Intraoperative management of CBD stones			
Detection CBD stones	4 (1.0%)	21 (4.8%)	**0.001***
CBDE	1 (0.2%)	5 (1.1%)	0.110
'Flushing' or 'milking'	2 (0.5%)	7 (1.6%)	0.104
Total intraoperative interventions	3 (0.7%)	12 (2.8%)	**0.023***
Perioperative interventions for CBD stones			
Preoperative (< 6 months) ERCP	95 (22.6%)	72 (16.6%)	**0.026***
Postoperative (< 6 months) ERCP	11 (2.6%)	18 (4.1%)	0.218
Days to postop ERCP; median (range)	42 (2-161)	6 (1-176)	**0.044***
Secondary CBDE	2 (0.5%)	0 (0.0%)	0.150
Total perioperative interventions	102 (24.2%)	83 (19.1%)	0.067

Success rate and extra operating time for IOC

Selective IOC was attempted in 25 patients, routine IOC in 260 patients (Table 1). The success rates were 91.7% and 86.5% respectively (p = 0.475). The reasons for failure of IOC were inability to cannulate the cystic duct (18), a fragile cystic duct (5), a very short cystic duct (4), leakage of contrast agent (4) and other reasons (6). In the first three months after implementation of routine IOC, the success rate was 90%.

The mean time for cholecystectomy with routine IOC was 110 minutes versus 100 minutes with selective IOC (p<0.001). These times include anesthesia and positioning time. As IOC was performed in 60% of cases compared with 6%, the average of 10 minutes time difference needs to be multiplied by 1/0.54. This yields an estimated 19 minutes per patient to perform IOC. This time includes cystic duct cannulation time, waiting time for the radiographer, interpretation time and possible time spent on intraoperative interventions.

DISCUSSION

This study assessed the outcome of cholecystectomies before and after implementation of routine intraoperative cholangiography (IOC). In our university hospital a relatively large proportion of patients have complicated biliary disease such as cholecystitis, choledocholithiasis and pancreatitis. These patients are at higher a-priori risk of bile duct injury (BDI) and remnant common bile duct (CBD) stones[4,7]. Also, more of our patients have severe co-morbidity than in general hospitals. The relatively high conversion rate is influenced by a large proportion of patients with previous abdominal surgery. An attempt at laparoscopic access is almost always made, but conversion is frequently necessary in this patient category. After introduction of routine IOC a marked reduction in major BDI was noted, as well as increased intraoperative management of CBD stones.

Generally, IOC is very infrequently employed in Dutch hospitals. In the era of open cholecystectomy, routine IOC was widely practiced. In the mid nineties surgeons and surgical residents adopted the laparoscopic cholecystectomy but the practice of routine IOC was abandoned. Probable reasons for this were the improved accessibility to endoscopic retrograde cholangiopancreatography (ERCP) facilities and the perception that laparoscopic IOC is a cumbersome and time consuming procedure. The guidelines of the Dutch Association for Surgery dictate the use of the critical view of safety, but currently do not recommend routine IOC. Furthermore, IOC is currently not reimbursed by Dutch health insurance companies. The reluctance of surgeons in the Netherlands to adopt a policy of routine IOC has been noted and questioned before(15), but no center other than ours has come forward with a change of policy as a result of it.

The decision to adopt a policy of routine IOC is unique in the Netherlands. It was made to offer trainee surgeons the opportunity to become familiar with the technique, to reduce the incidence of BDI and to increase intraoperative detection of CBD stones. Trainees as well as supervising surgeons completed a skills lab training. The policy of routine IOC was deliberately not strictly enforced upon surgeons at first. Instead, a period of gradual introduction allowed the surgical team to become familiar with the technique. For this reason, the compliance with IOC was relatively low immediately following introduction. At this time, some surgeons did not perform IOC for cases in which the anatomy was very apparent and in whom the risk of CBD stones was very low. Other reasons for not performing IOC, in a minority of patients, were pregnancy or unavailability of the fluoroscopy equipment. Three years after implementation of the policy, the proportion of attempted IOC was up to 80%.

This study demonstrated a substantial decrease in major BDI after the introduction of routine IOC from 1.9% to 0% (p=0.004). In hindsight it is difficult to conclude whether IOC would have prevented these injuries but the reduction in major BDI is remarkable. IOC lowers the risk of major BDI in different ways. Firstly, IOC will reveal if the ductotomy for the cholangiocatheter was accidentally placed in the CBD instead of the cystic duct, thus preventing complete transsection of the CBD. Secondly, IOC will demonstrate any aberrant biliary anatomy that may predispose to BDI, such as a right hepatic bile duct or posterior segment duct originating from or close to the cystic duct. Thirdly, if the ductotomy is placed in close proximity of the CBD this will be noted by IOC and thus stricture or leakage from clips placed too close to the CBD (compromising the vasculature of the CBD or causing stricture of the CBD) are prevented. Fourthly, any BDI already present may be detected early by extravasation of radiographic contrast agent, or obliteration of a duct that has been accidentally clipped. Finally, at a higher level, routinely performing IOC provides the (trainee) surgeon with increasing insight into the diversity of the biliary anatomical variations, particularly if they are trained to regularly identify the segmental ducts on the right side.

Since the introduction of the laparoscopic approach, open cholecystectomy (primary or converted) is applied only in 'difficult' cases. The historically lower risk of BDI using the open approach does not apply to this select group. Also, recent reports show BDI occurring after conversion as a result of inexperience with the open approach[16,17]. In the current study, too, several cases of BDI occurred in primary open cholecystectomy or after conversion. It therefore seems justified that routine IOC should also be employed in these patients, as it was prior to the adoption of the laparoscopic approach.

A landmark study appealing for IOC to prevent BDI was that by Fletcher et al of over 19 000 patients undergoing cholecystectomy. The adjusted odds ratio of BDI when IOC was performed was 0.50 (95%-CI 0.35 - 0.70)[7]. Moreover, the protective effect of the IOC was of greater magnitude in the more complex cases. Other large population-based studies yielded similar relative risks[18,8,19].

In an editorial comment in the JAMA, Talamini stated that if the relationship between IOC and lower rate of BDI is indeed causal *"[...] it will radically alter the current practice of cholecystectomy, since the standard practice for surgeons is to not routinely perform an IOC during laparoscopic cholecystectomy. [...] Therefore, if a patient sustained a CBD injury and the surgeon had not performed a routine IOC this could be used as possible evidence of malpractice*[20]*."* Currently, BDI is a common ground for claims against hospitals and individual doctor throughout the Western world, although the frequency and the magnitude of the average compensation is highest in the United States[21,22,23].

Reports of a switch from selective IOC policy to a routine IOC policy are rare. One of these infrequent reports is the publication by Nickkholgh et al in 2006[24]. They compared 800 laparoscopic with selective IOC (in the period 1992-1996) to 1330 cholecystectomies with routine IOC (1996-2001) and found rates of CBD injury of 0.3% in the selective IOC group versus 0% in the routine IOC group ($p = 0.09$). The current study supports these findings and also suggests that the protective effect of IOC is correlated with the a-priori odds of major BDI.

In addition to preventing BDI, IOC also serves to detect CBD stones intraoperatively. CBD stones may be treated during the operation by simple techniques like 'flushing' or 'milking' the stones out of the CBD, or by CBDE, including choledochotomy or transcystic CBD exploration. If the expertise for such procedures is not present, intraoperative detection of remaining stones is an accurate method to select patients for postoperative ERCP[25,26]. However, it is desirable to keep the number of ERCPs as low as possible, as they are associated with discomfort for the patient, extra hospitalization time for the two-step procedure, and the infrequent but potentially grave complications of ERCP such as post-papillotomy hemorrhage and post-ERCP pancreatitis.

In the present study, CBD stones were detected in four patients (1.0%) using selective IOC and in 21 patients (4.8%) using routine IOC ($p = 0.001$). These figures are similar to those found by Nickkholgh et al[24]. More CBD stones were also managed intraoperatively. There was a trend towards fewer peri-operative interventions for CBD stones; especially caused by a lower number of preoperative ERCPs. This reduction was the result of a change in hospital policy on patients with suspected choledocholithiasis after implementation of routine IOC. Before 2007, preoperative ERCP was performed in most patients with symptomatic gallstones and elevated liver function tests. After 2007, symptomatic gallstone patients with moderately elevated liver function tests (serum bilirubin < 50 mmol/L) and without radiological signs of large CBD stones (>10 mm) were primarily operated by (laparoscopic) cholecystectomy with IOC, in accordance with the single step procedure advocated by Cushieri[27]. Furthermore, the current study demonstrates that the median time between surgery and post-operative ERCP was reduced after implementation of routine IOC (6 days versus 42 days, $p = 0.044$), indicating that the patients requiring ERCP could be identified earlier, possibly before they become symptomatic. As a result of surgeon interest in IOC, intraoperative CBD exploration plays an increasing (though still modest) role at our centre. It is anticipated that as surgeons become more comfortable with laparoscopic duct exploration, the number of perioperative interventions for CBD stones will decline further.

Complications associated with IOC are rare and were not seen in this cohort. The risk of an allergic reaction to contrast medium administered in the biliary tract is very small, even in patients who have previously had an allergic reaction to intravenous contrast medium[28]. IOC does not seem to be associated with postcholecystectomy pancreatitis.

This study is limited in its retrospective design. Also, IOC was not attempted in some patients after implementation of the routine policy. The fact that no BDI occurred in these particular cases may partly be attributed to the fact that these were often cases of very apparent biliary anatomy. The protective effect of IOC may be lower in such cases. As mentioned earlier, patients with complicated biliary disease and severe co-morbidity are overrepresented in this cohort, which may have enhanced the yield of intraoperative cholangiography in terms of prevention of BDI and presence of CBD stones. Assuming the population norm of around 0.5% BDI, thousands of patients would be necessary to demonstrate a similar reduction in risk. Furthermore, one may argue that the reduction in major BDI could have been caused by attentional bias towards identifying the biliary anatomy. In other words: not the IOC itself but the mere intention to perform IOC could result in a lower rate of major BDI. Even so, this would be an intentional and welcome attentional bias during cholecystectomy. Finally, a type 2 error cannot be completely excluded as a cause of the reduction in BDI.

Whereas studies of patients in the late nineties may still have been affected by the global learning curve of laparoscopic cholecystectomy, this cohort was operated on from 2004 onwards, well after completion of the learning curve. The current study assesses the value of routine IOC in the CVS era. Although we can not provide a definitive answer on the issue of routine IOC during laparoscopic cholecystectomy, our study illustrates that units who are concerned about a high BDI rate ought to consider implementing a routine IOC policy. The institutional learning curve for IOC is short. Special attention should be paid to the evaluation of the cholangiograms, as there have been concerns about misinterpretation[29,30]. The cost-effectiveness of routine IOC was not assessed in this study, but a previous study by Flum et al demonstrated in a number of models that if the relationship between routine IOC and lower rates of BDI is indeed causal, then routine IOC is cost-effective[31]. We recognize that we need to improve our own performance and aim to achieve 100% compliance with cholangiography. The results of this study have further motivated surgeons at our center to perform IOC during every cholecystectomy. In addition to the benefit of cholangiography described above, the importance of it becoming a routine part of the procedure is that the whole team expects it, is ready for it and can plan for it. If this is achieved, it fits smoothly into the operative routine and operative skills are enhanced.

Conclusion

This study demonstrates a marked reduction in major BDI following the implementation of routine IOC in a university medical center with an unacceptable major BDI rate. Even in the first few years after the policy change reaching only 60% compliancy with IOC, there were no more major BDI in our unit. Also, there was a trend towards fewer perioperative interventions for remnant CBD stones.

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Chapter

5

Kumar versus Olsen cannulation technique for intraoperative cholangiography: a randomized trial

KT Buddingh, BM Bosma, B Samaniego-Cameron, HO ten Cate Hoedemaker, HS Hofker, GM van Dam, RJ Ploeg, VB Nieuwenhuijs

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ABSTRACT

Background and aim: There is resistance to routine intraoperative cholangiography (IOC) during cholecystectomy because it prolongs surgery and may be experienced as cumbersome. An alternative instrument may help to reduce these drawbacks and lower the threshold for IOC. This trial compared the Kumar cannulation technique to the more commonly used Olsen clamp for IOC (KOALA trial; Dutch Trial Register NTR2582).

Methods: Patients undergoing elective laparoscopic cholecystectomy were randomized between IOC using the Kumar clamp and the Olsen clamp. Primary endpoints were the time that the IOC procedure took and its perceived ease as measured on a visual analogue scale from 0 (impossible) to 10 (effortless). To detect a difference of 33% in IOC time, a total sample size of 40 patients was required.

Results: Fifty-nine patients were randomized. Nine were excluded because of conversion to open cholecystectomy before the IOC procedure. Twenty-eight patients underwent IOC with the Kumar clamp and 22 with the Olsen clamp.

The success rate was 23/28 (82.1%) for the Kumar clamp and 19/22 (86.4%) for the Olsen clamp ($p > 0.999$). The mean IOC time was 10 min 27s ± 6 min 17s using the Kumar clamp and 11 min 34s ± 7 min 27s using the Olsen clamp ($p = 0.537$). Surgeons graded the ease of the Kumar clamp as 6.8 ± 2.7 and the Olsen clamp as 6.8 ± 2.1 ($p = 0.977$).

Conclusion: IOC using the Kumar clamp was neither faster nor easier than using the Olsen clamp. Both clamps facilitated IOC in just over ten minutes. Individual surgeon preference should dictate which clamp is used.

INTRODUCTION

Surgical removal of the gall bladder is one of the most commonly performed operations on the digestive tract. A major complication of cholecystectomy, and especially laparoscopic cholecystectomy, is bile duct injury (BDI), which occurs in around 0.5% of cases. There is general consensus that the main factor that leads to BDI during laparoscopic cholecystectomy is misperception of the biliary anatomy[1]. Several techniques have been tested for intraoperative visualisation of the bile ducts, but the widely accepted golden standard remains intraoperative cholangiography (IOC)[2].

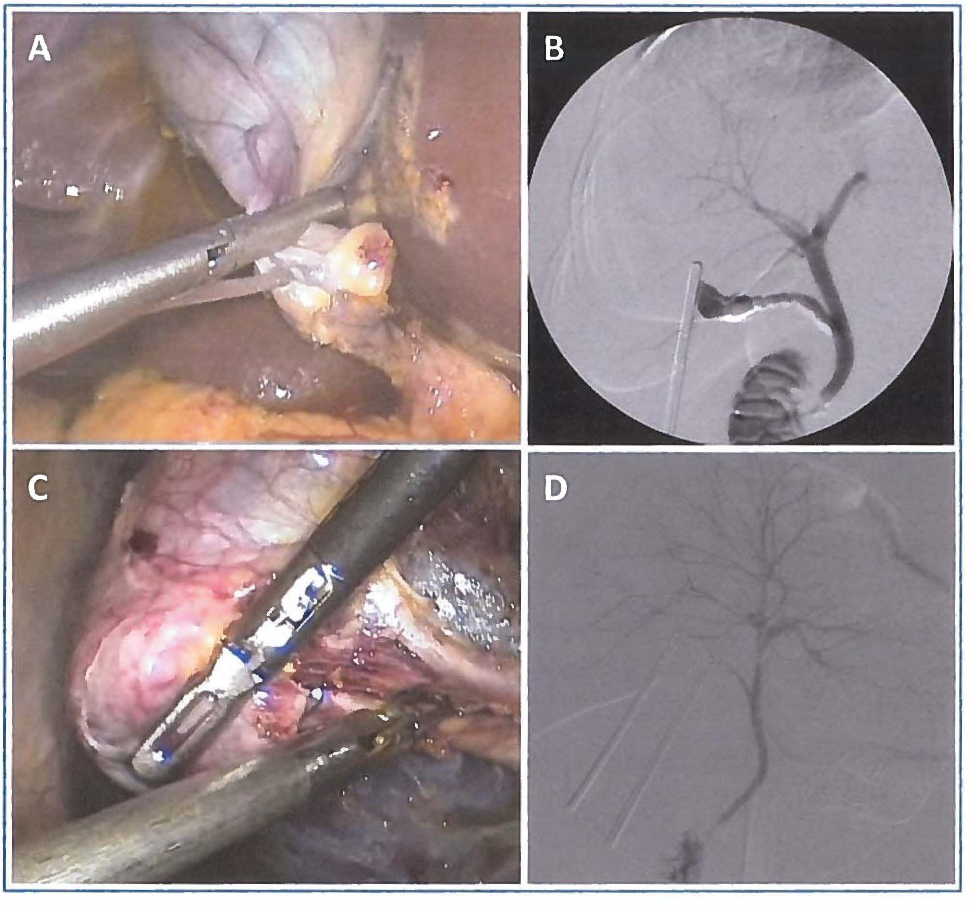
Whether IOC is performed routinely, selectively or not at all, varies widely between and within countries. High rates of IOC use are reported in Australia and the United States[3;4]. In a recent survey by our group, however, we found that IOC is hardly performed at all by the majority of the surgeons in the Netherlands[5]. It seems that, despite the frequently reported beneficial effects of IOC, there is resistance to its routine application during laparoscopic cholecystectomy. Important reasons for this objection to the procedure are the fact that IOC lengthens the operation time and that bile duct cannulation may be experienced as a cumbersome procedure.

The most commonly used technique for IOC is cystic duct cannulation. An incision is made in the cystic duct through which a catheter is advanced. The catheter is then fixed using a clamp. A frequently used instrument for this is the the Olsen Clamp ® (Cook medical, Limerick, Ireland).

An alternative to standard IOC via cystic duct cannulation, is cholangiography using the Kumar PRE-VIEW ® clamp (Nashville Surgical Instruments, Springfield, United States; in this paper referred to as 'Kumar clamp'). The instrument consists of a clamp which is placed over the base of the gallbladder and an attached needle which extends into the gallbladder to puncture Hartmann's pouch (figure 1). The radiopaque contrast is then injected through the needle. The Kumar clamp may decrease the time necessary for cholangiography and increase the ease with which it is performed.

To our knowledge, there are no studies that compare the efficacy of these two cannulation techniques. The aim of this study, therefore, was to assess whether IOC using the Kumar clamp is faster and easier to perform than IOC using the standard Olsen catheter in a randomized trial.

Figure 1: The Kumar clamp with needle tip extending into Hartmann's pouch (A) and the corresponding cholangiogram (B). In the lower row the Olsen clamp holding in place the catheter in the cystic duct (C) and the corresponding cholangiogram (D).



METHODS

Study design and primary outcomes

The primary endpoints were i) time necessary for IOC (defined as the time between start of the cholangiography procedure to the time that the IOC had been interpreted) and ii) the ease of the cholangiography procedure, recorded on a visual analogue scale (VAS) by the surgeon just after performing the operation. These two primary endpoints rather than one were chosen as it was felt that a substantial reduction in either one would result in a lower threshold to perform IOC. Statistical analysis on multiple primary endpoints has been previously described in the literature[6].

Secondary endpoints were: i),the success rate of IOC (defined as the proportion of patients in whom radiopaque contrast was seen at least in the common bile duct), ii) the number of biliary tree segments depicted on the cholangiogram (cystic duct, common bile duct, right, left and posterior hepatic ducts), iii) the total exposure to X-ray radiation (mGym$^{2)}$, iv) the number of bile duct injuries and v) the number of overall complications.

Sample size calculation

A sample size calculation was performed on the time needed for IOC (first primary endpoint); no reference numbers were available for the ease of IOC (second primary endpoint). Estimated time needed for standard IOC (Olsen clamp) is quoted in the literature at 15 ± 8 minutes[7], 10 minutes(8) and 27 minutes[9]. In a retrospective analysis of all cholecystectomies performed at our centre between 2007 and 2008, we found an added time of 18 minutes for procedures in which an IOC was performed (unpublished data). Based on these data we assumed that the standard IOC technique (Olsen catheter) time is 18 ± 8 minutes. To detect a difference of 33% with the Kumar clamp (thus assumed to be 12 ± 5 minutes) with a power of 0.80 and an alpha of 0.05, group sizes would be needed of 20 patients in each arm, totalling 40 (Dean et al. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 2.3; www.openepi.com, accessed September 2010). As these numbers are estimates and in order to allow for unexpected exclusions, this study continued until a total of 50 laparoscopic cholecystectomies was reached, as defined in the study protocol.

Ethics and registration

The study was approved by the local Ethics Board, study number METc 2009/339, and the Dutch Central Committee on Research involving Human Subjects (CCMO), study number NL30638.042.09. All patients gave written informed consent. The trial was registered in the Dutch Trial Register, study number NTR 2582 prior to inclusion. Results are presented in accordance with the CONSORT guidelines 2001.

Setting and follow-up

The study was conducted at a university hospital. The inclusion started on November 1st 2010 and the last patient was included on November 21st 2011. Follow-up was at least six weeks for all patients.

Patients

Patients were eligible for participation if they were 18 years or older and scheduled to undergo elective laparoscopic cholecystectomy with IOC. IOC is performed routinely at our center except in patients who are pregnant or allergic to radiopaque contrast agent. Patients in whom the operation date was planned to be within 72 hours were considered to be acute or semi-acute and were not included in this study. Patients were excluded if they did not provide informed consent or if they already participated in a different randomized trial.

Instruments and training

The Kumar PRE-VIEW* Cholangiography Clamp ® (Nashville Surgical Instruments, Springfield, United States) was ordered via Apgar, Brøndby, Denmark. It was used in conjunction with the Kumar PRE-VIEW Cholangiography Catheter ® (19ga. Needle, 76 cm long, 16ga.; Nashville Surgical Instruments, Springfield, United States; in this paper referred to as 'Kumar catheters').

The Olsen Clamp ® was ordered via Cook medical, Limerick, Ireland, as well as the catheters (C-NFEP3.0-18-43-P-NS-OECS; in this paper referred to as 'Olsen catheters'). Calibre (4 or 5 F) according to the surgeon's preference.

All participating surgeons received instructions on use of the Kumar clamp and practiced on a simulation model of the gallbladder. Most surgeons were familiar with the Olsen clamp and had used it before. If they were not familiar with the Olsen clamp, they received similar instructions on its use. Furthermore, instructions and videos were available on the hospital network on use of both of the clamps.

Randomization and blinding

Patients were randomized just after induction of anesthesia by opening an opaque unmarked envelope. The patients were blinded to the intervention until the day of discharge from the hospital. The surgeon and the investigator performing the time measurements were not blinded.

Procedure & time measurement

Laparoscopic cholecystecomy was performed using four laparoscopic ports. In the Kumar group, surgeons were free to use the Kumar clamp as a standard instrument from the start of the operation. However, the majority chose not to, introducing the Kumar clamp only for the IOC procedure. The critical view of safety was achieved in all patients and recorded on photo and video images. The following time points were recorded by an investigator not involved in the surgery: first incision, start of the cholangiography procedure (defined as opening the Kumar clamp or opening the scissors for IOC using the Olsen clamp), achievement of biliary access (defined as injection of saline with no leakage), the time the cholangiogram had been interpreted and time of removal of the scope from the abdomen.

Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows 17.0 (Chicago, Ill). Analysis was performed on an intention-to-treat basis. The Pearsons chi-square test was used to compare proportions. The Fisher's exact test was used when one of the cells had a count of less than 5. The independent Student's T-test was used to compare continuous normally distributed variables.

RESULTS

Patients

The recruitment of the patients is shown in figure 2. Out of 84 patients that met the inclusion criteria, 59 were enrolled and subsequently randomized. Nine patients were excluded because of conversion to open cholecystectomy before the IOC procedure took place. Twenty-eight patients underwent IOC using the Kumar clamp, and 22 using the Olsen clamp.

The baseline characteristics of the patient population is shown in table 1. There were no significant differences between the two groups at baseline. In two patients allocated to the Kumar group, however, a peroperative decision was made to use the Olsen clamp instead. In one case it was because a lesion in the cystic duct and in the other because of a very frail Hartmann's pouch. These cross-over patients were analyzed in the Kumar group (on intention-to-treat basis).

Figure 2: Inclusion flow chart

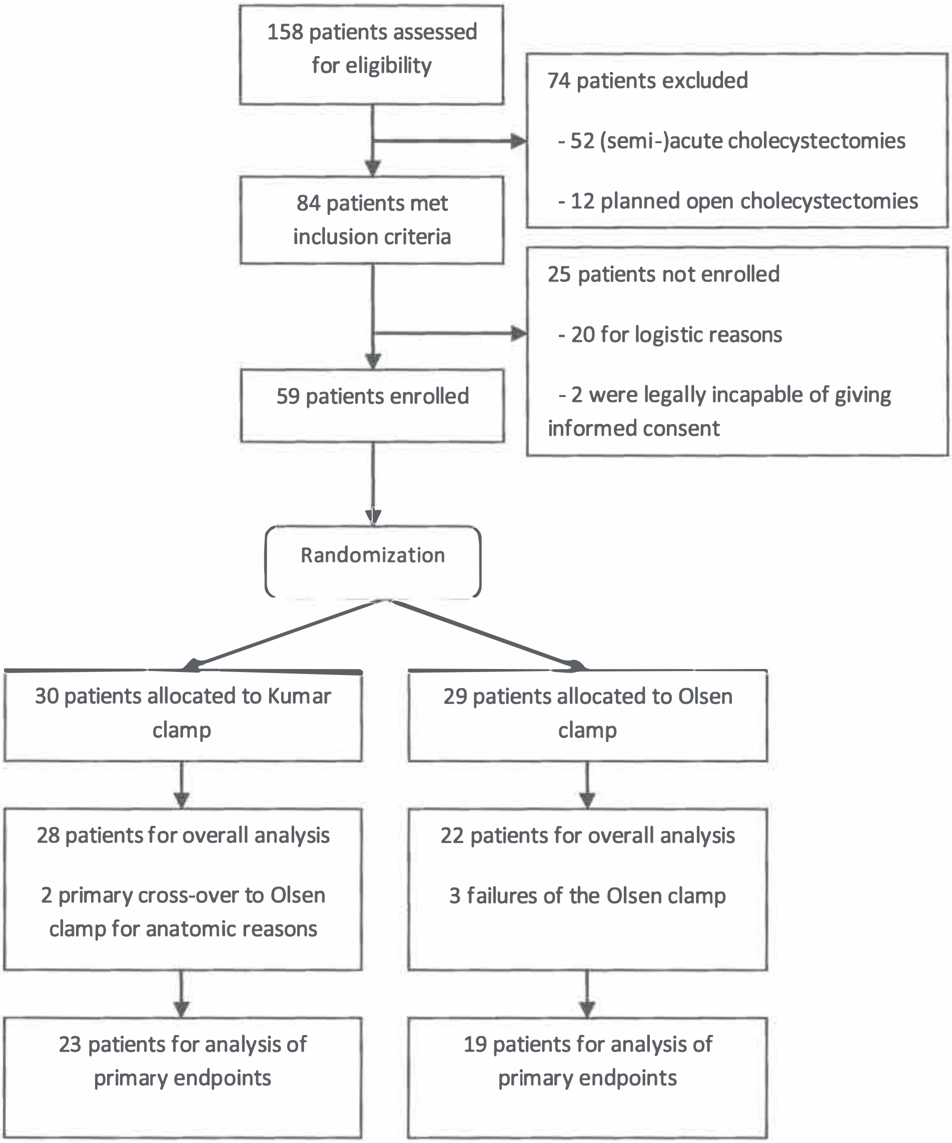


Table 1: Baseline characteristics

	Kumar (n = 28)	Òlsen (n = 22)	p
Age, mean ± SD	53 ± 13	48 ± 15	0.407
Female gender	17 (60.7%)	11 (50.0%)	0.568
ASA score, median (IQR)	2 (2-2)	2 (2-3)	0.239
BMI, mean ± SD	30.1 ± 7.3	30.5 ± 7.0	0.860
Indication			
Cholecystolithiasis	17 (60.7%)	15 (68.2%)	
Choledocholithiasis	4 (14.3%)	3 (13.6%)	
Cholecystitis (froid)	1 (3.6%)	3 (13.6%)	
Biliary pancreatitis	4 (14.3%)	0	
Other	2 (7.1%)	1 (4.5%)	
Surgeon experience*			0.289
Trainee year 1-3	7 (26.9%)	3 (14.3%)	
Trainee year 4-6	8 (30.8%)	9 (42.8%)	
Fellow in GE surgery	3 (11.5%)	2 (9.5%)	
GE surgeon	8 (30.8%)	7 (33.3%)	
Number of previous cholecystectomies*			0.462
<10	2 (7.7%)	1 (4.8%)	
10-50	12 (46.2%)	5 (23.8%)	
50-100	2 (7.7%)	3 (14.3%)	
>100	10 (38.5%)	12 (57.1%)	
Number of previous IOC*			0.849
<10	11 (42.3%)	8 (38.1%)	
10-25	8 (30.8%)	7 (33.3%)	
26-50	1 (3.8%)	1 (4.8%)	
>50	6 (23.1%)	5 (23.8%)	

*3 missing values; SD = standard deviation; ASA = American Society of Anesthesiology; IQR = interquartile range; BMI = body mass index; GE = gastrointestinal; IOC = intraoperative cholangiography

Primary outcome

The outcome of the cholecystectomies is shown in table 2. Success rates of both clamps were similar: 82.1% for the Kumar clamp and 86.4% for the Olsen clamp ($p > 0.999$). IOC using the Kumar clamp was not faster than using the Olsen clamp: 10 min 27s ± 6 min 17s, compared to 11 min 34s ± 7 min 27s ($p = 0.537$), as shown in figure 2a. When only the time was taken into account that it took to achieve biliary access, there was no significant difference either.

On average, surgeons judged IOC using both clamps as being equally easy: 6.8 ± 2.7 (Kumar) and the 6.8 ± 2.1 (Olsen, $p = 0.977$), as portrayed in figure 2b.

Secondary outcome

There were no differences in the success rate, the number of depicted segments of the biliary tree, the amount of radiation received, the number of bile duct injuries or the number of complications between the Kumar and the Olsen group (table 2). The only complication that occurred was an acute urinary retention in the Olsen clamp group. Two patients with choledocholithiasis were treated successfully by postoperative ERCP.

Further analyses

When a per-protocol analysis was performed, the time for IOC using the Kumar clamp was 9 min 48 s versus 12 min 05 s using the Olsen clamp ($p = 0.205$). In terms of ease of IOC, a per-protocol analysis yielded a score of 7.2 ± 2.5 (Kumar clamp) versus 6.5 ± 2.3 ($p = 0.321$). Results were similar when only the first half or only the second half of the patients were analyzed separately (data not shown).

DISCUSSION

This is the first randomized controlled trial to compare the Kumar clamp to the more standard cystic duct cannulation method (in this case the Olsen clamp). We found that both clamps were similar in time necessary for IOC and in perceived ease by the surgeon. No differences were found in secondary endpoints such as complications and total amount of radiation either.

Figure 3: Primary endpoints: (a) cholangiography time and (b) ease of cholangiography procedure; IOC = intraoperative cholangiography; VAS = visual analogue score; dotted line in figure B indicates the score that surgeons were instructed to view as 'average' ease of IOC

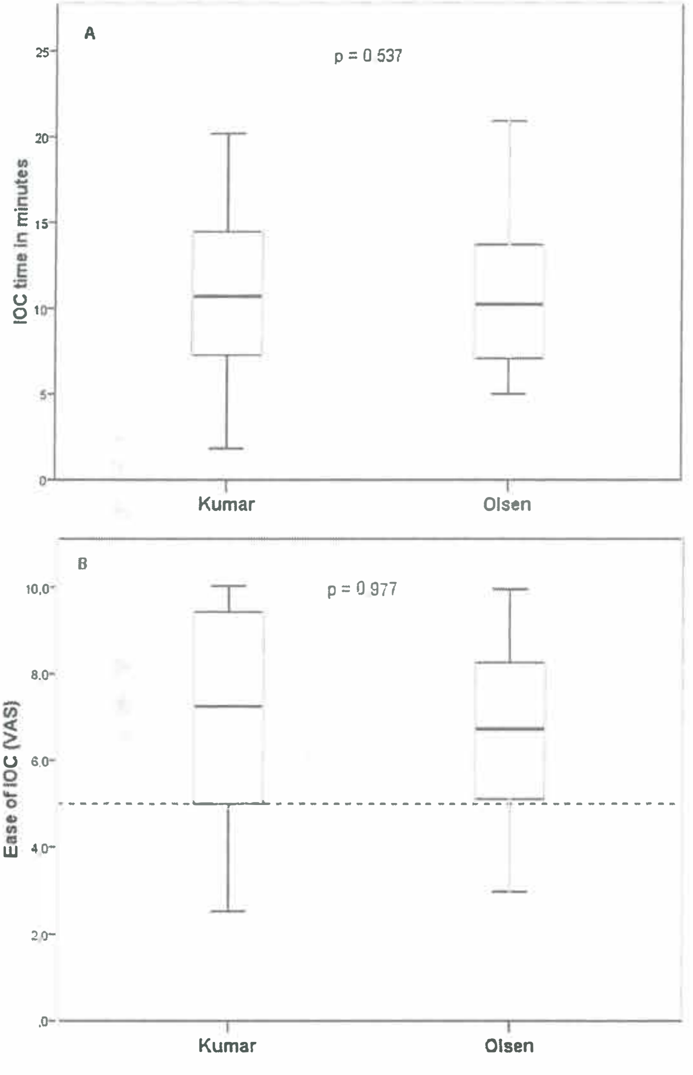


Table 2: Outcome

	Kumar (n = 28)	Òlsen (n = 22)	p
Succes rate	23 (82.1%)	19 (86.4%)	>0.999
Cannulation time, mean ± SD	4 min 14s ± 3 min 17s	5 min 33s ± 5 min 39s	0.349
Total IOC time, mean ± SD	10 min 27s ± 6 min 17s	11 min 34s ± 7 min 27s	0.537
Total surgery time, mean ± SD	75 min ± 29 min	83 min ± 37 min	0.461
Ease on VAS scale, mean ± SD	6.8 ± 2.7	6.8 ± 2.1	0.977
No. segments depicted, median (IQR)	5 (5 – 5)	5 (4 – 5)	0.115
Radiation received	0.41 ± 0.28 Gym^2	0.48 ± 0.40 Gym^2	0.542
Bile duct injuries	0	0	-
CBD stones	1/23 (4.3%)	1/19 (5.3%)	>0.999
Complications	0	1/22 (4.5%)	0.440

SD = standard deviation; VAS = visual analogue scale; IOC = intraoperative cholangiography

The Kumar clamp has been in production since 1992 but only two series(10;11) of laparoscopic cholecystectomies with IOC have been reported using the Kumar clamp. The first one was described by Kumar[11] in 1992. In a series of 50 cases IOC was performed using this clamp: 98% were successful, and no complications occurred.

In the second series described by Holzman et al. in 1994[10], of the 60 cases the Kumar clamp was used, 83% were successful. The time to insert the Kumar clamp and introduce the sclerotherapy needle was reported to be approximately two minutes, the time for completing the entire cholangiogram was ten minutes. These results are similar to the ones found in the current trial.

A possible additional advantage of the Kumar clamp is that, in contrast to the Olsen clamp, it allows visualization of the biliary tract *before* any tubular structures are incised or cannulated. Theoretically, where IOC using the Olsen clamp would downgrade a complete transection of the CBD (type D injury) to a CBD leak (type B), IOC using the Kumar clamp could prevent this injury altogether. The numbers in this trial were too small and no series of IOC with the Kumar clamp that are large enough to assess this possible benefit are known to us.

One limitation of this study is that there was a discrepancy between the expected and observed time for IOC. The power analysis for this study was performed using an estimate of 18 minutes for IOC using the Olsen clamp. Considering that the actual time was closer to twelve minutes, this study may be somewhat underpowered to detect small differences in time. However, from the results it seems likely that use of the Kumar clamp will not result in a clinically significant reduction of the time spent on IOC.

Another criticism may be that surgeons may have been more familiar with the Olsen clamp to start with. We provided model training to all surgeons who performed cholecystectomies in this trial, but this may not have been sufficient to completely counter the experience bias. On post-hoc analysis, there was no difference in IOC time when only the second half of cholecystectomies was analyzed, suggesting that also further in the learning curve, little reduction in time is to be expected from use of the Kumar clamp.

As bile duct injuries continue to plague (laparoscopic) cholecystectomies, the debate on the role of IOC continues. The Kumar clamp will probably not substantially lower the threshold for performing IOC. Further efforts are necessary to improve the safety of cholecystectomies. First of all, there is little doubt that global implementation of the 'critical view of safety' surgery technique will increase patient safety. Secondly, IOC needs to be addressed in the training programme of surgical trainees. Thirdly, novel techniques of assessing the biliary tree such as fluorescence cholangiography are being evaluated for safety and efficacy in clinical practice.

In conclusion, this randomized trial found no significant differences in speed or perceived ease of IOC using the Kumar clamp as compared to using the Olsen clamp. Individual surgeon preference should dictate which clamp is used.

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Chapter

6

Documenting correct assessment of biliary anatomy during laparoscopic cholecystectomy

KT Buddingh; AN Morks; HO ten Cate Hoedemaker; CB Blaauw; GM van Dam; RJ Ploeg; HS Hofker; VB Nieuwenhuijs

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ABSTRACT

Background: Correct assessment of biliary anatomy may be documented by photographs of the "critical view of safety" (CVS), but also by intraoperative cholangiography (IOC).

Method: Photographs of the CVS and IOC images of 63 patients were presented to three expert observers in a random and blinded fashion. The observers answered questions pertaining to whether the biliary anatomy had been conclusively documented.

Results: CVS photographs were judged as "conclusive" in 27%, "probable" in 35% and "inconclusive" in 38%. IOC performed better: "conclusive in 57"%, "probable" in 25% and "inconclusive" in 18% ($p < 0.001$ compared with photographs).

The observers indicated that they would feel comfortable transecting the cystic duct based on the CVS photographs in 52% of cases and based on the IOC images in 73% of cases ($p = 0.004$). The interobserver agreement was moderate for both modalities (kappa-values 0.4 – 0.5).

In patients with a history of cholecystitis, both the CVS photographs and the IOC images were less frequently judged sufficient to transect the cystic duct ($p = 0.006$ and 0.017 respectively).

Conclusion: In this series, IOC was superior to photographs of the CVS to document biliary anatomy during laparoscopic cholecystectomy. However, both modalities were judged conclusive only in a limited proportion of patients, especially in case of cholecystitis. Documenting assessment of the biliary anatomy is not as straightforward as it seems and protocols are necessary, especially if the images may be used for medico-legal purposes.

INTRODUCTION

Bile duct injury (BDI) is a dreaded complication during both laparoscopic and classic open cholecystectomy. The most severe type of BDI is the complete transsection of the common bile duct (CBD) and occurs when the CBD is mistaken for the cystic duct. An important safety measure to identify the cystic duct is to establish the so called critical view of safety (CVS)[1]. In addition, intraoperative cholangiography (IOC) may be used to assess the biliary anatomy. IOC is associated with a reduction in the incidence of major BDI[2,3,4,5], although opinions vary on whether it should be routinely or selectively performed.

Currently, the guidelines of the Dutch Society of Surgery advise that the CVS is to be documented for educational and medico-legal purposes[6]. CVS should be documented in the operation notes and preferably supported by intra-operative images. Two Dutch studies that assessed whether photographs or video images performed better at documentation of the CVS yielded contradictory results[7,8]. In both studies the CVS (and thus cystic duct identification) could only be registered conclusively in 34 – 70% of patients.

Besides photographs of the CVS, stored IOC images can also be used as documentation of correct identification of the cystic duct. IOC may actually constitute a better way than photographs of the CVS. However, this has never been assessed.

In our University Medical Centre the CVS is documented routinely by photographs and IOC is performed routinely. In this study we investigated the quality of the documentation of biliary anatomy using photography of the CVS and IOC.

METHODS

In the University Medical Centre Groningen most cholecystectomies are performed by surgical trainees under supervision of one of seven consultant surgeons specialized in gastrointestinal surgery. The standard operative technique for laparoscopic cholecystectomy in our center is the critical view of safety (CVS) technique as described by Strasberg et al[1] followed by routine IOC[9]. Digital registration of the CVS by means of photography has been hospital policy since November 2008.

Patients

All cholecystectomies between November 2008 and April 2010 were retrospectively reviewed. Patients were included in the analysis whenever (1) they had undergone a cholecystectomy which was completed laparoscopically, (2) achievement of the CVS was documented in the operation notes, (3) photographs of the CVS was stored in the digital medical records and (4) IOC had been successfully performed and saved in the digital medical file.

Reviewing of the images

The photographs of the CVS in Tagged Image File Format (.tiff) and the IOCs in Joint Photographic Expert Group format (.jpg) were reviewed and rated by three expert abdominal surgeons (H.O.C.H, R.J.P. and V.B.N.). Each surgeon has supervised more than 100 laparoscopic cholecystectomies after completion of surgical training. The photographs and the IOC images were presented in random, unmatched order without additional patient information. The surgeons answered consecutive questions pertaining to the quality of the images and the documentation of assessment of the biliary anatomy. Quality of the images was rated on a 10-point scale with 1 being very poor and 10 being excellent. The translated version of the scoring form is enclosed as appendix A.

Statistical analysis

Statistical analysis was performed with SPPS 16.0 for Windows (SPPS Inc, Chicago, Illinois). For analysis of continuous variables the mean of the three observers was used. For analysis of ordinal and nominal values the median of the three observers was used.

The paired samples t-test was used to compare continuous variables. The Wilcoxon paired samples signed ranks test and the McNemar test were used to compare paired ordinal and nominal variables. The Mann Whitney U test and the chi-squared test were used to compare unpaired ordinal and nominal variables. Interobserver agreement was assessed by calculating the kappa values. A p-value of < 0.05 was considered significant.

RESULTS

Patients

The critical view of safety (CVS) was explicitly reported to have been achieved in 130 out of 139 laparoscopically completed cholecystectomies. It was recorded by photograph in 81 patients. In the other 49 patients either no images (n = 35) or only videos (n = 14) of the CVS were stored. Intraoperative cholangiography (IOC) was attempted in 116 patients and successful in 97 patients. In 63 patients both photographs of the CVS and IOC images were available. The median num ber of photographs taken was 2 (IQR 1-3). The median number of IOC images stored, usually as a series in a short film, was 6 (I QR 5-12).

The indications for cholecystectomy were uncomplicated gallstone disease in 31 cases (49%), biliary pancreatitis or CBD stones in 13 (21%) and present or previous cholecystitis in 19 (30%). No bile duct injuries or bile leaks occurred in this series of patients.

Photography versus IOC

Ta ble 1 shows the experts' ratings of the photographs and IOC images. The quality of the photographs was rated lower than that of the IOCs (5.8±1.4 versus 6.7±1.3, $p < 0.001$). The CVS was documented "conclusively" by photography in only 17 patients (27%). It was rated as "probably" in 22 (35%) and "inconclusive" in 24 patients (38%). IOC was judged to document the cystic duct "conclusively" in 36 patients (57%), "probably" in 16 (25%) and "inconclusively" in 11 (18%). IOC was superior to photography of the CVS for documenting assessment of biliary anatomy ($p < 0.001$).

Based on the photographs, the surgeons deemed it justified to transect the cystic duct in 33 patients (52%). Based on the IOC, transecting the cystic duct was deemed justified in 46 patients (73%, $p = 0.004$). Correct documentation of the biliary anatomy was not associated with a higher number of photographs stored ($p = 0.747$), nor with a higher number of IOC images stored ($p = 0.950$).

In 14 patients, neither of the two modalities was judged conclusive. Upon review of the operative notes of these patients, doubts about the way the CVS is visualized or about the IOC are only expressed in 4/14 and 3/14 patients respectively. Figure 1 portrays a concusively documented CVS in three photographs. Figure 2 shows a case of correctly and a case of incorrectly documented IOC.

Table 1: Registration of cystic duct by photograph and intraoperative cholangiography

** indicates $p < 0.05$; SD = standard deviation; IOC = intraoperative cholangiography; CVS = critical view of safety*

	Photograph	IOC	p
Quality of the images (mean ± SD)	5.8 ± 1.4	6.7 ± 1.3	**<0.001***
CVS / cystic duct identified			**<0.001***
Yes	17 (27.0%)	36 (57.1%)	
Probably	22 (34.9%)	16 (25.4%)	
Inconclusive	24 (38.1%)	11 (17.5%)	
Safe to transect duct			**0.004***
Yes	33 (52.4%)	46 (73.0%)	
No	30 (47.6%)	17 (27.0%)	

The inflamed gallbladder

Table 2 shows the differences between patients who underwent cholecystectomy for present or previous cholecystitis and those with other indications. In the 19 patients with a (history of) cholecystitis, the surgeons deemed the photographs of CVS sufficiently conclusive to transect the cystic duct in 5 patients (26%). In patients undergoing cholecystectomy for other indications this was 28 out of 44 patients (64%, p = 0.004).

The same phenomenon was seen for IOC: transsection was deemed safe in 53% of the patients with past or present cholecystitis versus 82% of those with other indications (p = 0.017). The results are shown in table 2.

Interobserver agreement

The kappa for interobserver agreement on conclusiveness of photographs of the CVS was 0.416 between observers A and B, 0.499 between observers A and C, and 0.394 between observers B and C. The kappas for interobserver agreement on conclusiveness of the IOCs were 0.533, 0.478 and 0.407 respectively. These values have been described to indicate moderate agreement[10].

Figure 1: correct documentation of the critical view of safety in three photographs: A – medial view; B – lateral view, C – view with an instrument through one of the windows to enhance depth perception

Figure 2: documentation of biliary anatomy by intraoperative cholangiography: A – performed correctly, the trajectory of the cystic duct is clearly visible, as well as the intrahepatic bile ducts, the common bile duct and the duodenum; B – performed incorrectly, although the intrahepatic ducts and the duodenum is visualized, the cystic duct is not, and it could be the common bile duct that is cannulated instead of the cystic duct.

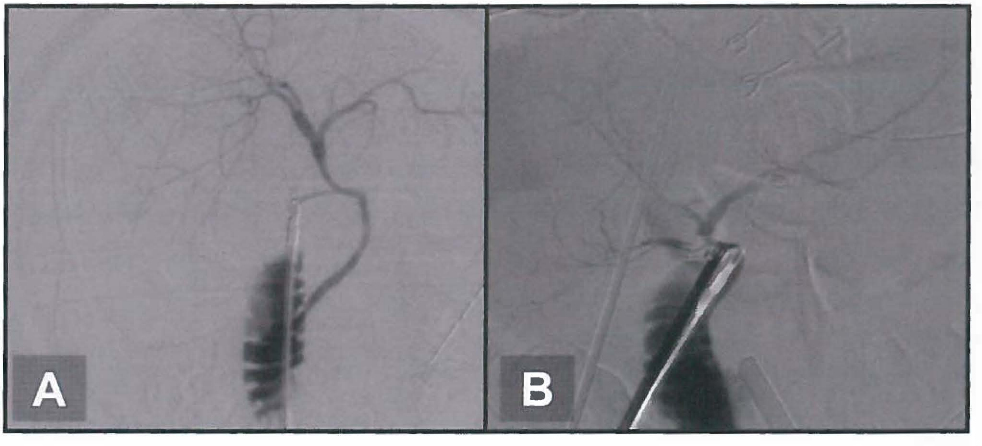

Table 2: Performance of photography and intraoperative cholangiography in patients with and without cholecystitis

	Present or previous cholecystitis (n = 19)	**Other indications (n = 44)**	**p**
Quality Photo	5.5 ± 1.4	6.0 ± 1.4	0.212
Quality IOC	6.5 ± 1.3	6.8 ± 1.3	0.351
CVS on photograph			**0.007***
Yes	2 (10.5%)	15 (34.1%)	
Probably	5 (26.3%)	17 (38.6%)	
Inconclusive	12 (63.2%)	12 (27.3%)	
Transect duct based on photo			**0.006***
Yes	5 (26.3%)	28 (63.6%)	
No	14 (73.7%)	16 (36.4%)	
Cystic duct identified by IOC			0.099
Yes	9 (47.4%)	27 (61.4%)	
Probably	3 (15.8%)	13 (29.5%)	
Inconclusive	7 (36.8%)	4 (9.1%)	
Transect duct based on IOC			**0.017***
Yes	10 (52.6%)	36 (81.8%)	
No	9 (47.4%)	8 (18.2%)	

* indicates $p < 0.05$; SD = standard deviation; IOC = intraoperative cholangiography; CVS = critical view of safety

DISCUSSION

This study investigated the documentation of correct assessment of biliary anatomy by photography of the critical view of safety (CVS) and by intraoperative cholangiography (IOC). The cystic duct was conclusively documented in 57% of the IOCs, compared to 27% of the photographs of the CVS. Conclusive documentation of biliary anatomy was especially poor in patients with (a history of) cholecystitis.

Several studies have previously evaluated photographs of the CVS[7,8,11]. The rate of conclusive photographs in the current study was lower than in the other studies. This difference may partly be explained by the high proportion of patients with cholecystitis in this series (table 3). In a recent commentary, Strasberg describes that achieving CVS is more challenging with an inflamed gallbladder[12]. As a result of the altered aspect of the anatomical structures during or after inflammation, it may be especially difficult to capture the CVS in one or two still images. Doubts were expressed about the CVS or IOC in the operative notes of only a minority of patients with inconclusive documentation in photographs or IOC. Therefore, the problem probably lies in the documentation rather than in unsafely performed surgery. Nonetheless, the proportion of properly documented CVS is unacceptably low and effort is currently being put into improving this aspect of gallbladder surgery at our center. New protocols including video images, and instructions during resident courses in laparoscopic surgery have been implemented for this purpose.

The CVS technique is fully accepted in Dutch surgical practice. A nationwide survey by our group revealed that 98% of the surgeons apply this technique[13]. Also, many surgeons document the CVS by photograph (43%) or video (30%). Considering the poor results of photography of the CVS at our center, it would be interesting to assess the quality of the images from other hospitals.

Previous studies assessed whether the CVS had been achieved "certainly", "probably" or "inconclusively"[7,8]. In the current study, a binary response ("yes" or "no") was also elicited from the observers by asking them whether they would feel comfortable transecting the identified duct based on the images. Half of the responses marked as "probably" then changed to "yes", the other half changed to "no". This illustrates the range of responses that may be classified as "probably". The interobserver agreement on the photographs was moderate with kappa values between 0.4 and 0.6. The only previous study to assess interobserver agreement on CVS photographs found a slightly higher kappa of 0.69 (fair agreement)[7]. This study cannot with certainty explain the low inter-rater agreement, but we feel that the it would benefit from higher quality photographs according to a standardized protocol.

The merits of IOC have been described in large population-based studies[2,3,4]. There is however, concern that IOCs are not always correctly interpreted[14,15]. In this series, the cystic duct could be conclusively documented in only 57% of cases. In the cases where IOC did not correctly document the cystic duct, this was caused by projection of the cystic duct over the CBD and/or incomplete filling of the biliary tree. The interobserver agreement on the IOCs was moderate. An unexpected finding was that a lower proportion of IOC was conclusive in

Table 3: documentation of CVS by photograph in previous studies and the current study.

CVS = critical view of safety; IOC = intraoperative cholangiography

	Rawlings[11] (single port)	Plaisier[8]	Emous[7] (mean of two observers)	Current study (photo CVS)	Current study (IOC)
CVS / cystic duct identified					
Yes	64%	62%	40%	27%	57%
Probably	24%	16%	36%	35%	25%
Inconclusive	12%	22%	26%	38%	18%
Present / previous cholecystitis	0%	10%	28%	30%	30%

patients with an inflamed gallbladder. This may be caused by adhesions or alterations in the morphology of the cystic duct that make the situation more prone to overprojection or insufficient filling of the biliary tree during IOC.

Attention should be paid to the legal implications of documentation of biliary anatomy. This seems evident for IOC as it is part of the radiology studies in the patient medical file. However, stored laparoscopic images, and images of the CVS in particular, are relatively new items in the patient' medical records. The medico-legal value of these images has not been determined. Once a selection of intra-operative images is stored, the images are considered 'personal data' under Article 2 of the Dutch Personal Data Protection Act (in Dutch abbreviated as WBP). According to this Act special requirements regarding quality and admissibility of data processing must be met (Article 6-15 of the Personal Data Protection Act). One of these requirements is the patient's consent to store CVS. Generally, it is accepted that the patient's consent for surgery also comprises consent for CVS documentation and storage.

Under Dutch law (Article 453 and 454 of the Medical Treatment Contracts Act, in Dutch abbreviated as WGBO), the CVS should be documented in the patient medical records to comply with the care provider's responsibility in view of the applicable professional standard (in case of cholecystectomy the Dutch Guidelines and Best-Practice for laparoscopic cholecystectomy[6]). The patient has certain rights in relation to his medical file, such as the right to access to the file and to copy his file, including radiology studies and laparoscopic images. The patient may use such copies in a court of law, for example in case of bile duct injury (BDI). On the other hand, documentation of the biliary anatomy can be used by the surgeon to substantiate measures taken in order to ensure safe cholecystectomy. In particular circumstances, the physician may use documents and images from the patient's file in legal procedures without the patient's consent to prove he has met requirements of due care under the professional standard. This exception is based upon Article 6 of the European Convention of Human rights that everyone, including physicians, has the right of fair trial.

Besides the patient and the physician, the Public Prosecutor and the Health Care Inspectorate may also claim the medical file. Dutch regulations on quality of healthcare require that any calamity (an unintended adverse event resulting in the death or serious harm of a patient) in a health care institution must be reported to the Health Care Inspectorate. In case the Inspectorate encounters any violation of these regulations the Public Prosecutor is informed.

Several studies have assessed litigation claims for iatrogenic BDI during cholecystectomy(16,17,18,19,20) and conclude that litigation for BDI continues to play a role in modern surgical practice. Very little data exists on the role of patient safety interventions in these cases; most of the injuries occurred before widespread implementation of the CVS technique. It would be interesting to assess claims for BDI in the years following introduction of the CVS, especially in the Netherlands as documentation of the CVS is incorporated into the national guidelines. At the moment, documentation of the CVS in the operation notes is probably enough to convince a court of law that the appropriate safety measures were taken. However, it is clear that the operation notes in (gallbladder) surgery are limited in their correlation with the actual procedure(21). As the storing of laparoscopy images becomes more widely practiced, operation notes supported by images will probably become the new standard of care.

This study was conducted retrospectively and no protocol was used how to take the photographs of the CVS. This is, however, the first study to assess the value of IOC for documenting the cystic duct. It would be interesting to compare IOC to videos, in addition to photographs, of the CVS. Emous et al. have suggested that videos of the CVS are superior to photographs(7), although Plaisier et al claimed that photographs are superior(8). Further study on this topic is currently ongoing at our centre.

Conclusion

In this series, IOC was superior to photographs of the CVS to document the correct assessment of biliary anatomy during laparoscopic cholecystectomy. However, both modalities were conclusive only in a limited proportion of patients, especially in case of cholecystitis. Our study highlights that the documentation of the biliary anatomy is not as straightforward as it seems and that protocols are necessary, especially since the images may be used for medico-legal purposes. Documentation of cystic duct identification should be addressed during training courses for laparoscopic surgery.

Appendix: Questions answered by each observer (translated from Dutch)

Part 1: Critical view of safety (CVS)

1. What is the quality of the photo's (grade best photo)?

(Very poor) 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10 (Excellent)

2. Has the CVS been achieved?

- Yes
- Probably
- Inconclusive

3. Would you transect the cystic duct based on this image?

- Yes
- No

Part 2: Intraoperative cholangiography (IOC)

1. What is the quality of the IOC (grade best image)?

(Very poor) 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10 (Excellent)

2. Is the duct that is cannulated the cystic duct?

- Yes
- Probably
- Inconclusive

3. Would you transect the cannulated duct based on this IOC?

- Yes
- No

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Chapter 7

Peroral cholangioscopy for diagnosis of indeterminate bile duct lesions: disappointing yield of Spybite biopsies

Buddingh KT; Hemel B; Annet Gouw; Nieuwenhuijs VB; Weersma RK

In preparation

ABSTRACT

Background: Patients with a suspected malignancy of the biliary tract can form a diagnostic challenge. Conventional investigations such as ERCP, CT, MRCP and EUS are not always conclusive. In such patients, peroral cholangioscopy is a promising technique. Aim of this study was to report the diagnostic accuracy of cholangioscopy and cholangioscopy guided lesions.

Method*:* Retrospective review of all patients in a tertiary referral center who underwent peroral cholangioscopy for indeterminate bile duct lesions over a period of 44 months.

Result: A total of 45 patients were included in the analysis. Nearly all patients had undergone previous endoscopic retrograde cholangiopancreatography, many had also undergone magnetic resonance cholangiopancreatography, endoscopic ultrasound or computed tomography scanning. Spybite biopsies were taken in 29 patients; brush cytology was done in 27. Of the 45 patients, 14 (31%) were ultimately diagnosed with bile duct cancer. The rest had a median follow-up of 15 months (inter-quartile range 4 – 27).

The accuracy of cholangioscopy impression was 35/45 (78%). The sensitivity was 7/14 (50%) and the specificity was 28/31 (90%). The 29 Spybite biopsies yielded benign cells in 13 (45%), atypical cells in 6 (21%) and insufficient material in 10 patients (35%). Of the 13 patients with benign biopsies, 4 turned out to have cholangiocarcinoma nonetheless.

The overall accuracy of cholangioscopy, brush and Spybite biopsy together was 82%.

Conclusion: Cholangioscopy is a useful investigation in patients with indeterminate bile duct lesions. The yield of Spybite biopsies in this series, however, was disappointing and lower than reported in literature. Future studies are warranted to determine whether the poor performance in our study is an outlier.

INTRODUCTION

Patients with a suspected malignancy of the biliary tract can pose a diagnostic challenge. Traditional work-up of such patients consists of endoscopic retrograde cholangiopancreatography (ERCP), by which the location and shape of filling defects may be seen. These images alone are seldom sufficient for a diagnosis. Brush cytology of the biliary tract during ERCP can provide histopathologic proof of cholangiocarcinoma, but the sensitivity and thus the negative predictive value is relatively low at 50-80%[1]. Newer techniques are magnetic resonance imaging (MRI), computed tomography (CT) and endoscopic ultrasound (EUS).

Three dimensional MRI and CT seem to perform equally well at identifying the cause of biliary obstru ction. In a recent comparative study both modalities had an accuracy of around 85%[2]. EUS is highly sensitive for distal tumours and performs reasonably for proximal bile duct tumours. EUS-guided fine needle aspiration, like brush cytology, is highly specific but not very sensitive. Again, it performs better in distal tumours than in proximal lesions[3].

A particularly challenging group of patients are those with primary sclerosing cholangitis (PSC). These patients are at high risk of developing cholangiocarcinoma. However, the disease itself may mimic malignant lesions in the biliary tract[4].

Notwithstanding the abovementioned diagnostic options, there remains a group of patients in whom the nature of the bile duct lesion cannot be determined with certainty. The consequences of a diagnosis are severe, as aggressive surgery, for example pacreaticoduodenectomy, is the only curative therapeutic option.

Peroral cholangioscopy allows direct visualization of the endoluminal surface of the bilary tree, and facilitates targeted biopsy of any lesion at suspicion for malignancy. As such it may be a valuable investigation for patients in whom earlier investigations were inconclusive[5,6]. Peroral cholangioscopy has been performed for many decades. Until recently, however, the technique had not been widely adopted. The original technique required two endoscopists trained in advanced ERCP. With the introduction of improved cholangioscopes that allow single-operator cholangioscopy, the technique is gaining popularity. As such, there is a growing body of evidence for peroral cholangioscopy. To establish its role in modern medicine, it is important to assess the value of cholangioscopy in 'real life' clinical practice, and not just in prospective trials in specialized centres.

The objective of this study was to determine the accuracy, sensitivity and specificity of peroral cholangioscopy at identifying the nature of indeterminate biliary lesions.

METHODS

A retrospective analysis was performed of patients who underwent peroral cholangioscopy for indeterminate bile duct lesions at our tertiary referral centre between November 2007 and July 2011. All procedures were performed at the endoscopy unit of the department of Gastroenterology and Hepatology of the University Medical Centre Groningen in Groningen, the Netherlands.

Main endpoints

The main investigational parameters were visual impression of the bile duct lesion by peroral cholangioscopy and histopathology analysis of biopsies taken during peroral cholangioscopy. With regard to the visual impression, special attention was paid to the presence of neovascularization. The presence of a tumour vessel has previously been shown to be highly specific for malignancy[7]. Also, tumours were assessed for a benign fibrotic aspect or an irregular, vulnerable malignant appearance[8].

The main outcome parameter was malignant or benign status of the lesion as determined by surgery and histopathology analysis. The lesions in patients that did not undergo surgery and developed no malignancy during follow-up were considerd benign.

Patients

Patients aged 18 or older were included who were referred to our tertiary centre in whom previous investigation had revealed indeterminate bile duct lesions. Patients in whom previous investigations had confirmed the presence of stones were excluded.

Cholangioscopy procedure

Standard protocol was used for all procedures. All cholangioscopies were performed by the same gastroenterologist (RKW). Antibiotic profylaxis consisted of ceftriaxon 2 grams intravenous. The majority of the procedure was performed under 'conscious sedation' with midazolam and pethidine and four procedures were performed under complete anesthesia.

In all patients, regular ERCP was first performed with a videoduodenoscope (Olympus Netherlands BV, Zoeterwoude). Passage of catheters or spincterotomes through the stenosis is avoided where possible. Then, the cholangioscope was introduced via the 'mother-baby' technique over a long guidewire (450cm Jagwire). All patients were treated with the SpyGlass cholangioscopy system (Boston Scientific Netherlands BV, Nieuwegein).

Cholangioscopy guided Spybite biopsies

Biopsies were obtained under direct visual control using Spybite biopsy forceps that can be passed through the working channel of the cholangioscope. We try to perform four to six biopsies of suspected biliary strictures.

Histopathological examination:

Most pathologic examinations were performed by the same pathologist (AG) with extensive experience in biliary pathology.

Data collection

Data on the cholangioscopy procedures was collected prospectively. Further patient data was collected retrospectively from medical records including laboratory values, cholangioscopy and surgery notes and discharge summaries. Also, data was collected on all imaging studies that had taken place in the twelve months prior to the cholangioscopy. If patients underwent multiple cholangioscopy procedures (for example if the first procedure was inconclusive, only the first successful cholangioscopy was used to determine the diagnostic value of peroral cholangioscopy.

Statistical analysis

The investigational parameters (visual inspection and biopsy during cholangioscopy) were compared to the gold standard (either surgery and histopathology analysis or follow-up). Accuracy, sensitivity and specificity were calculated for visual inspection and biopsy both separately and combined.

Accuracy was defined as the number of correctly diagnosed patients divided by the total number of patients. Sensitivity was defined as the number of patients with correctly diagnosed malignant lesions divided by the total number of patients with malignant lesions. Specificity was defined as the number of patients with correctly identified benign lesions divided by the total number of patients with benign lesions. The positive predictive value was defined as the number of patients that were correctly diagnosed with malignancy divided by all patients that were allocated as such by the test. The negative predictive value was defined as the number of patients that were correctly diagnosed with benign disease divided by all the patients that were allocated as such by the test.

SPSS 16.0 (SPSS Inc, Chicago, Ill) was used for statistical analysis.

RESULTS

Patients

A total of 65 patients underwent peroral cholangioscopy between November 2007 and July 2011. All patients were aged 18 or older. In 19 patients the procedure was performed for previously diagnosed large common bile duct stones. In one patient, cholangioscopy failed due to cardial complaints and was not re-attempted.

Thus, a total of 45 patients were included in this analysis. Characteristics of the patient population are portrayed in table 1. Around one third of the patients had PSC. Nearly all patients had previously undergone ERCP. Around half of the patients had undergone previous either brush cytology, MRCP and/or CT investigation of the bile ducts. A minority had undergone EUS or PET-scan investigation.

Outcome

Of 45 patients, 14 (31.1%) were histopathologically diagnosed with a bile duct malignancy (13 cholangiocarcinomas and one chloroma) at one point or another during follow-up. Nine of these patients died after a median of 11 months (IQR 5 – 15). Five patients were alive after a median of 4 (IQR 2 – 26) months of follow-up. Thirty-one patients did not develop cholangiocarcinoma. Follow-up in these patients was 14 months (IQR 4 – 27).

Procedure details

Cholangioscopy was performed under conscious sedation in 41 patients (91.1%); full anesthesia was necessary in 4 patients (8.9%). Introduction was easy in 40 patients and difficult in 5. Visibility was judged as good in 36 patients (80.0%), fair in 6 (13.3%) and poor in 3 (6.7%).

Table 1: patient characteristics	**n = 45**
Female gender; n	19 (42.2%)
Age in years; mean ± SD	56 ± 15
Primary sclerosing cholangitis; n (%)	15 (33.3%)
Previous investigations of the biliary tract	
ERCP; n (%)	43 (95.6%)
ERCP-guided brush pathology; n (%)	22 (48.9%)
MRCP; n (%)	20 (44.4%)
CT; n (%)	21 (46.7%)
EUS; n (%)	16 (35.6%)
PET; n (%)	1 (2.2%)
Location of bile duct lesion	
Hilar	21 (46.7%)
Mid CBD	7 (15.6%)
Distal CBD	8 (17.8%)
Diffuse / non-applicable	5 (11.1%)

SD = standard deviation; ERCP = endoscopic retrograde cholangiopancreatography; MRCP = magnetic resonance cholangiopancreatography; CT = computed tomography; EUS = endoscopic ultrasound; PET = positron emission tomography; CBD = common bile duct

Cholangioscopy impression

The impression of the tumour appearance was available of all 45 patients: ten had malignant appearance and 35 appeared benign. The correlation between tumour appearance and outcome is shown in Table 2. The accuracy of cholangioscopy impression was 35/45 (77.8%). The sensitivity was 7/14 (50.0%) and the specificity was 28/31 (90.3%). The positive predictive value was 7/10 (70.0%) and the negative predictive value was 28/35 (80.0%).

Neovascularization was seen in eight patients. Seven of these had cholangiocarcinoma (positive predictive value 87.5%). Brush and biopsies revealed chronic inflammation in one patient with apparent neovascularization. He was doing well after 17 months of follow-up.

Table 2: diagnostic accuracy

		Outcome	
		Malignant	**Benign**
Cholangioscopy impression (n = 45)	Malignant	7	3
	Benign	7	28
Biopsy (n=29)	Malignant	0	0
	Benign	4	9
	Inconclusive	1	5
	Insufficient material	7	3
Brush (n = 27)	Malignant	6	0
	Benign	4	13
	Inconclusive	1	3
Cholangioscopy impression, biopsy and brush combined (n = 45)	Malignant	9	3
	Benign	5	28

Biopsies and brush cytology

Spybite biopsies were taken in 29 patients. The histopathological analysis yielded benign cells in 13 (44.8%), atypical cells in 6 (20.7%) and insufficient material in 10 patients (34.5%), as portrayed in Table 2. No malignant cells were seen in any of the Spybite biopsies. Of the 13 patients with benign biopsies, 4 were nonetheless confirmed to have cholangiocarcinoma. The accuracy of the Spybite biopsies was 9/29 (31.0%). The sensitivity was 0/29 (0%) and the specificity was 9/31 (31.0%). The positive predictive value could not be calculated. The negative predictive value was 9/13 (69.2%). However, most samples 16/29 (55.2%) were not usable or inconclusive and thus had no predictive value at all.

Brush cytology was performed in 27 patients. The cytology analysis yielded benign cells in 17 patients, atypical cells in 4 patients and malignant cells in 6 patients. The sensitivity was 6/11 (54.5%) and the specificity was 13/16 (81.3%). The six patients with malignant cells in the brush cytology, were all confirmed to have cholangiocarcinoma (positive predictive value of 100%); the negative predictive value was 13/17 (76.5%).

Combined accuracy

The combined accuracy of cholangioscopy impression, biopsy and brush was 37/45 (82.2%). The sensitivity was 9/14 (64.3%) and the specificity was 28/35 (80.0%). The positive predictive value was 9/12 (75.0%) and the negative predictive value was 28/33 (84.5%). The overall accuracy was 14/15 (93.3%) in patients with PSC versus 23/30 (76.7%) in patients without PSC (p = 0.338).

Complications

There was one complication (2.2%): a patient developed fever postoperatively for which antibiotics were continued for several days. The patient recovered uneventfully.

DISCUSSION

This study represents a relatively large cohort on the accuracy of peroral cholangioscopy and biopsy for indeterminate bile duct lesions. We found a fairly good overall accuracy at 82%, although it was considerably less than some previously published series at 93 and 94% (Table 3). Of particular interest was the poor performance of the Spybite biopsies: over half the biopsies were not sufficient for histopathologic analysis or inconclusive. This was in sharp contrast with excellent results of biopsies by Ramchandani et al and Chen et al. On the other hand, conventional brush cytology during peroral cholangioscopy had additional value compared to cholangioscopy alone in this series.

It should be kept in mind that the patient group is a challenging one. Conventional diagnostics failed to yield a definitive diagnosis in all patients despite MRCP and/or CT and/or EUS. One third of the patients had primary sclerosing cholangitis (PSC) as complicating factor. In the light of these circumstances, an overall accuracy of 82% may not seem so unacceptable. Furthermore, the results of cholangioscopy should always be interpreted together with that the other investigations and the clinical context.

In the group of patients with PSC, the stakes of accurate diagnosis are especially high as these patients may require liver transplantation at one point or another. Eligibility for such a transplantation, and thereby fair use of the limited supply of donor organs, depends on the accurate distinction between malignant and benign lesions. Any additional accuracy in this patient group is welcome. The risk of cholangioscopy is low, as demonstrated by the low

Table 3: medium to large sized studies of peroral cholangioscopy for patients with indeterminate bile duct lesions upon conventional imaging. Studies published before 1990 were not included.

Study	No of patients	Accuracy of cholangioscopy only	Accuracy of biopsies	Accuracy of cholangioscopy and biopsy
Current study	45	35/45 (78%)	9/29 (31%)	37/45 (82%) **
Draganov[11]	26	NA	22/26 (85%)	NA
Kalaitzakis	117	NA	43/74 (58%)	102/117 (87%)
Siddiqui et al[12]*	30	NA	NA	23/30 (77%)
Doi et al[13]	36	Assesses the image quality and not diagnostic accuracy		
Chen et al[5]	226	95/119 (80%)	85/119 (75%)	NA
Albert et al[14]	22	Accuracy not deductable from presented data		
Ramchandani et al[6]	36	32/36 (89%)	27/33 (82%)	34/36 (94%)
Itoi et al[15]	144	Patients were unselected (had not undergone previous conventional investigation)		
Kawakami et al[16]	44	Assesses the ability to diagnose intraepithelial spread in patients with confirmed malignancy		
Moon et al[17]	32	Assesses success rate of procedure and not diagnostic accuracy		
Chen et al[18]	20	17/20 (85%)	18/20 (90%)	18/20 (90%)
Shah et al[19]*	62	NA	NA	NA
Fukuda et al[8]	97	NA	NA	93% **
Wang et al[20]	99	Assesses success rate of procedure and not diagnostic accuracy		
Igarashi et al[21]	99	Assesses success rate of procedure and not diagnostic accuracy		

* abstract only

** includes brush cytology during cholangioscopy; NA = not available complication rate in this series and others. In our series cholangioscopy in patients with and without PSC was equally accurate.

The accuracy of cholangioscopy impression in our series (78%) was similar or slightly lower than that published in previous series (80-90%) as shown in table 3. The overall accuracy (82%), too, was comparable to other studies (77-93%). As stated earlier, the largest difference was the poor performance of Spybite biopsies in our series at 31%. Closest to our findings is the study by Kalaitzakis et al, who report an accuracy of 58%.

The taking, processing, analyzing and interpreting of biopsies is a multidisciplinary affair. Differences in pathologist profiles may influence the amount of material needed to confidently interpret cells as benign or malignant.

As this was a single center, single operator study, an operator effect on the quality of biopsies cannot be excluded. However, the volume of patients was relatively high, which would be expected to increase the quality of the biopsies. The discrepancy between our results and that of others warrants the publication of more large patient cohorts so that the real value of biopsies can be assessed.

The complication rate in this series was low (1/46 patients).This is in accordance with previous series reporting a complication rate around 5%[6,9]; the main complications being pancreatitis, cholangitis and bile duct perforation. It is plausible that cholangioscopy may be accompanied by a higher complication rate than ERCP because of the increased irrigation and manipulation of the bile ducts, but there are currently no data to support this.

A major strength of this study is that it presents a relatively large cohort of patients. It is somewhat limited by its partly retrospective nature, although the records and follow-up were of sufficient quality to ensure representative results.

To improve tumour visualization, targeted imaging strategies may be employed in the future. Near-infrared fluorescence imaging is a technique that may enable tumour-specific imaging. To achieve this, fluorescent molecules would need to be conjugated to markers that are specifically expressed in cholangiocarcinoma. Examples of such markers are p53 mutation, cyclins, proliferation indices and mucins[10]. Such markers can be further explored using pre-set criteria, for example the TASC criteria described by Van Oosten et al[11].

In conclusion, this study confirms that peroral cholangioscopy is a useful investigation in patients with indeterminate bile duct lesions in whom conventional investigations failed to yield a diagnosis. The disappointing yield of Spybite biopsies cannot be readily explained. Further research will determine whether the poor performance in this series is an outlier.

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Chapter

8

Multispectral real-time fluorescence imaging: theory and practice

Previously published as

Novel technique: intraoperative fluorescence imaging

Nederlands tijdschrift voor Geneeskunde 2012

Multispectral real-time fluorescence imaging for intraoperative detection of the sentinel lymph node in gynecologic oncology

Journal of Visualized Experiments 2010 - video supplement freely accessible at www.jove.com/video/2225/multispectral-real-time-fluorescence-imaging-for-intraoperative?ID=2225)

In the first part of this chapter we discuss the theory behind near-infrared fluorescence imaging and its potential applications. In the second part we demonstrate the technique by means of a video article and corresponding protocol.

1 - THEORY

Technique

Fluorescence imaging consists of activating a fluorescent contrast agent (excitation), which in turn emits light of a slightly longer wavelenght. The excitation and registration of the emitted light is performed by fluorescence cameras which visualize the contrast agent (tracer). Near infrared (NIR) fluorescent light, at a wavelength of 700 – 900 nanometers has a number of advantages for the purpose of imaging of human tissue compared to visible light. It has a lower absorption in tissue and thus penetrates deeper than regular light. Currently, there are two clinically available NIR fluorescent agents: indocyanine green (ICG) and methylene blue. Another optical contrast agent that is used is fluoresceine isothiocyanate (FITC), but the wavelength of FITC is not in the NIR spectrum.

After subcutaneous or intravenous injection of the fluorescent agent, lymph nodes and or blood vessels (among others) may be visualized to a depth of up to one centimeter. If the fluorescent agent is conjugated to a tumourspecific moleculе, tumours and metastases may be specifically visualized[1]. There are a number of fluorescence cameras currently in use in the Netherlands; laparoscopic as well as open systems. The newer generation cameras combine the fluorescence images with the white light images of the surgical field. Also, they correct for light absorbtion and reflection to prevent false positive and false negative signals. With the integrated fluorescence and white light images, the surgeon can translate the fluorescent images directly to the surgical field and operate accordingly.

Need for the technique

Pre-operative imaging studies such as CT, PET and MRI provide the surgeon insight into the anatomy, location of tumours and their position with regards to vital structures. The translation of these images to the surgical field can be difficult. This leaves the surgeon dependent on his or her sight and touch. Complications such as iatrogenic damage to anatomical structures (for example ~ 0.5% major bile duct injuries) and irradical tumour resections (for example 11-21% R1 resections in breast-spearing surgery) do occur as a result.

A technique that would aid in clarifying the anatomy and identifying tumour margins would be of great value.

Possibles areas of application

Sentinel lymph node procedures

Most experience with fluorescence imaging is during sentinel lymph node procedures in surgical oncology. The sentinel lymph node is the first lymph node to which a tumour metastasizes. Analysis of this node often determines the further treatment and-or prognosis of the cancer. The current technique of sentinel lymph node detection with radioactive tracer and blue dye has drawbacks such as the perioperative logistics, the short half-life of the radiotracer, the use of radioactive material and the blue discoloration of the surgical field. NIR fluorescence imaging has no such drawbacks. After peritumoral injection of ICG the surgeon receives real-time visual information up to depths of 1cm (fatty) tissue. Sentinel node procedures have been conducted in experimental setting in breast cancer[2] (figure 1A), colon cancer, gastric cancer, melanoma, head and neck tumours, cervix cancer and vulva cancer.

Recognition of vital structures

Non-specific fluorescent agents scan be used to delineate anatomic structures. Intraoperative NIR fluorescence for assessment of the vascularisation of skin-muscle resconstructions is an example of such an application. ICG is mainly excreted through the biliary tract and can thus be used to visualize bile ducts during liver or gallbladder surgery. Intravenously injected methylene blue is excreted mainly in the kidneys and can therefore be used to visualize the ureters during intra- and retroperitoneal procedures (Figuur 1B).

Visualization of tumours and metastases

Superficial liver tumours and metastases (up to 8mm under the liver capsula) may be detected with non-specific fluorescent tracers. After intravenous injection of ICG a fluorescent ring is seen around the lesions[3]. This is probably caused by stasis of ICG as a result of the interrupted bile flow around the lesions. In this manner small, non-palpable tumours are detected that are missed by intra-operative ultrasound. Preoperative imaging remains necessary to identify the deeper located lesions.

Recently, the first pilot study was performed of a tumourspecific contrast agent in patients with ovarian cancer[1]. A fluorescent tracer was used that consisted of folate and FITC. The folate binds to folate receptor alpha, a receptor expressed by 85% of ovary tumours but not by healthy cells. After internalization of the tracer, cancer cells can be visualized by the camerasystem (Figure 2). Fluorescent signal was seen in all malignant tumours and metastases (up to a diameter of 0.5mm) and in none of the benign lesions.

Efficacy

As of yet, efficacy studies have only been peformed for non-specific NIR fluorescence imaging in sentinel node procedures. In a pilot study of 141 patients with breast cancer, a similar sensitivity was achieved to that with the gold standard[4]. Large clinical trials on the differend applications of NIR fluorescence imaging will ultimately determine the value of the technique.

Learning curve

Fluorescence camerasystems and software are user-friendly. Image guided surgery requires a certain eye-hand co-ordination but the learning curve is hort, especially for surgeons who have experience with laparoscopic procedures. There are initiatives for short fluorescence surgery training modules in Dutch medical centres.

Future perspectives

Recently, grants have been awarded in the Netherlands to further validate this experimental technique. Camera systems and contrast agents are being optimalized. Increasing the depth of penetration of the fluorescent light is an important area of research.

Novel applications of NIR fluorescence imaging are for example visualization of nerves and instable atherosclerotic plaques. New clinical grade contrast agents will enter the market. A national network of physicians and scientists from different academic centres is developing standardized protocols and data registration. These efforts will result in an efficiënt and safe introduction of this technique into clinical practice.

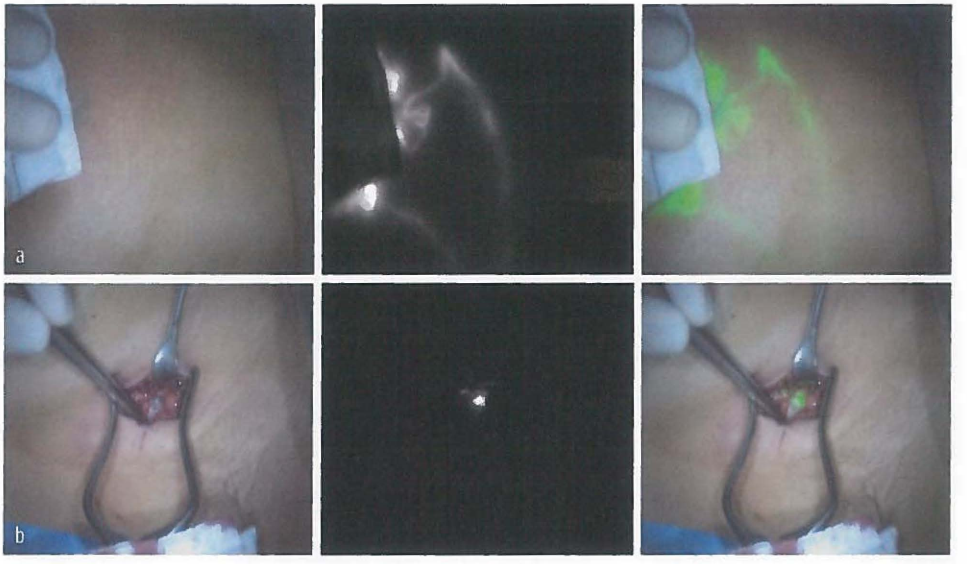

Figure 1. (A) Sentinel node procedure with NIR fluorescence in a patient with breast cancer (colour image on the left NIR fluorescence imaging in the centre and an overlay on the right). After periaureolar injection of ICG two subcutaneous lymphe vessels (white triangles) can be traced in the direction of the axilla (upper row), after which the sentinel node (arrow) is visualised (lower row). (B) Intra-operative visualisation of a ureter after intravenous injection of methylene blue (arrow).

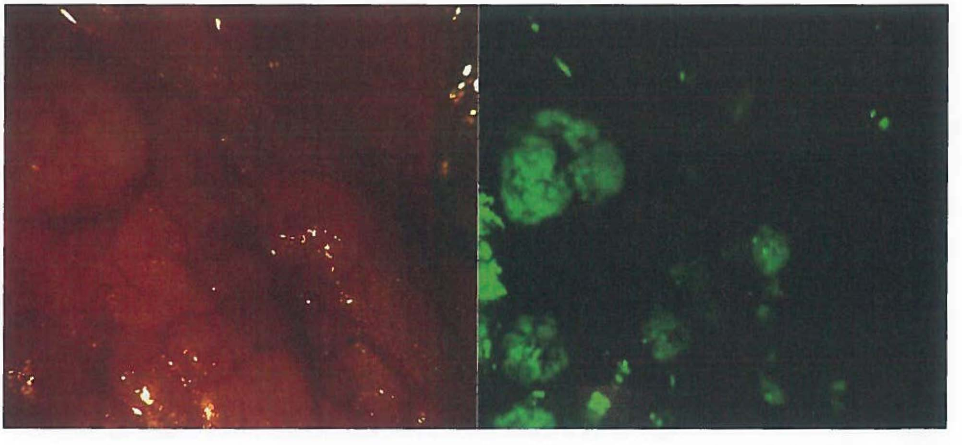

Figure 2. Intraoperative visualization of peritoneal tumour deposits of ovarian carcinoma after intravenous injection of the tumour specific tracer folate-FITC (colour image on the left, fluorescence image on the right).

2 - PRACTICE

The aim of this video article is to demonstrate the detection of the SLN using intraoperative fluorescence imaging in patients with cervical and vulvar cancer. Fluorescence imaging is used in conjunction with the standard procedure, consisting of radiocolloid and a blue dye. In the future, intraoperative fluorescence imaging might replace the current method and is also easily transferable to other indications like breast cancer and melanoma.

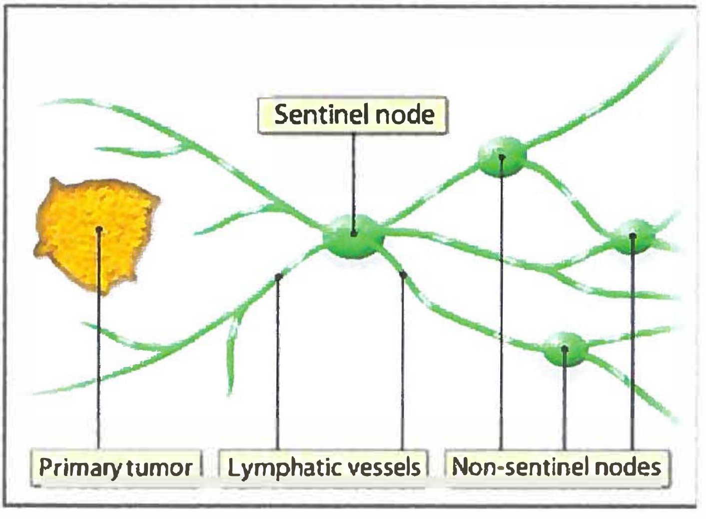

Figure 1. The sentinel lymph node (SLN) theory. *The SLN is the first draining node from the tumor.*

1. Intraoperative Multispectral Fluorescence Camera

A custom-made camera system was developed at developed at the Institute for Biological and Medical Imaging (IBMI, Technical University / Helmholtz Zentrum, Munich, Germany) in close in collaboration with SurgOptix (SurgOptix Inc, Redwood Shores, CA, USA). The setup of the intraoperative multispectral fluorescence camera system is shown in Figure 2.

1. Light passes through a system of optics and is separated into visible light, light at the emission (fluorescence) wavelength band and light at the excitation wavelength band. These bundles are detected by CCD-cameras (CCD) (Figure 2). Multi-spectral signals from all cameras are processed in order to correct for artifacts and yield true quantitative fluorochrome bio-distribution. Color and fluorescence signals can be displayed as separate images on external monitors or superimposed in one image.
2. The excitation and emission filters of the camera are set in the measurement herein to collect at 750 nm and 800 ±20 nm respectively.

2. Optical Contrast Agent Preparation

1. The fluorescent contrast agent indocyanine green (ICG, Pulsion AG, Munich, Germany) is prepared under sterile conditions. A concentration of 0.5 mg/mL is used. It is important to use sterile distilled water and not sodium chloride (NaCl), as the latter will cause the ICG to aggregate
2. After preparation, the solution must be stored in a dark, cool place to avoid fast deterioration of the fluorescence intensity by bleaching. Note: from this point forward keep the ICG protected from light

3. Intraoperative Imaging - Setup and Injection of ICG

1. The camera is positioned and initiated in the operating theatre prior to surgery to minimize interference with the standard surgical procedure, and connected to the high-definition screens (Figure 2B).
2. The camera is covered in standard sterile drapes (Carl Zeiss Vision BV, Sliedrecht, the Netherlands, OPMI Drape REF 306071) by the investigator in sterile OR clothing.
3. Note: care is taken to use only clear disinfecting agents, as colored disinfecting agents are often autofluorescent and might interfere with the imaging procedure. Moreover, sterile drapes and surgical markers can be autofluorescent. It is advised to test all materials used in the OR and the operating field for autofluorescence prior to surgery.
4. The fluorescent contrast agent indocyanine green (ICG) is prepared under sterile conditions. A concentration of 0.5 mg/mL is used. It is important to use sterile distilled water and not NaCl, as the latter will cause the ICG to aggregate. After preparation, the solution must be stored in a dark, cool place to avoid fast deterioration of the fluorescence intensity. Note: it is advisable to change gloves after preparing ICG, as even a small amount of spill of ICG may influence the image quality.
5. The imaging procedure starts after opening the abdomen. When the area of interest is exposed, the camera is maneuvered into the operating field. The zoom and focus are adjusted under sterile conditions. Lights in the operating theatre are switched off for better detection of the fluorescence signal.

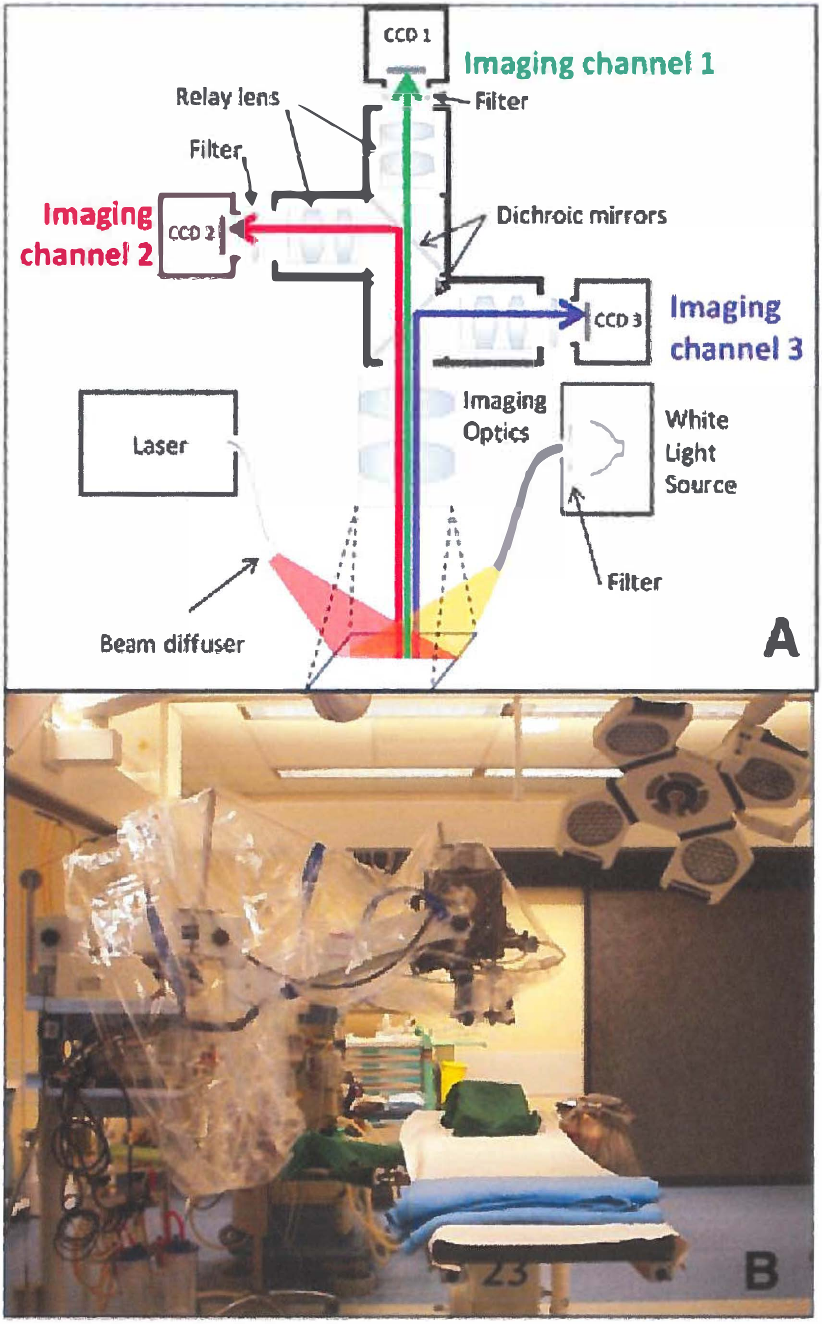

Figure 2. Schematic picture of the multispectral fluorescence camera system (A). The basic setup of the camera system in the operating theatre (B).

6. 1.0 mL of 0.5 mg/ mL ICG is mixed with 1.0 mL of the standard blue dye (patent blue / bleu patenté, Guerbet, France) in one syringe. The surgeon injects the contrast agent in four quadrants around the primary tumor, preventing spill of the agent. Note: in case of spill of ICG on the surgical gloves, it is necessary to change gloves. Still images or real-time videos are acquired of the lymph flow and the appearance of the fluorescent sentinel lymph node (Figure 3). All images and videos are directly saved on the computer.

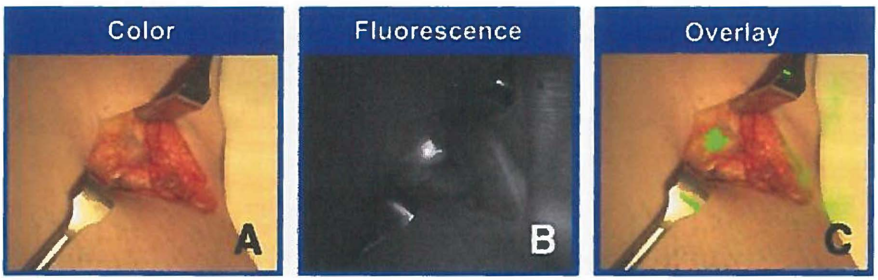

Figure 3. Multispectral fluorescence imaging of a lymph node in vulvar cancer. Color image of a lymph node in vivo (A). Fluorescence image of the same lymph node, in vivo (B). Pseudocolor fluorescence image superimposed on the color image (C).

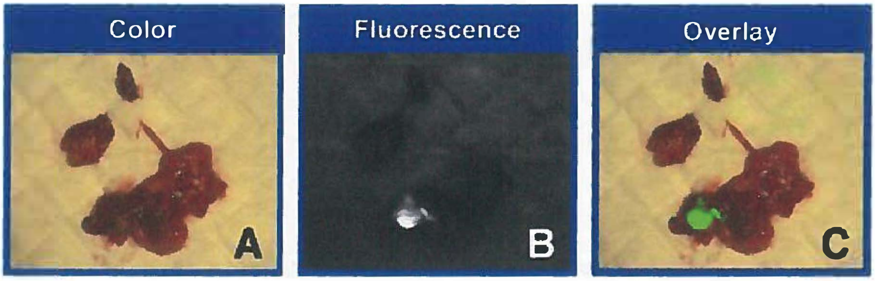

Figure 4. Multispectral fluorescence imaging of a lymph node ex vivo in cervical cancer. Color image of a lymph node ex vivo (A). Fluorescence image of the same lymph node, ex vivo (B). Pseudocolor fluorescence image superimposed on the color image (C).

7. Apart from fluorescence, the SLN is also detected according to the standard protocol, either using a gamma probe or by visual inspection for a blue discoloration, or both. The radioactive tracer is generally administered one day prior to surgery, after which a lymphoscintigram is performed for detection of a radioactive SLN. This is part of the standard procedure and has no place in the fluorescence imaging protocol.
8. Apart from fluorescence, the SLN is also detected according to the standard protocol, either using a gamma probe or by visual inspection for a blue discoloration, or both. The radioactive tracer is generally administered one day prior to surgery, after which a lymphoscintigram is performed for detection of a radioactive SLN. This is part of the standard procedure and has no place in the fluorescence imaging protocol.
9. Real-time excision of the SLN is guided by both fluorescence and blue discoloration of lymph nodes. The real-time feature of the camera helps to detect for any remnant fluorescence or unexpected localizations of fluorescent nodes.
10. After excision of the SLN, *ex vivo* images are acquired of all excised lymph nodes for the presence of a fluorescent signal. The exposure time can be prolonged for higher resolution when capturing still images (Figure 4).
11. Histopathological examination of the lymph nodes reveals the presence or absence of tumor cells in the sentinel lymph node.

4. Representative Results

Fluorescent lymph nodes can be detected with a high signal-to-background ratio. Also, flow of ICG through lymphatic vessels can be monitored allowing real-time lymph node mapping. Results may be influenced by increasing depth of the node, possibly requiring different illumination procedures to achieve detection. Future application of specific tumor targeted fluorescent agents may provide intraoperative detection of a positive SLN with cancer cells using this technology. Results are shown in the video supplement.

DISCUSSION

This video demonstrates the application of multispectral intraoperative fluorescence imaging technology for intraoperative detection of the sentinel lymph node (SLN) in gynecologic oncology. The methodology has certain advantages over the conventional SLN procedure. The injection takes place during the surgical procedure itself with the patient anesthetized rather than a day prior to surgery, which is more patient-friendly, especially in gynecologic cancers. Furthermore, intraoperative imaging provides the surgeon with direct visual feedback of the lymph flow and its drainage pattern to the SLN, rather than indirectly via a Geiger-teller. In cervical cancer, where lymph nodes are located deep in the pelvis, this may help improve detection.

Nonetheless, the greatest significance lies in the step-up approach towards targeted imaging. Targeted fluorescent contrast agents may be fused with tumor-specific antibodies or substrates specifically directed at tumor cells. In this manner, intraoperative fluorescence imaging has great potential to radically alter the current practice of oncologic surgery

Disclosure: VN and GMvD are member of the scientific board of SurgOptix Inc. Prior to the procedure, the research protocol is approved by the local Investigational Review Board (IRB) and informed consent from the patient is acquired.

Acknowledgements: We are indebted to Mrs. Ina Wesselman for training and planning of the OR personnel. Wendy Kelder, Susanne van der Velde, Niels Harlaar, Merlijn Hutteman en Joost van der Vorst contributed to the original manuscript.

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Chapter

9

Intraoperative fluorescence cholangiography: preclinical considerations and future perspectives

KT Buddingh, JS de Jong, RG Pleijhuis, VB Nieuwenhuijs, GM van Dam

In preparation

ABSTRACT

Introduction: The current golden standard for bile duct visualization is intraoperative cholangiography (IOC) using radiopaque contrast. A promising new technology for bile duct visualisation is intraoperative fluorescence cholangiography (IFC). Prior to the initiation of IFC in human studies, the aim of this study was to describe the preclinical considerations such as optimal concentrations of indocyanine green (ICG) in human bile, optimal excitation and emission wavelengths and penetration depth. Furthermore we compared ICG to IRDye® 800CW-CA, a novel clinical grade fluorophore potentially suitable for IFC:.

Methods: Dilution series of ICG and IRDye® 800CW-CA in human bile imaged at different excitation and emission wavelengths. Fat-simulating tissue of different thickness was used to assess maximal penetration depth. ICG and IRDye® 800CW-CA were injected into extrahepatic bile ducts of two explanted pig liver specimens and compared to conventional cholangiography of the same specimens.

Results: In human bile, the optimal concentration of ICG is >0.005 and <0.01mg/ml; for IRDye® 800CW it is ~0,02mg/ml. Optimal excitation and emission wavelengths for NIRF imaging were 745nm and 840 nm respectively. The penetration depth of IRDye® CW800-CA through fat resembling plaques was 7mm versus 5mm for ICG. Intrabiliary administration of ICG made it possible to identify the cystic duct and its confluence with the common bile duct. The obtained images were comparable with conventional cholangiography as far the extrahepatic bile ducts were concerned.

Conclusion: IFC seems a promising new modality for intraoperative visualization of the extrahepatic bile ducts. The current study has described several important preclinical aspects that need to be taken into account in order to achieve optimal bile duct imaging in humans.

INTRODUCTION

Intraoperative visualization of bile ducts is necessary to prevent bile duct injury during cholecystectomy. Different modalities have been developed for this purpose[1], the most frequently used being intraoperative cholangiography (IOC) using radiopaque contrast agents. Other less common modalities include cholecystocholangiography, laparoscopic ultrasound and dye cholangiography[1]. A promising new modality is bile duct mapping using fluorescence in the near-infrared spectrum, also known as intraoperative fluorescence cholangiography (IFC).

In theory, IFC has several important advantages over IOC. It may be performed repeatedly and if the fluorescent contrast agent is administered intravenously it does not require selective bile duct cannulation. Furthermore, the real-time images are acquired in an earlier stage at the earliest start of the procedure, even prior to dissection in the triangle of Calot providing both color and fluorescence information of the localization of the extrahepatic bile ducts.

IFC has been performed earlier in animals yielding excellent images. Tanaka et al mapped bile ducts in pigs and could detect artificial inclusions resembling bile duct stones in the common bile duct[2]. Figuiredo et al demonstrated detection of bile duct injury in a mouse model[3]. IFC has also been performed in several patients[4]. However, the images obtained in human subjects are of inferior quality to those achieved in animals, and do not meet the quality of the gold standard which is conventional IOC.

Prior to the initiation of IFC in human studies at our centre, the aim of this study was to explore preclinical aspects of bile duct mapping. We aimed to compare the technique ex vivo with IOC, and describe the optimal excitation and emission wavelengths and the optimal concentration of indocyanine green (ICG) and IRDye 800CW-CA in human bile. Furthermore, we compared ICG to a novel clinical grade optical contrast agent IRdye® 800CW-CA in terms of intensity of the fluorescent signal and penetration depth through fat-simulating fantom tissue, resembling the often fatty triangle of Calot.

METHODS

Fluorophores

Indocyanine green (ICG) was obtained from Pulsion Medical Systems AG, Munchen Germany. IRDye® 800CW-CA was obtained from LI-COR® Biosciences (Lincoln, Nebraska).

Optimal concentration of ICG and IRDye® 800CW-CA in human bile

Because increasing concentrations of ICG may not correspond to an increased fluorescence signal due to self-quenching of ICG, different concentrations of ICG in human bile was evaluated for fluorescence activity. Human bile was obtained with permission from a patient with a T-drain in the common bile duct after reconstruction. Varying concentrations of ICG were dissolved in the bile after which images were obtained using the IVIS Spectrum® (Caliper Life Sciences, Hopkinton, MA) . The same was done using IRDye® 800CW-CA dissolved in human bile.

Optimal excitation and emission wavelengths for ICG and IRdye® 800-CW fluorescence imaging

ICG and IRDye® 800CW-CA in the optimal concentration found in the previous experiment (approximately 0.007mg/ml and 0.02mg/ml respectively) were imaged at the different excitation and emission wavelength options present at the IVIS Spectrum®. In this way an optimal excitation and emission wavelength could be determined.

Penetration depth of ICG and IRdye® 800CW fluorescence through fat-simulating tissue

In order to determine the maximal penetration depth of the fluorescent signal of ICG and IRDye® 800CW-CA, two thin transparent plastic tubes (PVC, 0.4mm thickness) were filled with human bile with the predetermined optimal concentration of ICG and IRDye® 800CW-CA respectively. Subsequently, layers of fat-simulating tissue (Intralipid® 20% (Sigma–Aldrich)) were placed over the tubes. Next, the fluorescent signal was measured using a prototype intraoperative near-infrared fluorescent imaging system[5].

ICG in ex-vivo porcine gallbladder specimens

To assess the feasibility of intraoperative fluorescence cholangiography, two porcine specimens were obtained of liver, gallbladder and pancreas. Indocyanine green was injected into the gallbladder in an amount calculated to obtain the optimal concentration of ICG in bile. The specimens were then placed in the IVIS Spectrum® and colour and fluorescence images were obtained. In addition, standard radiographic cholangiography was performed on the biliary system.

RESULTS

Optimal concentration of ICG and IRDye® 800CW-CA in human bile

The fluorescent strength of ICG and IRDye® 800CW-CA at different concentrations are shown in Figure 1. The optimal concentration for ICG was found to be in between 0.005 and 0.01 mg/ml. IRDye® 800CW-CA had an optimum 0.02 mg/ml.

Optimal excitation and emission wavelength for ICG and IRDye® 800CW-CA fluorescence imaging

Both ICG and IRDye 800CW-CA were tested in a 96-wells plate. The wells were imaged with the excitation wavelengths at 710 nm and 745 nm. The emission wavelengths were 780nm, 800nm, 820nm and 840nm. IRDye® 800CW-CA emitted signal of higher intensity than ICG at all wavelengths: average signal strength was $4.8*10^{10}$ counts for IRDye® 800CW-CA versus $7.4*10^{4}$ counts for ICG ($p < 0.001$). The optimal excitation wavelength was 745nm for both fluorophores. In ICG the average counts measured were $1.0*10^{6}$ at 745 nm and $9.8*10^{5}$ at 710 nm ($p = 0.027$). For IRDye® 800CW-CA the values were $5.9*10^{11}$ at 745 nm versus $5.5*10^{11}$ at 710 nm ($p = 0.028$). The optimal emission wavelength was 840nm for both fluorophores.

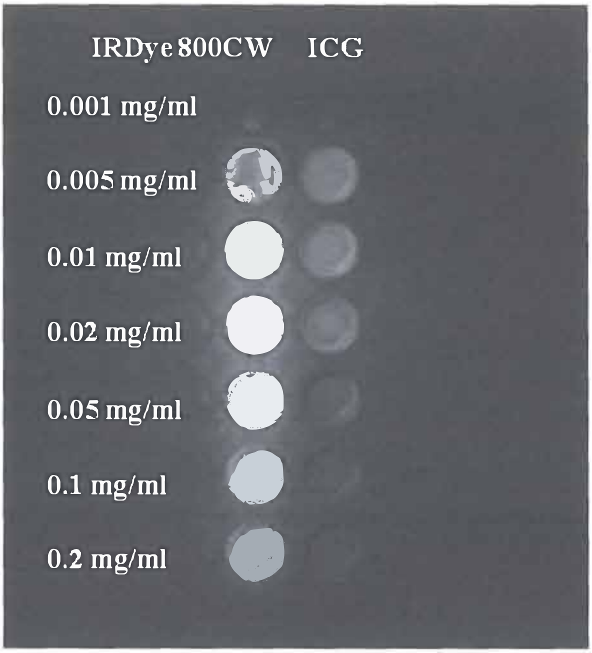
Penetration depth of ICG and IRDye® 800CW-CA fluorescence through fat-simulating tissue

Plastic tubes filled with ICG (0.007 mg/ml) remained visible under a fat-simulating layer of up to 5mm. IRDye® 800CW-CA had a stronger fluorescent signal (235 versus 71 arbitrary units, $p < 0.001$) and was clearly visible at up to 7mm. (Figure 2).

ICG in ex-vivo porcine gallbladder specimens

The porcine extrahepatic biliary tract could be clearly delineated with the ICG solution of ~0.007mg/ml. The image obtained corresponds fairly well with the regular cholangiography image. However, on the regular IOC image, several intrahepatic branches are visible too which could not be visualized by using IFC. (Figure 3).

Figure 1: fluorescent signal of ICG and 800CW-CA at different concentrations in human bile



DISCUSSION

Bile duct injuries have been called the scourge of laparoscopic cholecystectomy. Although the incidence has been somewhat reduced in the course of the global learning curve and the introduction of the 'critical view of safety' technique, it remains an important issue in surgical practice. The classic method of bile duct visualization and thus prevention of bile duct injury is intraoperative cholangiography using radiopaque contrast and X-ray imaging[1]. Important limitations of the technique are the fact that it can be cumbersome and time consuming, and that it requires the availability of a radiology assistant. A minor limitation is the use of low dose ionizing radioation. Of the (experimental) alternatives, near infrared fluorescence cholangiography seems to be the most promising modality[1]. It is potentially a fast, real-time, radiation-free method of intraoperative bile duct visualization.

In this study we have demonstrated several important pre-clinical aspects of fluorescence cholangiography necessary prior to human use. Clearly, there is an optimal concentration of the fluorophore for bile duct imaging. As has also been described by other groups, when the concentration of ICG is exceeds the optimal concentration the strength of the signal significantly decreases (known as 'self-quenching')[6]. Moreover, signal strength differs between fluorophores based on their chemical characteristics. ICG, currently most frequently used for IFC in patients, is certainly not the strongest of them, as demonstrated in this comparison with IRDye® 800CW-CA based on their signal strength when dissolved in bile and the penetration of their signal through fat-simulating tissue. The wavelength at which the fluorophore is excited and imaged should be carefully chosen as this, too, greatly affects the strength of the signal. Finally, we demonstrated in ex vivo pig specimen the feasibility of accurate delineation of the bile ducts, which is, in regards to the extrahepatic bile ducts, comparable to conventional radiographic cholangiography. The abovementioned factors need to be optimized before fluorescence cholangiography can be successfully implemented in a clinical (operating theatre) setting.

Firstly, the excitation en emission specifications of the camera system need to be optimized. This should not pose a problem as most (prototype) camerasystems allow for changing of lenses and lasers.

Secondly, the optimal fluorophore needs to be used. The choice in types of fluorophores is greatly limited by their (FDA) registration for use in patients. Currently, ICG is probably the most used fluorophore on the market for in-human use. It is expected that other fluorophores, such as IRDye® 800CW-CA, will undergo the necessary toxicity tests and registration progresses in order to achieve FDA registration in the nearby future.

Thirdly, the optimal concentration of fluorophore needs to be achieved in the biliary tract after intravenous administration. This will be fluorophore-dependent but there may also be an inter-patient variation. Dose finding studies will provide answers to these questions. Naturally this step can only follow FDA registration as described in the previous paragraph.

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Figure 2 IRDye 800CW and ICG seen through layers of fatty simulating tissue of different thicknesses

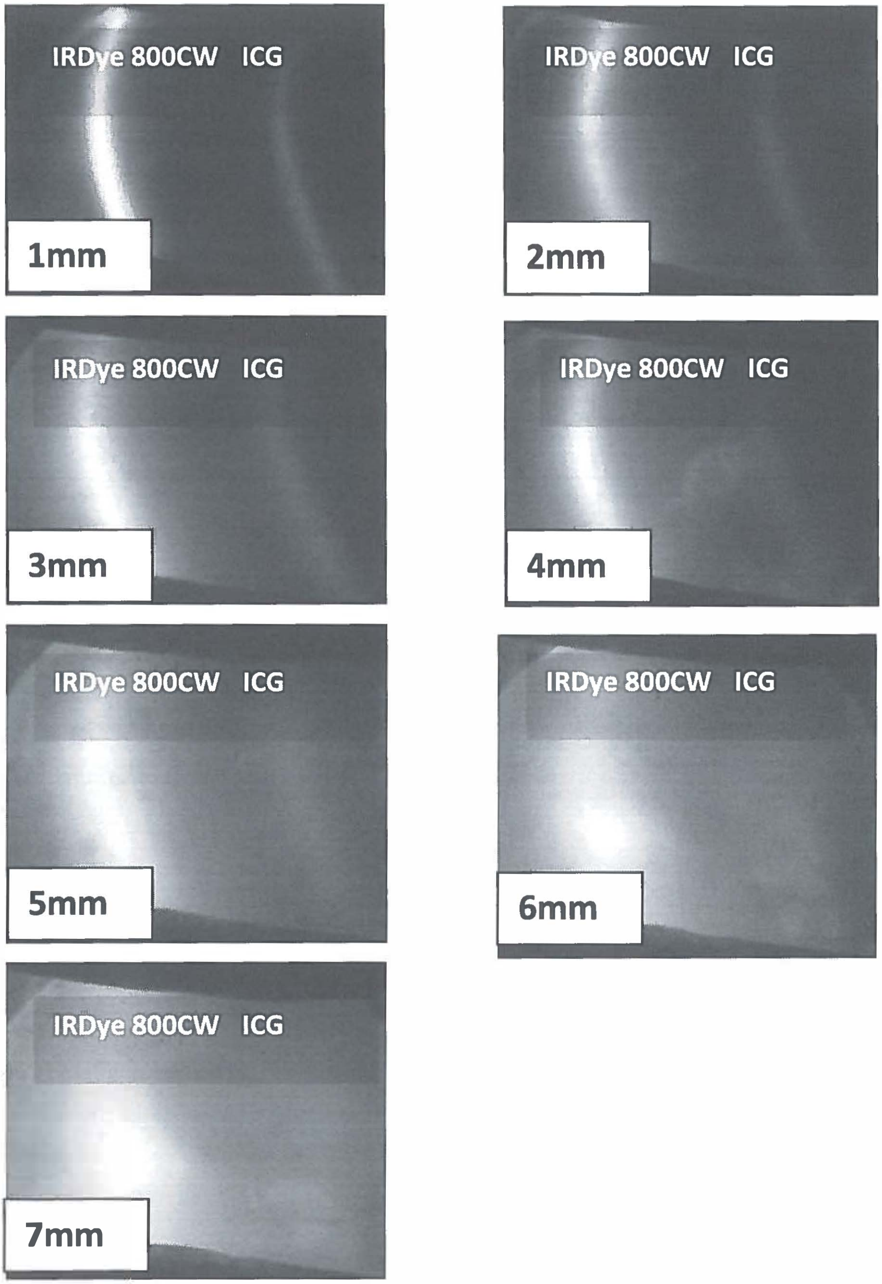
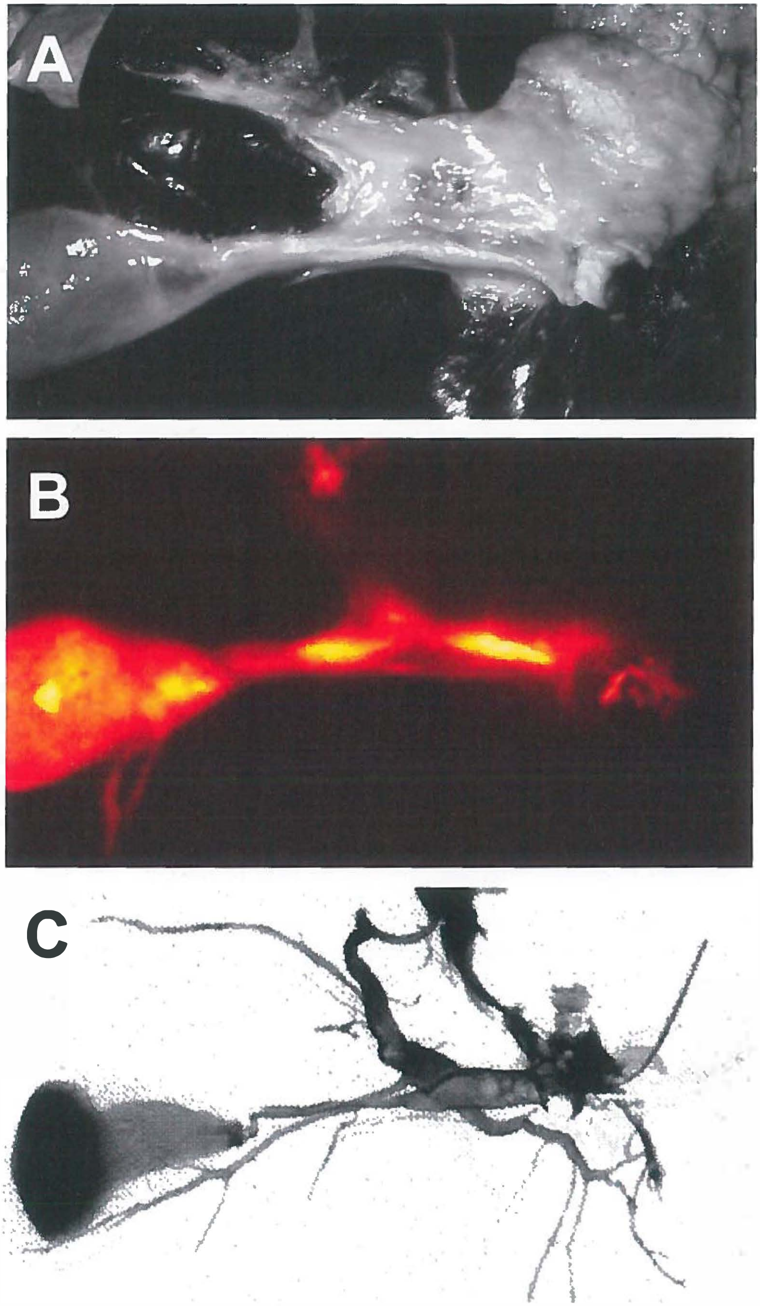


Figure 3 Ex-vivo pig gallbladder specimens perfeused with indoyanine green imaged at white light (A), with near-infreared fluorescence imaging (B) and an overlay reconstruction (C)



In conclusion, the success of intraoperative fluorescence cholangiography depends on achieving the following critical components: i) the fluorophore with the highest intensity of fluorescent signal, ii) optimal concentration of fluorophore in the bile ducts and iii) imaging at the optimal wavelengths. If these conditions are met, fluorescence cholangiography can indeed be a fast, real-time, radiation-free method of intraoperative bile duct visualization.

Acknowledgements

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Chapter 10

Summary, general discussion and recommendations

SUMMARY

Intraoperative cholangiography

Chapter 1 describes several important developments that paved the way for modern gallbladder surgery. An important step was the recognition in 1609 of gallstones as the cause of serious conditions such as cholecystitis and choledocholithiasis. This led to practice of cholecystostomy (surgical stone removal). The next important development was the recognition that gallstone disease could be cured by removing the entire gallbladder, and that patients did not suffer grave consequences from this operation. Cholecystectomy further evolved with the advent of laparoscopy approximately 100 years after the first open cholecystectomy. However, this development came at a price: the rate of major bile duct injury (BDI) more than doubled in the following years.

In response to the increased risk of BDI with laparoscopic cholecystectomy, safety precautions to improve the intraoperative assessment of the biliary anatomy were implemented. The evidence in favour of the different techniques is presented in **Chapter 2**. The 'critical view of safety' (CVS) approach is accepted by most guidelines and commentaries as the surgical technique of choice to minimize BDI risk. Data on the efficacy of this technique in preventing BDI is, however, is scarce. Intraoperative cholangiography is associated with lower BDI risk in a pooled analysis of large cohort studies (OR 0.68, CI 0.61-0.75). However, it carries extra costs, prolongs the procedure and may be experienced as cumbersome. The evidence for IOC dates largely from the pre-CVS era. Further research is necessary to fully establish the role of IOC in laparoscopic cholecystectomy anno 2010.

An established reliable alternative to IOC is laparoscopic ultrasound, but its longer learning curve limits widespread implementation. Cholecystocholangiography (injection of radio contrast directly into the gallbladder) and dye cholangiography (using colored dye) are simple techniques but yield poor quality images. Light cholangiography, requiring retrograde insertion of an optical fiber into the common bile duct, is too unwieldy for routine use. Experimental techniques are passive infrared cholangiography, hyperspectral cholangiography and near-infrared fluorescence cholangiography. The latter two are performed non-invasively and provide real-time images, making them promising options and warranting further research.

After summarizing the available evidence in the literature, we aimed to describe what actually takes place in daily practice. The safety precautions taken by surgeons and in the Netherlands were assessed by means of a nationwide survey in **Chapter 3**. The number of cholecystectomies performed yearly by the respondents accumulated to around around 60%

of the number performed yearly in the Netherlands. The distribution of the respondents with regard to types of hospitals was similar to that in the general population of Dutch surgeons. Thus, the survey provided a reliable representation of Dutch surgical practice.

The CVS technique is currently used by 98% of the surgeons. In the majority of cases it is documented in the operative notes and often (> 60%) augmented by photography or video images. Of all Dutch surgeons, 53% never perform IOC, 41% perform it incidentally and only 3% of the surgeons perform IOC routinely. A total of 105 BDI were reported, of which 19 were major BDI involving the common bile duct. In conclusion, the CVS approach in laparoscopic cholecystectomy is embraced by virtually all Dutch surgeons, but IOC seems to be an endangered skill.

To explore the role of IOC in modern surgery (i.e. in the CVS-era), a retrospective cohort study was conducted of cholecystectomies before and after implementation of a routine IOC policy, described in **Chapter 4.** The rate of major BDI was 1.9% before implementation, opposed to 0% after implementation of routine IOC (p=0.004). The rate of minor BDI did not differ significantly between the two groups.

Besides fewer BDI, more CBD stones were detected after implementation of routine IOC (4.8% versus 1.0%, p=0.001) and they were managed intraoperatively more frequently (2.8% versus 0.7%, p=0.023). There was also a trend towards a reduction in preoperative and postoperative ERCPs and other interventions for CBD stones (19.1% versus 24.2%, p=0.067). These results suggest that routine IOC has a place in modern gallbladder surgery.

Notwithstanding its documented benefits, there is resistance to IOC by many surgeons, as may be apparent from **Chapter 3**. One of the reasons for this phenomenon is that the IOC procedure can be time-consuming and cumbersome. To address this concern, we assessed an alternative instrument for IOC: the Kumar clamp. **Chapter 5** describes the results of this randomized trial. Twenty-eight patients underwent cholangiography using the Kumar cannulation technique and 22 using the Olsen technique. Success rates of IOC were similar for both clamps. The Kumar clamp was neither faster nor easier than the Olsen clamp. Therefore, individual surgeon preference should dicate which clamp is used. From the results of this trial, unfortunately, the Kumar clamp cannot be seen as an instrument that will lower the threshold for surgeons to perform IOC.

Documenting biliary anatomy

The guidelines of the Dutch Assocation of Surgery recommend documenting achievement of the CVS for educational and medicolegal purposes. From the survey presented in **Chapter 3** it became apparent that most of the surgeons document the CVS in the operation notes and support it with a photograph. Stored IOC images may also serve as a way to document correct identification of the cystic duct. In **Chapter 6** photographs of the CVS and IOC images of 63 patients were assessed by three expert abdominal surgeons. Photographs of the CVS were conclusive in only 27% of patients, IOC was conclusive in 57% ($p<0.001$). Both photographs and IOCs performed especially poorly in patients with (a history) of cholecystitis. This study illustrates that protocols and training are necessary for adequate documentation of assessment of biliary anatomy. Furthermore, photographs may simply just not do the trick and we may need to move on to video recordings of surgical procedures.

Documenting biliary anatomy has legal implications as BDI is not an uncommon ground for litigation claims against surgeons. Athough the precise role of stored laparoscopy images in court of law has yet to be determined, they are personal data under the Dutch Personal Data Protection Act (Wet Bescherming Persoonsgegevens). Ergo, they are subject to insight from physicians, the patient and the public prosecutor. It therefore seems desirable also from a medicolegal point of view that surgeons document operation details as precisely as possible.

Cholangioscopy

Moving from benign to malignant biliary disease and from the outside of the bile ducts to the endoluminal surface, in **Chapter 7** we assessed the diagnostic accuracy of peroral cholangioscopy in patients with indeterminate biliary irregularites. Cholangioscopy yielded valuable extra information compared to conventional investigations. The accuracy of cholangioscopy combined with biopsy and brush was 82%, compared to >90% in previous studies. The yield of the cholangioscopy guided biopsies alone was outright disappointing; over half the specimens were inconclusive or not usable. In previous studies the accuracy of biopsies was above 80%. More studies are needed to demonstrate whether the poor performance in our series is an outlier or that previously published series do not accurately portray daily practice.

Fluorescence imaging

Chapter 8 describes the technique of intraoperative fluorescence imaging, a novel technique that may prove highly useful in delineating the biliary tree, both for benign conditions and malignant lesions. The technique relies on the fact that specific molecules (fluorophores), when 'excited' by a laser at a particular wavelength, subsequently emit light at a slightly higher wavelength. The key to intraoperative imaging is to mark the organ (or tumor) of interest with a higher concentration of said fluorophore in order to visualize it with an intraoperative imaging system.

Chapter **9** explores several preclinical aspects of bile duct imaging that need to be considered for optimal bile duct imaging. Successful fluorescence cholangiography requires the optimal fluorophore in optimal concentration imaged at the optimal wavelength. In our pre-clinical studies IRdye 800CW seems to compare favourably to the more commonly used ICG, but it has not been cleared for use in patients yet. When using ICG, the optimal concentration lies between 0.005 and 0.01 mg/ml. The optimal excitation and emission wavelengths of ICG in bile are 745nm and 840nm respectively. A penetration depth of the fluorescent signal of up to 5mm may be expected.

GENERAL DISCUSSION

Main results

The goal of this thesis was to evaluate established and experimental techniques for intraoperative assessment of the biliary tree. We have shown that of the different protective measures to prevent bile duct injury, there is a large body of evidence in support of intraoperative cholangiography (IOC). In fact, there is more evidence for the much disputed IOC than for the critical view of safety (CVS), which seems to be widely accepted. In the modern surgical era we documented the reduction of bile duct injuries after implementation of a routine IOC policy. As a consequence of this policy change, areduction in peri-operative ERCPs was also seen. Our nation-wide survey among surgeons reveals that IOC is hardly ever practiced anymore in the Netherlands. In the second part of this thesis we introduced fluorescence cholangiography as a possible alternative for IOC and described the parameters that need to be controlled for optimal imaging. Finally, our study confirms the additional value of peroral cholangioscopy where indeterminate strictures of the biliary tract are concerned.

Intraoperative cholangiography for delineating the biliary tract

The practice of intraoperative cholangiography varies greatly within and between countries. In a large cohort of Australian cholecystectomies, IOC was performed in 60%[1]. A survey among American surgeons revealed that around 25% routinely performs IOC[2], figures from upper GI surgeons in Great Britain are similar[3]. A recent paper from Western France reports that 83% of the respondents practiced routine IOC[4]. Although the numbers vary, all are substantially higher than the 3% routine IOC use we found among Dutch surgeons[5].

The reason for the low rate of IOC use is probably in part related to the fact that ERCP is readily available in Dutch hospitals. In the past, ERCP has been used as a diagnostic tool as well as therapeutic tool for common bile duct stones. With the introduction of ERCP, IOC no longer seemed necessary for stone detection. The positive effect of IOC on the odds of bile duct injury (BDI) appears to have been overlooked and the baby may have been thrown out with the bathwater.

Another cause contributing to the abandoning of IOC is the feeling among surgeons that the procedure is cumbersome and prolongs surgery. Especially in the context of so-called 'gallbladder streets', the 10-15 minutes extra surgery time per case allows the operation of five instead of six patients per day. In addition, the number of patients that have to undergo cholecystectomy with IOC to prevent one BDI (i.e. the number needed to treat), is high. The 'reward' for performing IOC may therefore not be clearly felt by the surgeon. Finally, concern has been raised about the ability of surgeons to correctly interpret intraoperative cholangiograms. Reports have been published on incorrectly interpreted IOCs that did not lead to intraoperative detection of BDI. We feel, however, that this is a strong argument *in favour* of incorporating IOC in the surgical training (thus developing the ability to interpret IOC) rather than an argument against it.

As discussed in the Chapter 2, there is no level A evidence that IOC lowers the odds of BDI. Unfortunately, in this thesis, we were not able to provide this level A evidence either. It has been postulated that a sufficiently powered randomized controlled trial to demonstrate the beneficial effect of IOC on BDI requires 15'000 – 30'000 subjects[6]. The level B evidence (i.e. homogenous large cohort studies) that was presented in this thesis has been criticized. All of these cohort studies looked at whether IOC was performed, and not whether IOC was *attempted*. Patients in whom IOC is hard to perform due to the local anatomy or inflammation may be at increased risk for BDI. However, a bias in the opposite direction is also plausible, as we have described in one of our brief communications. In this scenario, IOC could have been attempted *more* often in patients of whom the surgeon thought were at increased risk of BDI or where BDI was already suspected.

There have been reports of small to medium-sized series of cholecystectomies without IOC with a low BDI rate. However, as the absolute incidence of BDI is low anyhow, the results of these series may be attributable to expected variation.

The 'number needed to treat' (i.e. the number of IOCs that need to be performed to prevent one BDI) depends on two factors. The first factor is the protective effect of IOC, which has been reported to be between 25% and 50%. In the meta-analysis we presented in Chapter 2 it was 32%. The second factor is the incidence of BDI in cholecystectomies *without* IOC. The interaction between protective effect, baseline BDI and number needed to treat is shown in figure 1. It shows clearly that the higher the baseline BDI rate, the lower the number needed to treat to prevent one BDI. From this figure it seems rational to compel institutions with a BDI rate of 1% or higher to implement a routine IOC policy. At a 33% reduction in BDI, this would yield a number needed to treat of 300; at 50% reduction, the number needed to treat would be 200.

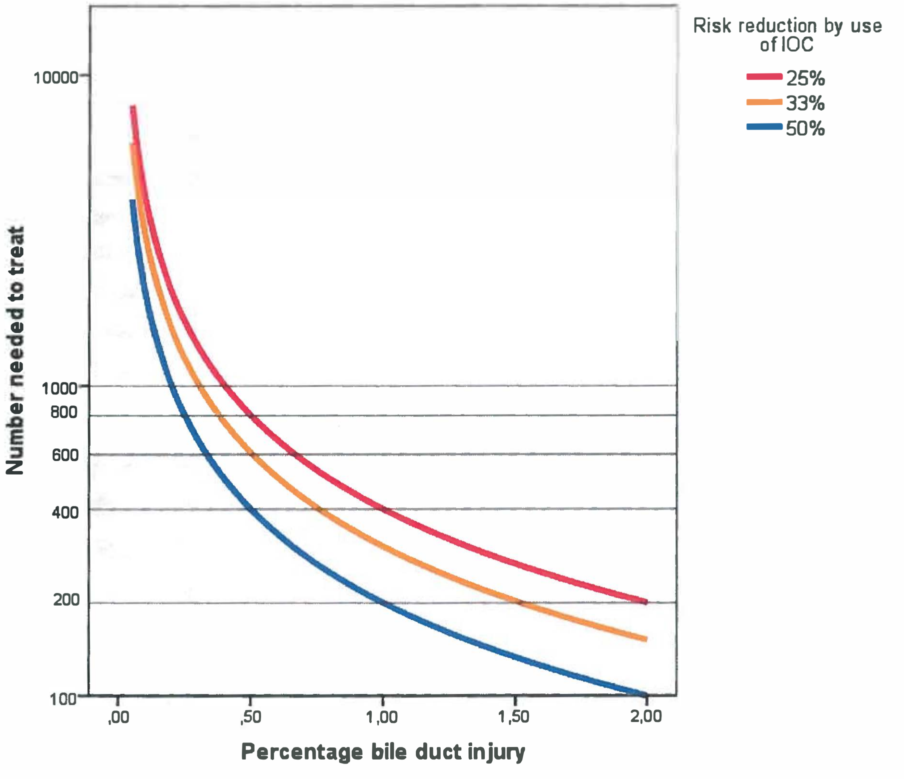

Figure 1: graph portraying the number needed to 'treat' with intraoperative cholangiography to prevent one major bile duct injury, taking into account different magnitudes of the protective effect of IOC.

It is important for institutions to be aware of their BDI rate. A nation-wide registry of cholecystectomies and BDI, in analogy with the Dutch Colorectal Audit, could serve in providing institutions with insight into their complication rate in comparison with the national complication rate or with a prespecified acceptable complication rate.

It is possible to calculate the cost-effectiveness of IOC. Anderssen et al calculated the costs of major bile duct injury in Sweden to be around EUR 15’000 in hospital costs and a staggering EUR 92’500 in cost of sick leave and loss of production. Adjusted for the average inflation of 2.08% per year in the Euro zone this amounts to around EUR 18’500 hospital costs and EUR 113’500 other costs per BDI. Assuming a 0.5% major bile duct injury, IOC could cost EUR 165-330 to be overall cost-effective. If only hospital costs are included, IOC would be cost-effective at EUR 23-46. This analysis does not take into account the cost ‘savings’ of the low but definitive mortality associated with bile duct injury, the cost of medico-legal claims, nor the savings of MRCP or ERCP not being executed.

We recognize that this thesis does not provide the level A evidence that is necessary to close the discussion on IOC. The cohort study describing the rate of bile duct injury before and after introduction of IOC (chapter 4) may be criticized for its relatively small size. In case of the generally reported major bile duct injury rate of 0.5%, it would indeed be underpowered to demonstrate a beneficial effect of IOC. In our centre, however, we had an unacceptably high major bile duct injury rate of 1.9% before introduction of IOC, and as such, the number needed to treat to prevent one BDI was relatively low.

The study serves to demonstrate that institutions concerned about their bile duct injury rate should consider implementing routine IOC. The study is also the first to describe the beneficial effects of IOC in a cohort of patients in which the critical view of safety approach was consistently used.

Patient safety attitude

An attitude change on patient safety protocols, towards one comparable to that in commercial aviation, may be necessary before IOC can become a routine procedure in the Netherlands. Increasingly, lessons are being learnt from pilot safety protocols. An important example is the introduction of the SURPASS checklist into the peri-operative process. The SURPASS checklist is an extensive list of items that need to be checked by various members of the surgical team, including the planner, surgeon, resident, anesthesiologist and (scrub) nurse. Different parts of the list are completed in the pre-, intra- and post-operative trajectory. A landmark paper by De Vries et al[7] found that mortality in surgical patients dropped from 1.5% to 0.8% after introduction of the SURPASS checklist. In control hospitals where the checklist was not introduced, the mortality did not change. Besides the development of this specific checklist, the study is important because it provides the evidence that adopting such protocols does indeed improve the quality of care for patients.

A pre-flight list used by pilots, but to our knowledge not yet by surgeons, is the 'I'M SAFE' acronym. With this acronym, the pilot assesses himself for Illness, Medication, Stress, Alcohol, Fatigue and Emotions. Such a self-examination provides insight into factors that may impair decision making and technical skills.

Besides scientific evidence and intrinsic motivation, externally motivating factors may play a role. This could be in the form of national recognition for performing safety interventions such as IOC. Another important incentive for a change for the better would be that health insurers start to compensate the surgeon for the time and material spent on IOC. Considering the evidence that IOC is probably cost-effective[8] in the long run, this seems reasonable.

Transparency in (surgical) care

Surgeons are increasingly required to provide transparency concerning their treatment of patients. It is plausible that operation notes alone will soon not be sufficient to prove correct treatment of the patient. We demonstrated that one third of the Dutch surgeons takes photographs of the critical view of safety. However, although still images are more objective than operation notes, this may not be enough either. Video fragments[9] or even recordings of the entire procedure[10] are the future of laparoscopic surgery.

Additionally, all spoken text and other sounds in the operating theatre could be recorded. In this way, the interpretation of the images may be better documented. Part of the interpretatation is not expressed in words and is therefore not captured in this way. Nonetheless, there is a lot of similarity between maximal transparency in the operating theatre and black box recorder used in commercial aviation.

Intraoperative cholangiography for detection and treatment of stones

We demonstrated that more common bile duct stones were detected when IOC was used routinely. The number of peri-operative ERCPs decreased. IOC is a useful method to identify the need for post-operative ERCP in low to intermediate risk patients, as demonstrated for example in patients with mild to moderate pancreatitis[11]. Taken one step further, IOC facilitates the extraction of common bile duct stones *during* surgery.

There is increasing evidence that such a one-step approach to choledochocholecystolithiasis has advantages over a two step approach. One option is the surgical one-step approach (transcystic stone extraction or choledochotomy). This approach requires an experienced surgeon, but substantially decreases the duration of hospital admission[12]. Another one-step approach is the so-called rendez-vous procedure consisting of ERCP at the same time as cholecystectomy.

In a meta-analysis the rendez-vous procedure was shown to decrease complications and hospital stay in patients with cholecystocholedocholithiasis[13]. As sub-specialization continues in the Dutch health care, it is plausible that specialized upper GI surgeons will do more one-step procedures for these patients, with or without the help of their gastroenterology colleagues.

Peroral cholangioscopy

Direct visualization of the biliary tract by peroral cholangioscopy has evolved substantially in the past decades as a result of improved fiberoptical endoscopes that now allow single user cholangioscopy. One application for this increasingly popular technique is 'difficult' common bile duct stones. These are exceptionally large or impacted stones in which previous conventional techniques such as ERCP en shock wave lithotripsy have failed. The medical literature on the topic, including reports from our own medical centre reveal a success rate of around 90% for stone clearance using peroral cholangioscopy[14].

Novel techniques for bile duct imaging

In addition to dedication to safety protocols, safer gallbladder surgery will be made possible by the development of novel techniques to delineate the biliary anatomy. Novel cannulation techniques for IOC, such as the Kumar clamp, are probably not the answer. Rather, we should look in the direction of alternative imaging possibilities, such as fluorescence imaging. This technique has the potential of being a radiation-free real-time imaging modality to provide improved insight into the (biliary) anatomy. Until now, the most important infrared dye that has been used is indocyanine green, as it has been cleared for use in patients (table 1). However, there are important disadvantages to indocyanine green. Firstly, it is retained in the liver for a relatively long time after intravenous administration. The visibility of the bile ducts is therefore impaired when viewed upon a background of liver tissue. Secondly, the fluorescent signal emitted by ICG is inferior to, for example that of 800-CW. Novel fluorophores for patient use may therefore improve the penetration strength to beyond what is currently possible with ICG.

Fluorescence imaging can also be directed towards detection of malignant lesions of the bile ducts. To achieve this, fluorescent molecules need to be conjugated to tumor-specific molecules. This feat was recently accomplished for the first time in ovarian cancer[15]. In the case of biliary cancer such an imaging modality could serve to improve diagnosis during fluorescence cholangioscopy and improve surgical resection margins peroperatively. Suitable targets can be selected using the TASC criteria[16].

Combined with other radiological markers, fluorescence imaging may play an important role in translating pre-operative radiological studies to the surgical field. As of yet, the technique is still experimental. Efficacy and validation studies need to be done and, if successful, major training and equipment changes will be necessary before it can be widely implemented.

FINAL OUTLOOK AND RECOMMENDATIONS

This thesis confirms that intraoperative assessment of biliary anatomy is crucial for prevention of bile duct injury (BDI). There are opportunities to re-integrate the management of common bile duct stones and gallbladder stones to offer patients a one-step approach and to spare them unnecessary invasive procedures.

The critical view of safety approach should be used for every laparoscopic cholecystectomy. We recommend routine intraoperative cholangiography (IOC) for medical centres concerned about their BDI rate, or with a BDI rate of ≥ 1%. The number needed to treat to prevent IOC decreases when the baseline BDI rate is high. IOC should play an integral role in the programme of surgical trainees. For surgeons who are not, or insufficiently, familiar with IOC, the threshold to perform it is high, even in patients in whom the anatomy is unclear. Alternatively, laparoscopic ultrasound is an excellent intraoperative imaging modality for those dedicated to its use.

The critical view of safety and the intraoperative cholangiogram should be carefully documented for transparency, safeguarding of quality of care and medicolegal reaons. Video images should be used wherever possible.

In patients at intermediate risk of common bile duct stones, we advocate a ‘cholecystectomy first’ approach with IOC. In this way, patients without common bile duct stones may be spared unnecessary ERCP. In those that do turn out to have common bile duct stones, various options are possible. Patients at intermediate risk may be identified by neural networks incorporating clinical signs and symptoms, laboratory values and ultrasound characteristics[17].

Small solitary stones (<5mm), may be flushed through the common bile duct after intravenous administration of glucagon to relax the sphincter of Oddi. Stones 5-10mm in diameter may be retrieved intraoperatively by transcystic extraction. Larger stones and stones in the proximal common bile duct associatied with a dilated common bile duct may be managed intraoperatively by choledochotomy. However, this requires considerable surgeon experience. In patients with altered upper gastrointestinal anatomy such as after B2 gastric resection, choledochotomy, if the expertise is present, should be first choice. Other patients are best managed by post-operative ERCP.

In the category of patients with proven difficult common bile duct stones, peroral cholangioscopy with laser lithotripsy should be considered as an alternative therapy where conventional means fail. Peroral cholangioscopy is also the method of choice in characterizing indeterminate bile duct lesions where conventional imaging modalities were inconclusive.

Novel routes towards easier, faster and cheaper bile duct imaging, such as near-infrared fluorescence cholangiography, warrant further exploration. The potential applications of such novel modalities encompass both assessment of biliary anatomy and characterization of indeterminate bile duct lesions.

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Chapter

11

Samenvatting, discussie en aanbevelingen

SAMENVATTING

Intraoperatieve cholangiografie

Hoofdstuk 1 beschrijft de belangrijke ontwikkelingen die ten grondslag liggen aan de galblaaschirurgie zoals die wij nu kennen. Het besef dat de aanwezigheid van galstenen samen hangt met aandoeningen als cholecystitis en choledocholithiasis was een belangrijke stap hierin. Dit leidde tot het verrichten van cholecystostomie (een chirurgische procedure waarbij niet de hele galblaas maar enkel de stenen worden verwijderd). De volgende ontdekking was dat galsteenlijden verholpen kon worden door de gehele galblaas te verwijderen zonder dat patiënten hier veel hinder van ondervinden.

De cholecystectomies evolueerde verder met de komst van de laparoscopie, circa 100 jaar na de eerste open cholecystectomies. Deze ontwikkeling had echter een schaduwzijde: het percentage majeure galwegletsels verdubbelde in de daaropvolgende jaren.

Het verhoogde risico op galwegletsel leidde tot betere technieken om de galboom peroperatief in beeld te brengen. Het bewijs voor de verschillende technieken wordt uiteengezet in **Hoofdstuk 2**. De 'critical view of safety' (CVS) techniek wordt in de meeste richtlijnen aangeraden als eerste keus om galwegletsel te voorkomen. Het ontbreekt echter aan harde data over de effectiviteit van deze techniek. Intraoperatieve cholangiografie (IOC) gaat gepaard met een lager risico op galwegletsel in een analyse van grote cohortstudies (OR 0.68, CI 0.61-0.75). Nadelen van IOC zijn extra kosten, verlenging van de operatieduur en het de procedure kan als moeizaam worden ervaren. Het bewijs voor IOC dateert veelal uit de periode voor introductie van de CVS. Verder onderzoek is nodig om de plaats van IOC te bepalen in de 21ste eeuw.

Een alternatief voor IOC is laparoscopische echografie, maar deze techniek kent een lange leercurve. Cholecystocholangiografie (het inspuiten van röntgencontrast direct in de galwegen) en dye cholangiografie (injectie van kleurstof) zijn gemakkelijk maar leveren slechte beelden. Licht cholangiografie, door middle van retrograde positionering van een optische vezel in de ductus choledochus is te omslachtig om routinematig te gebruiken. Experimentele technieken zijn passief infrarood cholangiografie, hyperspectral cholangiografie en nabij-infrarood fluorescentiecholangiografie. De laatste twee zijn veelbelovende non-invasieve technieken die real-time beelden opleveren.

Volgend op de samenvatting van de literatuur verrichten wij een inventarisatie van de dagelijkse praktijk. Middels een landelijke enquete vroegen wij chirurgen naar de veiligheidsmaatregelen die zij nemen, de resultaten zijn beschreven in **Hoofdstuk 3.** Het jaarlijks aantal cholecystectomieen wat door de respondenten kwam overeen met circa 60% van de cholecystectomieen die jaarlijks in Nederland worden verricht.

De verdeling onder de chirurgen wat betreft types ziekenhuizen leverde een representatief beeld van de nederlandse situatie.

De CVS techniek wordt momenteel gebruikt door 98% van de chirurgen. In de meeste gevallen wordt dit vastgelegd in het operatieverslag. Vaak wordt het tevens door middel van foto- of videobeelden vastgelegd. Van alle Nederlandse chirurgen verricht 53% nooit een intraoperatief cholangiogram, 41% doet dit sporadisch en slechts 3% doet dit routinematig. Er werden 105 galwegletsels gerapporteerd van welk 19 ernstig waren. Wij concludeerden dat de CVS wijds is ingeburgerd maar dat de techniek van intraoperatieve cholangiografie verloren lijkt te gaan in Nederland.

Om de plaats van IOC in de 21ste eeuw te onderzoeken voerden wij een retrospective cohort studie uit van de cholecystectomieen vóór en ná de invoering van routinematig IOC. Dit wordt beschreven in **Hoofdstuk 4.** Het percentage ernstig galwegletsel was 1.9% vóór invoering van IOC en 0% erna. Het percentage milde galwegletsels was niet verschillend.

Behalve minder galwegletsels, werden er meer choledochustenen intraoperatief opgespoord met routinematig IOC (4.8% versus 1.0%, p=0.001). Deze werden tevens vaker intraoperatief behandeld (2.8% versus 0.7%, p=0.023). Er leek een reductie van het aantal peri-operatieve ERCPs met routinematig IOC (19.1% versus 24.2%, p=0.067). Deze resultaten zijn een aanwijzing dat IOC zeker een plaats heeft in de hedendaags galblaaschirurgie.

Ondanks de beschreven voordelen is er weerstand tegen IOC bij veel chirurgen, zoals bleek in **Hoofdstuk 3**. Een van de redenen hiervoor is dat de IOC procedure extra tijd kost en als moeizaam kan worden ervaren. Om deze bezwaren te trachten te verminderen onderzochten wij een alternatief instrument voor IOC: de Kumar klem. **Hoofdstuk 5** beschrijft de resultaten van dit gerandomiseerde onderzoek. Achtentwintig patiënten ondergingen IOC met de Kumar cannulatie techniek en 22 met de conventionele Olsen techniek. Het succespercentage was vergelijkbaar voor beide technieken. De Kumar klem was niet sneller en ook niet makkelijker in gebruik dan de Olsen klem. De voorkeur van de chirurg moet bepalen welke klem gebruikt wordt. Deze trial toont dat de Kumar klem de drempel om IOC te verrichten niet zal verlagen.

Vastleggen van de galweganatomie

In de richtlijnen van de Nederlandse Vereniging voor Heelkunden wordt aangeraden het behalven van de 'critical view of safety' (CVS) vast te leggen voor opleidings- en medicolegale doeleinden. Uit de inventarisatie in **Hoofdstuk 3** werd duidelijk dat de meeste chirurgen dit doen in het operatieverslag, en dit ondersteunen met een foto. Opgeslagen IOC beelden zouden ook kunnen dienen als bewijs dat de galweganatomie correct is beoordeeld. In **Hoofdstuk 7** werden foto's van de CVS en opgeslagen IOC beelden beoordeeld door drie ervaren gastro-intestinaal chirurgen. Foto's van de CVS waren slechts conclusief in 27% van de gevallen, IOC beelden in 57% ($p<0.001$). Zowel foto's als IOC beelden waren vaak inconclusief bij patiënten met een (doorgemaakte) cholecystitis. Deze studie illustreert dat protocollen en training noodzakelijk zijn voor het correct vastleggen van de galweganatomie. Ook zou het zo kunnen zijn dat fotobeelden simpelweg onvoldoende zijn en dat we moeten streven naar video-opnames van chirurgische procedures.

Het vastleggen van de galweganatomie heeft medicolegale implicaties. Galwegletsel leidt met enige regelmaat tot claims tegen chirurgen. Hoewel de precieze waarde van laparoscopiebeelden in de rechtszaal nog moet blijken, betreft het persoonlijke data die valt onder de Wet Bescherming Persoonsgegevens. Zij mogen worden ingezien door behandelend artsen, de patient en de openbaar aanklager. Het is daarom wenselijk dat chirurgen de operatieve procedure zo nauwkeurig mogelijk vastleggen.

Cholangioscopie

In **Hoofdstuk 7** onderzochten wij de waarde van perorale cholangioscopie in patiënten met onverklaarde galwegonregelmatigheden. Cholangioscopie leverde extra informatie ten opzichte van conventionele onderzoeken. Wel was de nauwkeurigheid lager dan door anderen gepubliceerd. De nauwkeurigheid van cholangioscopie met biopsie en brush in ons onderzoek was 82%. In eerder gepubliceerde onderzoeken was dit >90%. De waarde van cholangioscopisch genomen biopten was teleurstellend; meer dan de helft van de biopten waren inconclusief of niet bruikbaar. In eerdere onderzoeken was de nauwkeurigheid van de biopten >80%. Verder onderzoek moet uitwijzen of onze resultaten afwijkend zijn of dat de eerder gerapporteerde effectiviteit niet overeenkomt met de dagelijkse praktijk.

Fluorescentiebeeldvorming

Hoofdstuk 8 beschrijft de techniek van intraoperatieve fluorescentiebeeldvorming, een nieuwe techniek die van grote waarde kan voor de beeldvorming van de galwegen, zowel voor benigne als maligne aandoeningen. De techniek maakt gebruik van de eigenschap van bepaalde stoffen om, wanneer zij worden 'aangestraald' op een bepaalde golflengte, zij een lichtpuls afgeven van een iets grotere golflengte. Wanneer de concentratie van een dergelijke stof (fluorofoor) in de structuur in kwestie hoger is dan de achtergrond kan men deze in beeld brengen met een intraoperatieve fluorescentiecamera.

In **Hoofdstuk 9** onderzoeken wij een aantal preklinische aspecten van galwegbeeldvorming met fluorescentie. Succesvolle fluorescentiecholangiografie is wordt bereikt wanneer het optimale fluorofoor in de optimale concentratie wordt aangestraald op de optimale golflengte. In onze pre-klinische studies deed IRdye 800CW het beter dan het vaak gebruikte ICG. IRdye 800CW is echter nog niet vrijgegeven voor gebruik in patiënten. Voor ICG ligt de optimale concentratie in gal tussen de 0,005 en 0,01 mg/ml. De optimale excitatie en emissiegolflengtes liggen op 745nm en 840nm respectievelijk. Het afgegeven licht heeft een penetratiesterkte door vetweefsel van ongeveer 5mm.

ALGEMENE DISCUSSIE

Belangrijkste resultaten

Het doel van dit proefschrift was het evalueren van conventionele en experimentele technieken om intraoperatief de galwegen te beoordelen. We hebben aangetoond dat van de verschillende veiligheidsmaatregelen er veel bewijs is voor een beschermend effect van IOC op galwegletsel. Voor de algemeen geaccepteerde 'critical view of safety' (CVS) techniek is minder bewijs. We rapporteren de toegevoegde waarde van IOC ook in een setting waar de CSV reeds de standaard is. Een grootschalige enquete toonde dat IOC als techniek verloren dreigt te gaan in Nederland.

In het tweede deel van dit proefschrift verkennen we de mogelijkheden om de galwegen af te beelden met fluorescentiebeeldvorming. We beschrijven belangrijke voorwaarden waaraan voldaan moet worden voor succesvolle fluorescentie-cholangiografie. Tot slot bevestigt dit proefschrift de toegevoegde waarde van perorale cholangioscopie bij onbegrepen onregelmatigheden van de galwegen.

Intraoperatieve cholangiografie voor het beoordelen van de anatomie

Het gebruik van intraoperatieve cholangiografie wisselt sterk in en tussen landen. In een groot Australisch cohort werd IOC in 60% van de cholecystectomieen uitgevoerd. Een enquete onder Amerikaanse chirurgen toonde dat circa 25% van de artsen routinematig IOC verrichten. De cijfers uit een rapportage van Britse gastrointestinaal chirurgen zijn vergelijkbaar. Een recent artikel uit westelijk Frankrijk beschrijft dat 83% van de respondenten routinematige IOC verricht. Hoewel de cijfers verschillen is het percentage chirurgen dat routinematige IOC uitvoert overal hoger dan de 3% die wij vonden in Nederland.

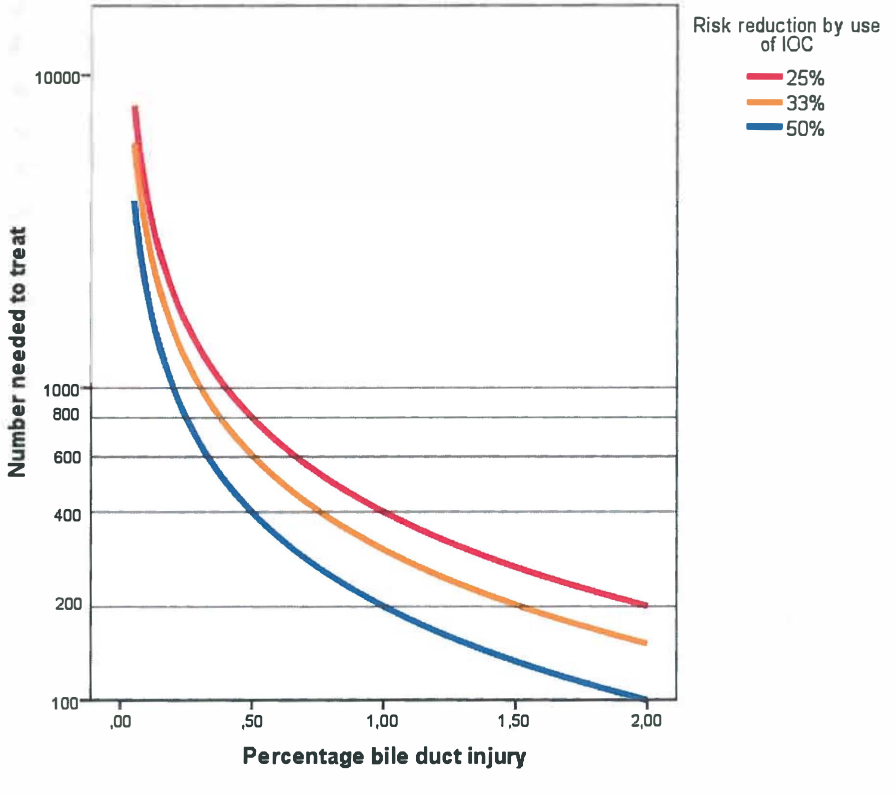
Een van de redenen dat er weinig IOC wordt verricht is dat ERCP laagdrempelig beschikbaar is de Nederlandse ziekenhuizen. Voorheen werd ERCP vaak zowel als diagnostisch en therapeutisch onderzoek gebruikt. Toen de ERCP zijn intrede deed leek IOC niet langer noodzakelijk voor het opsporen van choledocholithiasis. Het preventieve effect van IOC op galwegletsel lijkt te zijn vergeten en op deze manier werd het kind met het badwater weggegooid.

Een andere reden waarom IOC weinig meer verricht wordt is de opvatting van chirurgen dat IOC een omslachtige procedure is en de ingreep verlengd. Vooral in de context van 'galblaas-straatjes' leidt een extra 10-15 minuten per operatie tot vijf in plaats van zes operaties per dag. Daarbij komt het feit dat het aantal IOC's dat men moet uitvoeren om één galwegletsel te voorkomen (oftewel de 'number needed to treat') hoog is. De 'beloning' voor het IOC wordt daarom niet duidelijk gevoeld. Tot slot zijn er in het verleden zorgen geuit over het vermogen van chirurgen om IOC's te beoordelen. Er zijn publicaties die verkeerd geinterpreteerde IOC's beschrijven. In onze mening, echter, is dit eerder een argument *voor* het incorporeren van IOC in de chirurgie opleiding dan een argument er*tegen.*

Zoals bepleit in Hoofdstuk 2 is er geen 'level A' bewijs dat IOC leidt tot minder galwegletsels. Ook in dit proefschrift zijn wij er helaas niet in geslaagd om dat level A bewijs te leveren. Er wordt gesteld dat een trial met voldoende power om een positief effect van IOC aan te tonen een patiëntenaantal van 15'000 tot 30'000 zou moeten includeren. Het 'level B' bewijs (homogene grote cohort studies) in het voordeel van IOC heeft in het verleden kritiek ontvangen. Alle cohortstudies analyseren de gevallen waarin IOC was *uitgevoerd,* en niet in welke patiënten het werd *gepoogd*. Patienten in wie IOC niet goed lukt vanwege afwijkende anatomie of doorgemaakte cholecystitis zouden, onafhankelijk van of er wel of geen IOC wordt uitgevoerd, een hoger risico op galweglekkage lopen. Het omgekeerde is ook mogelijk, zoals wij eerder beschreven in en korte ingezonden brief. In dit scenario zou IOC vaker worden uitgevoerd in die patienten waarvan de operateur inschat dat zij een verhoogd risico op galweglekkage lopen, of zelfs vooral in patiënten die ervan verdacht werden al galwegletsel op te hebben gelopen.

Er zijn klein tot middelgrote studies gepubliceerd van cholecystectomieen zonder IOC met een laag percentage galwegletse. De absolute incidentie van galwegletsel is echter laag en deze series zouden aan de te verwachten variatie kunnen worden toegeschreven.

De 'number needed to treat' (het aantal IOCs dat verricht moet worden om één galwegletsel te voorkomen) hangt af van twee factoren. De eerste factor is de grootte van het beschermende effect van IOC. Dit wordt gerapporteerd op tussen 25% en 50%. In onze meta-analyse bereikten wij een gemiddelde van 32%. De tweede factor is de incidentie van galwegletsel in cholecystectomieen *zonder* IOC. De interactie tussen effectgrootte, basisincidentie van galwegletsel en 'number needed to treat' is weergegeven in afbeelding 1. Duidelijk is te zien dat hoe hoger de basale incidentie van galwegletsel, hoe lager het aantal IOCs dat verricht moet worden om een galwegletsel te voorkomen. Hieruit zou voortkomen dat het rationeel zou zijn om klinieken met een galwegletsel incidentie van boven de 1% te verplichten IOC te verrichten. Als de beschermend effectgroo tten 33% zou zijn, zou de 'number needed to treat' om een galwegletsel te voorkomen 300 zijn. Als het beschermend effect 50% zou zijn, zou het aantal neerkomen op 200.



Afbeelding 1: de 'number needed to treat' met IOC om een majeur galwegletsel te vookómen, afhankelijk van de de grootte van het beschermend effect van IOC.

Het is derhalve van belang dat instellingen zich bewust zijn van hun galwegletselpercentage. Een nationale registratie van cholecystectomieen en galwegletsels, analoog aan de Dutch Colorectal Audit, zou kunnen dienen om instellingen inzicht te geven in hun complicaties en hoe dit in vergelijking staat in die van andere klinieken of een vantevoren gespecificeerd acceptabel percentage.

Het is mogelijk om de kosteneffectiviteit te berekenen van IOC. Anderssen et al berekenden de kosten van majeur galwegletsel in Zweden en kwamen uit op circa EUR 15’000 aan ziekenhuiskosten en circa EUR 92’500 aan kosten aan ziekteverlof en verlies aan produktie. Rekening houdend met de een gemiddelde inflatie van 2.08% in de euro zone zou dit neer komen op een EUR 18’500 ziekenhuiskosten en EUR 113’500 aan overige kosten per majeur galwegletsel. Uitgaande van een 0.5% absolute incidentie van majeur galwegletsel, zou IOC 165-330 euro mogen kosten om kosteneffectief te zijn.

Deze analyse laat nog buiten beschouwing de ‘winst’ aan reduktie van de laag maar zekere mortaliteit geassocieerd met galweglekkage, de kosten van medico-legale claims en de bespaarde kosten door het terugdringen van het aantal MRCPs en ERPCs.

Wij onderkennen dat dit proefschrift niet het level A bewijs levert dat nodig is om de discussie over IOC te beeindigen. De cohortstudie naar het percentage galwegletsel vóór en na invoering van een routinematig IOC beleid (Hoofdstuk 4) beschrijft een relatief klein aantal patiënten. Bij een percentage majeur galwegletsel wat doorgaans wordt gerapporteerd van circa 0.5% zou de studie inderdaad onvoldoende power hebben om een voordelig effect van IOC aan te tonen. In ons medisch centrum hadden wij echter een onacceptabel hoog percentage galwegletsel van 1.9%. Derhalve was de ‘number needed to treat’ om één galwegletsel te voorkomen relatief laag.

De studie toont dat instellingen met zorgelijke percentages galwegletsel routinematig IOC zouden moeten overwegen. De studie is tevens de eerste studie die een voordeel aantoont van IOC in een cohort patiënten die geopereerd zijn middels de ‘critical view of safety’ techniek.

Houding ten aanzien van patientveiligheid

Een verandering in houding ten aanzien van patientveiligheidprotocollen, zoals die in de commerciële luchtvaart bestaat, zou nodig kunnen zijn voordat IOC een routinematig toegepaste procedure wordt in Nederland. Meer en meer worden lessen getrokken uit de veiligheidsprotocollen die piloten hanteren. Een belangrijk voorbeeld hiervan is de SURPASS checklist, een uitgebreide lijst van items die afgevinkt moeten worden door verschillende leden van het chirurgisch team (als planner, chirurg, arts-assistent, anesthesist en OK-assistent). Verschillende onderdelen worden ingevuld in het pre-, intra-, en postoperatief traject. Een belangrijke publicatie van De Vries en al beschrijft hoe de mortaliteit van chirurgische patiënten daalde van 1.5% tot 0.8% na de invoering van de SURPASS checklist. In controle ziekenhuizen waar de checklist niet werd ingevoerd bleef de mortaliteit gelijk. Behoudens de ontwikkeling van deze specifieke checklist is het een belangrijke studie omdat het bewijs levert dat de invoering van dergelijke protocollen werkelijk de zorg voor chirurgische patiënten verbeterd.

Een checklist die door piloten wordt gebruikt maar voor zover wij weten nog niet door chirurgen is het 'I'M SAFE' acronym. Met dit acronym onderzoekt de pilot zichzelf op 'Illness, Medication, Stress, Alcohol, Fatigue en Emotions'. Zo kan inzicht worden verkregen in factoren die het nemen van de juiste beslissing zou kunnen beinvloeden.

Naast wetenschappelijk bewijs en intrinsieke motivatie, zou ook extrinsieke motivatie een rol kunnen spelen in het wel of niet toepassen van veiligheidsmaatregelen. Dit zou kunnen bestaan uit nationale erkenning voor het implementeren van veiligheidsmaatregelen. Een ander belangrijke motivatie zou kunnen zijn dat de operateur vergoed wordt door de verzekeraar voor het toepassen van veiligheidsmaatregelen zoals IOC. Gezien het bewijs dat IOC waarschijnlijk kosten-effectief is, lijkt dit niet onredelijk.

Transparantie in de (chirurgische) zorg

Chirurgen worden steeds geacht transparantie geven in hun behandeling van patiënten. Het is voorstelbaar dat een operatieverslag binnenkort niet meer afdoende is om de juiste behandeling van de patient te documenteren. Wij toonden aan dat een derde van de Nederlandse chirurgen reeds fotomateriaal van de ´critical view of safety´ opslaat. Hoewel foto´s objectiever zijn dan operatieverslagen zouden deze ook wel eens onvoldoende blijken te zijn. Video fragmenten of zelfs opnames van de gehele procedure zijn de toekomst van de laparoscopische chirurgie.

Als uitbreiding daarop zouden zelfs de gesproken tekst en andere geluiden in de operatiekamer opgeslagen kunnen worden. Op die manier wordt ook de interpretatie van de beelden zo goed mogelijk vastgelegd. Er ontstaan zo veel overeenkomsten tussen maximale transparantie op de operatiekamer en de black box die gebruikt wordt in de commerciële luchtvaart.

Intraoperatieve cholangiografie voor het opsporen en behandelen van stenen

Wij toonden aan dat meer choledochusstenen werden gedetecteerd wanneer IOC routinematig wordt toegepast. Het aantal peri-operatieve ERCP procedures daalde. IOC is een geschikte methode om de noodzaak tot ERCP aan te tonen in patiënten met een lage tot matige a priori kans op choledochusstenen. De volgende stap is dat IOC leidt tot intraoperatieve extractie van choledochusstenen.

Er wordt steeds meer bewijs gepubliceerd date en eenstapsprocedure voor cholecystocholedocholithiasis te prefereren valt boven een tweestapsprocedure. Een zo´n eenstapsprocedure is de chirurgische techniek (transcystische steen extractive of choledochotomie). Deze aanpak vereist een ervaren chirurg maar verkort aanzienlijk de opnameduur. Een andere aanpak is de zogenaamde ´rendez-vous´ procedure, welke bestaat uit ERCP tijdens de cholecystectomie.

In een meta-analyse bleek de rendez-vous procedure het aantal complicaties te verminderen en de opnameduur te verkorten in patiënten met cholecystocholedocholithiasis. Nu er steeds meer sprake is van subspecialisatie binnen de Nederlandse gezondheidszorg is het denkbaar dat gastro-intestinaal chirurgen meer eenstapsprocedures zullen uitvoeren, al dan niet met hulp van de maag-darm-leverartsen.

Perorale cholangioscopie

Directe visualisatie van de galwegen door middel van perorale cholangioscopie is de afgelopen decennia sterk ontwikkeld. Door middel van verbeterde fibre-optics is voor cholangioscopie nog maar één endoscopist nodig. Eén van de toepassingen van deze techniek betreft de ´moeilijke´ choledochusstenen. Dit zijn bijvoorbeeld buitengewoon grote of geimpacteerde stenen waarbij conventionele technieken als ERCP en schock wave lithotripsie geen of onvoldoende resultaat bereikten. Een tweede belangrijke toepassing van perorale cholangioscopie is het beoordelen van onbegrepen galwegonregelmatigheiden. Deze techniek levert hierbij meerwaarde ten opzichte van conventionele technieken.

Nieuwe technieken voor galwegbeeldvorming

Naast het implementeren van veiligheidsmaatregelen zal de galblaaschirurgie veiliger worden door middel van nieuwe technieken om de galboom in beeld te brengen. Nieuwe cannulatietechnieken voor IOC, zoals de Kumar klem, zijn waarschijnlijk niet de optimale manier om de drempel voor galwegbeeldvorming te verlagen. In plaats daarvan kan men zich beter richten op alternatieve beeldvormingsmodaliteiten zoals fluorescentiebeeldvorming.

Deze techniek is potentieel een stralingsvrije directe beeldvormingsmodaliteit voor de anatomie van de galboom. Tot op heden is indocyanine groen het meest gebruikte fluorofoor omdat het geschikt is bevonden voor gebruik in patiënten (zie ook tabel 1). Er zijn echter ook nadelen aan indocyanine groen. Ten eerste wordt het na intraveneuze toediening relatief lang opgeslagen in de lever. De zichtbaarheid van de galwegen wordt derhalve beperkt tegen de achtergrond van de lever. Ten tweede is het fluorescent signaal wat wordt afgegeven door indocyanine groen inferieur aan dat van nieuwere fluoroforen zoals bijvoorbeeld 800-CW.

Fluorescentiebeeldvorming kan ook worden aangewend om kwaadaardige afwijkingen van de galwegen aan te tonen. Om dit te bereiken dienen fluorescente moleculen te worden geconjugeerd aan tumor-specifieke moleculen. Deze techniek is recent voor het eerst gedemonstreerd in patiënten met ovariumcarcinoom. In geval van cholangiocarcinoom zou deze techniek zowel de opsporing van de tumoren als de radicale resectie ervan kunnen verbeteren. Geschikte ´targets´ op tumoren kunnen worden geselecteerd met de TASC criteria.

In combinatie met radiologische markers kan fluorescentiebeeldvorming een belangrijke rol spelen in het maken van de vertaalslag van pre-operatieve beeldvorming naar de operatietafel. Vooralsnog is de techniek nog expermenteel. Verder onderzoek zal de meerwaarde van dergeljke technieken moeten aantonen voordat geld wordt gestoken het implementeren ervan.

VOORUITZICHTEN EN AANBEVELINGEN

Dit proefschrift bevestigd dat intraoperatieve beoordeling van de galweganatomie cruciaal is om galwegletsel te voorkomen. Daarnaast bieden beeldvormingstechnieken van de galwegen de mogelijkheid om de behandeling van galblaasstenen en galwegstenen als een éénstapsprocedure uit te voeren en patiënten onnodige invasieve procedures te besparen.

De 'critical view of safety' techniek dient gebruikt te worden voor elke laparoscopische cholecystectomie. Wij bevelen routinematig IOC aan voor centra die bezorgd zijn over hun percentage galwegletsels en in ieder geval voor centra met een galwegletsel-percentage van ≥ 1%. De 'number needed to treat' om galwegletsel te voorkomen neemt af naar mate het uitgangspercentage galwegletsels hoger ligt. IOC dient behandeld te worden in de opleiding tot chirurg. Immers, voor chirurgen die de techniek onvoldoende beheersen is de drempel om IOC uit te voeren hoog, zelfs bij patiënten met een onduidelijke anatomie van de galwegen. Laparoscopische echografie is een uitstekend alternatieve beeldvormingsmodaliteit voor chirurgen die deze techniek meester zijn.

De ‘critical view of safety’ en het intraoperatief cholangiogram dienen nauwkeurig te worden gedocumenteerd voor transparantie, bewaking van kwaliteit van zorg en om medicolegale redenen. Waar mogelijk dienen videobeelden gebruikt te worden.

Voor patiënten met intermediair risico op choledochusstenen adviseren wij een ‘cholecystectomy first’ aanpak met IOC. Patienten die een intermediair risico lopen kunnen worden geselecteerd aan de hand van programma’s waarin klinische symtpomen, laboratoriumwaarden en echografisch onderzoek zijn geincorporeerd. Door eerst een IOC te verrichten wordt patiënten zonder choledochusstenen een ERCP bespaard. Bij patienten die tijdens IOC wel stenen blijken te hebben kunnen verschillende strategieën gehanteerd worden.

Kleine solitaire stenen (<5mm) kunnen door de ductus choledochus gespoelt worden na intraveneuze toediening van glucagon om de sphincter van Oddi te relaxeren. Stenen van tussen de 5 en 10 mm kunnen intraoperatief worden verwijderd door transcystische extractie. Grotere stenen en stenen in de proximale ductus choledochus met een verwijding van de galwegen kunnen operatief verwijderd worden door choledochotomie. Deze techniek vereist echter aanzienlijke ervaring van de operateur. In patiënten met veranderde galweganatomie, bijvoorbeeld na B2 maagresectie, is choledochotomie de eerste keus. In andere patiënten kan ook post-operatieve ERCP verricht worden.

Voor patienten met bewezen ‘moeilijke’ galstenen biedt perorale cholangioscopie met laserlithotripsie uitkomst. Deze techniek is ook aangewezen bij afwijkingen van de galwegen waarbij conventionele technieken geen duidelijkheid bieden.

Nieuwe beeldvormingsmodaliteiten die sneller en goedkoper zijn, zoals nabij-infrarode fluorescentiecholangiografie, dienen verder onderzocht te worden. Het potentiele toepassingsgebied van dergelijke technieken beslaat zowel de intraoperatieve beoordeling van de galweganatomie als de duiding van onbegrepen afwijkingen aan de galwegen.

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Appendices

APPENDIX A

Assessing the protective effect of intraoperative cholangiography on bile duct injury in population-based studies (letter)

KT Buddingh, ER van den Heuvel, RJ Ploeg

British Journal of Surgery (E-pub only, Feb 7th 2011)

Sir,

Giger et al[1] recently analyzed over 30'000 cholecystectomies and found almost identical rates of bile duct injury (BDI) in cholecystectomies with and without intraoperative cholangiography (IOC). From these figures one might conclude that IOC has no protective effect on BDI. Two important matters, however, were not considered.

Our first concern is that many surgeons who normally rarely perform IOC may use IOC every time a BDI occurs to assess the extent of the damage. Thus, a disproportionately large number of patients with BDI might be included in the 'LC with IOC' group. To illustrate this, consider the following. During a period of selective IOC policy at our own centre (2004-2006), IOC was performed in 25 out of the 421 cholecystectomies (5.9%). Eight BDI's occurred initially without IOC, but three of them were followed by IOC to assess the extent of the damage. If these three cases would be classified as BDI *with* IOC, the BDI rate with IOC would be 3/25 = 12% compared to 5/396 = 1.3% BDI without IOC. The unobservant reader may even be lured into thinking that IOC *increases* the risk of BDI ($p<0.001$). Returning to the paper by Giger et al: it is possible that of the 40 patients with BDI 'despite' IOC a similar proportion of three out of eight IOC's were misclassified and 13 IOC's were only performed because BDI was already noted. If these cases were considered as LC without IOC, the two-sided Pearson chi-square test would actually show a significant protective effect of IOC ($p=0.041$).

Our second concern is that no data is shown on the severity of BDI that occurred. IOC prevents transsection of a common bile duct that is mistaken for the cystic duct and cannulated for cholangiography. In such cases, IOC downstages a common duct transection to a common duct leak. Unfortunately, Giger et al did not assess differences in severity of BDI in cholecystectomies with and without IOC.

In summary, the paper by Giger et al is an impressive feat of nation-wide quality monitoring in laparoscopic surgery. The figures presented, however, do not justify dismissal of IOC as a patient safety measure during cholecystectomy.

APPENDIX B

The critical view of safety technique and intraoperative cholangiography complement each other as patient safety interventions (letter)

KT Buddingh, VB Nieuwenhuijs

Journal of Gastrointestinal Surgery 2011

Dear Editor,

We read with great interest the study by Sanjay et al in which they describe the outcome of 447 cholecystectomies using the critical view of safety (CVS) technique[1]. The authors are to be congratulated for performing a medium-sized series of cholecystectomies for acute pathology with no bile duct injuries or leaks. We, too, fully endorse the practice of careful dissection in the triangle of Calot and achievement of the CVS before clipping and dividing any tubular structures. However, rather than viewing the CVS as a replacement for routine IOC, we feel that the two safety measures complement each other.

Sanjay and colleagues rightly argue that the large population-based studies often used to propagate routine IOC date from the pre-CVS-era[2,3]. They continue to suggest that this protective effect is therefore not to be expected in modern surgical practice. In our point of view this is an unlikely assertion.

The CVS has been standard practice in the Netherlands for several years. A recent nation-wide survey by our group confirmed that 98% of the Dutch surgeons uses this technique. Nonetheless, common bile duct (CBD) injuries remain a substantial problem in the Netherlands with an incidence that is estimated to be higher than the 0.5% often quoted in literature[4]. Referrals to the largest tertiary referral centre for BDI in the Netherlands show no decreasing trend in the course of the past decade[5]. In our own centre, eight CBD injuries (1.9%) occurred between 2004 and 2006 despite the use of the CVS technique. In January 2007 routine IOC was implemented and no CBD injuries were observed in the three years thereafter ($p = 0.004$) (unpublished data).

IOC reduces the risk of BDI in several ways at different levels ranging from revealing which duct has been cannulated and demonstrating aberrant anatomy to increasing surgeon insight into the diversity of anatomical variations. These advantages can not be replaced by CVS technique.

It may be argued that IOC could be performed selectively in case of uncertain anatomy. There are two arguments against this option. Firstly, it is unclear whether surgeons can reliably identify patients at higher risk for BDI. Secondly, the importance of IOC becoming a routine part of the procedure is that the whole team expects it, is ready for it and can plan for it. Only then does it fit smoothly into the operative routine. Selectively performing IOC may lead to unfamiliarity with the technique and raise the threshold to perform it.

Sanjay et al mention that opponents of IOC caution that it is a potentially hazardous procedure. However, there is virtually no evidence that IOC leads to complications rather than prevents them. The negligible amount of radiation received, too, is not a valid argument against its use in the adult population[6].

Although we applaud the efforts of Sanjay et al to further advocate the CVS technique as optimal surgical technique to prevent BDI, we feel that routine IOC should not be abandoned as an additional safety measure. Bile duct injury has serious, sometimes fatal, consequences[7]. It is a frequently performed "routine" operation and such complications are especially difficult for patients and surgeons to accept. We advocate, therefore, that both the CVS technique and routine IOC are used to complement each other for the safest way to remove the gallbladder.

APPENDIX C

Pie sharing in complex clinical collaborations: a piece of cake?

KT Buddingh, GM van Dam, LMA Crane

British Medical Journal (Christmas Edition 2010)

Loosely based on an old folk tale

A Little Red Hen lived in a university hospital where she took care of the sick animals in the different wards. She did this under the overseeing eye of her wise and learned mentors. There was the Cow, who had a degree from a prestigious overseas university. There was the Pig, who had led mergers of several high standing hospitals in the country. And there was the Sheep, who had an outstanding treatment record with almost no animal morbidity and mortality.

One day the Little Red Hen thought: "Why don't I see if I can use my scarce free hours at the end of the day and make an excellent pie. Not only will this pie add to the gastronomic knowledge, it could be that the sick animals will benefit from this pie in the long run."

So the Little Red Hen ran her idea past her mentors.

"Great idea," said the Cow. "I will supply the milk and the butter. Of course, I would like a piece of the pie when it is baked."

"Excellent," said the Pig. "I happen to know the editor of a prestigious cook book. I expect a piece of the pie once it is finished."

"Good thinking," said the Sheep. "My laboratory will provide the necessary utensils. Just make sure I get a share of the pie."

The Little Red Hen wasted no time. Every day, after taking care of the sick animals she spent the last few hours of daylight planning the pie. She took classes in pie making, wrote pie making protocols and even obtained approval from the institutional pie review board. And after a few months, all preparations were in place.

The Little Red Hen first went to the Cow and asked for the milk and the butter. "I have the milk and the butter for you. However, I heard that the Sheep will also have a part of the pie. I want you to make sure that my piece of the pie is larger than that of the Sheep."

The Little Red Hen continued to the Pig. "Hold on," said the Pig. "I have submitted a grant application for possibly even a bigger pie, so I cannot actively co-operate any longer on the current pie. However, if you do bake it, don't forget to give me a piece."

The Little Red Hen then visited the Sheep. The Sheep was abroad for a conference on animal wellbeing with an extended post-conference tour, and his laboratory had received no instructions to provide any utensils.

The Little Red Hen went to work. She tested her own recipes, made do with her limited utensils, and fluttered between different departments to keep everybody satisfied. Finally, after many long hours and many failed pies, an acceptable pie came out of the oven.

Overjoyed, the Little Red Hen called together her mentors to share the news.

"Welcome everyone," said the Cow. "I would like to present the outstanding result of our co-operation." He then took half of the pie and left the room. The Pig was next. "Excellent work, Little Red Hen." He cut himself a sizeable piece of the pie and left the room. Then the Sheep stepped forward. "What a feat of culinary craftsmanship did we achieve! Congratulations on your first pie." He cut a small piece of the pie, and took the rest.

The Little Red Hen sat in the conference room and stared at the small piece of pie that remained. Although happy to have baked her first pie and to have contributed to the gastronomic knowledge, she was left with an inexplicable feeling of disappointment. It did take quite some time before the Little Red Hen attempted to bake another pie.

Disclaimer:

This tale is based upon coffee table stories and a compilation of reported experiences in the academic hospital at no specific place. Any names, characters, places, and incidents are either the product of the tale or are used fictitiously. Any resemblance to actual events or locales or persons, living or dead, is entirely coincidental.

Contributors:

KT Buddingh came up with the idea and wrote the first draft. LMA Crane gathered opinions and experiences from colleagues in the university hospital and contributed significantly to the description of the characters in the tale. GM van Dam ran a spell check on the document and demanded that, as senior investigator, he received a prime author position. After negotiations, he edited the paper for style, contributed to the plot of the tale and settled for the middle author position.

Biography and acknowledgements / dankwoord

BIOGRAPHY

The author of this thesis was born on June 11th 1986 in Qalandarabad, Pakistan, as the eldest of four sons to two tropical doctors. He attended primary school in Gutu, Zimbabwe, and secondary school in Khartoum, Sudan. In 2003 he passed the Dutch state exam of secondary education in Zwolle and enrolled into medical school at the Rijksuniversiteit Groningen in that same year. He attended his senior internships at the Deventer Hospital. His final internships were in the field of abdominal surgery at the UMC Groningen.

After receiving his medical degree in 2010, the author worked as a PhD-fellow at the UMC Groningen for three quarters of a year. During this period he laid the foundation for the current thesis. Besides the studies presented here, he published papers in gastroenterology, pediatric surgery and surgical oncology.

For the greater part of 2011, he worked as a resident in the Surgical Intensive Care Unit of the UMC Groningen. Subsequently, he worked for a year at the Urology department of the Academic Medical Centre in Amsterdam. Since November 2012 he has been working as a resident in Surgery and Urology at the St Elisabeth Hospital in Willemstad, Curacao.

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