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ANNE KRISTIINA MATTILA

MODERN MANAGEMENT OF GALLBLADDER AND COMMON BILE DUCT STONES

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ABSTRACT

During the last 20 years, an important development emerged in the management of gallstone disease and common bile duct (CBD) stones. Laparoscopic cholecystectomy (LC) has been confirmed to be safe and effective as a day-care procedure. In complicated gallstone disease, single-stage treatment of concomitant gallstones and CBD stones with laparoscopic CBD exploration (LCBDE) has been shown to be equally efficient and safe as two-stage endoscopic CBD stone clearance followed by LC (ERCP+LC). However, there is still controversy surrounding the optimum management of patients with concomitant gallbladder and bile duct stones.

The aims of this study were to assess the outcomes of day-care LC comparing ultrasonic versus diathermy dissection methods, and to examine the success and the costs of different treatment options of concomitant gallbladder and CBD stones in the short-and long-term.

In study I, we carried out a prospective study in a standardized day-care pathway setting. A total of 169 elective patients with symptomatic gallstones from Central Hospital of Central Finland were randomized to receive treatment with either ultrasonic scissors (88) or a diathermy hook (79). Both methods resulted in excellent same-day discharge of 87%, with the ultrasonic dissection method not displaying any clinical advantage over diathermal dissection.

In study II, the short-and long-term outcomes of 288 patients who underwent single-stage laparoscopic CBD stone removal and LC were examined in two Finnish hospitals in the time period 1999-2011. Successful CBD clearance was observed in 83.2% of patients; after conversion to open surgery, the clearance rate increased to 93.2%. Failed primary laparoscopic CBD clearance was associated with stone size > 7 mm, difficult anatomy, transductal approach and impacted CBD stones. Transcystic CBD stone removal resulted in a two day shorter postoperative hospital stay than was the case with transductal removal. The cumulative long-term CBD stone recurrence rate was low at both 5 and 10 years.

In study III, hospital costs and success of CBD clearance of 217 patients with concomitant gallbladder and bile duct stones were compared between one-stage (LCBDE + LC) and two-stage (endoscopic removal of CBD stones followed by LC) management. The biliary clearance rates were similar between the study groups, although the hospital stay was shorter in the one-stage group. No significant difference was detected in the mean hospital costs between the one-stage (6785 €) and two-stage (6913 €) groups. The transcystic method proved to be the most economical strategy of all three concomitant gallbladder and bile duct stone treatment options in our hospital. The conclusion of studies II and III suggests that the method of choice in concomitant gallbladder and bile duct stones treatment is laparoscopic transcystic CBD clearance followed by transductal and endo-laparoscopic approach when feasible.

In study IV, the fate of patients having calculous gallbladder after endoscopic CBD stone clearance was analyzed retrospectively. The study included 174 patients in whom a wait-and-see policy was adopted due to underlying severe illnesses or patients' refusal to undergo cholecystectomy. The incidence of biliary-related complications and biliary mortality was low during the median follow-up of 3.9 years, but was related to a relatively high overall mortality.

In conclusion, ultrasonic dissection compared to conventional diathermy does not further improve results in an optimized day-care setting. Cholecystocholedocholithiasis is preferably treated by single-stage laparoscopic transcystic removal compared to ERCP+ LC due to its lower costs, shorter hospital stay and similar success rate. A wait-and-see policy is acceptable in high-risk elderly patients after a thorough perioperative risk assessment.

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TIIVISTELMÄ

Sappikivitaudin ja sappitiehytkivien hoidossa on viimeisen 20 vuoden aikana tapahtunut huomattavaa kehitystä. Päiväkiruginen sappirakon poisto (LC) tähystysmenetelmällä on todettu olevan turvallinen ja tehokas toimenpide. Komplisoituneessa sappikivitaudissa yksivaiheisen hoitomenetelmän, jossa sappirakko ja sappitiehytkivet poistetaan samalla kertaa tähystysleikkauksella (LCBDE), on osoitettu olevan yhtä tehokas ja turvallinen kuin kaksivaiheisen endoskooppisen sappitiehytkivien poiston, jota seuraa sappirakon poisto myöhemmin tähystysleikkauksella (ERCP+LC). Ihanteellinen komplisoituneen sappikivitaudin hoito on edelleen kuitenkin kiistanalainen asia.

Tämän tutkimuskokonaisuuden tarkoituksena oli selvittää (i) päiväkirurgisen tähystysmenetelmällä leikattavan sappikivitaudin kirurgista hoitoa kahdella vaihtoehtoisella menetelmällä, jossa sappirakon irrotus tapahtuu joko diatermiakoukulla tai ultraäänisaksilla, ja (ii) tutkia sappi- ja sappitiehytkivien erilaisten hoitovaihtoehtojen lyhyt- ja pitkäaikaistuloksia ja kustannuksia.

Keski-Suomen keskussairaalassa toteutettiin satunnaistettu tutkimus (tutkimus I), jossa verrattiin kahta erilaista kirurgista tekniikkaa tähystysmenetelmällä tehdyssä sappirakon poistossa. Tutkimukseen osallistui 169 elektiivistä potilasta (88 ultraäänisaksiryhmässä ja 79 sähkökoukkuryhmässä). Molemmissa tutkimusryhmissä saavutettiin erinomainen 87 %:n kotiutuminen leikkauspäivänä. Ultraäänisakset eivät tuoneet kliinistä etua verrattuna sähkökoukun käyttöön.

Tutkimuksessa II selvitettiin lyhyt- ja pitkäaikaisvaikutuksia kahden suomalaisen sairaalan 288 potilaalta, joille tehtiin samanaikainen sappirakon ja sappitiehytkivien poisto tähystysmenetelmällä vuosina 1999 - 2011. Tähystysmenetelmällä tehty tiehytkivien poisto onnistui 83,2 %:lla leikatuista. Muuttamalla leikkaus avoimeksi onnistuttin tiehytkivet poistamaan 93,2 %:lla potilaista. Epäonnistunut tähystyskirurginen sappitiehytkivien poisto liittyi seuraaviin tekijöihin: tiehytkivien koko > 7 mm, vaikea anatomia, yhteisen sappitiehyeen kautta tehty poisto ja yhteisen sappitiehyeen laskukohtaan kiilautuneet kivet. Sappirakkotiehyeen kautta tehty tiehytkivien poisto johti 2 päivää lyhyempään leikkauksen jäkeiseeen sairaalassaoloaikaan kuin yhteisen sappitiehyeen kautta tehty poisto. Kumulatiivinen sappitiehytkivien uusiutumisriski oli matala 5 ja 10 vuoden kuluttua.

Tutkimuksessa III verrattiin 217 potilaan sappitiehytkivien ja sappirakon poiston kustannuksia ja hoidon tuloksia yksivaiheisen (LCBDE) ja kaksivaiheisen (ERCP + LC) menetelmän välillä. Ryhmien välillä sappitiehytkivet saatiin poistettua yhtä hyvin, mutta yksivaiheisessa ryhmässä sairaalassaoloaika oli lyhyempi. Sairaalahoidon kokonaiskustannuksissa ei todettu merkittävää eroa yksivaiheisen (6785 €) ja kaksivaiheisen (6913 €) ryhmän välillä. Kun yksivaiheinen hoito jaettiin sappirakkotiehyeen ja yhteisen sappitiehyeen kautta tehtävään poistoon, osoittautui ensin mainittu ryhmä kaikkein edullisimmaksi sappikivitaudin ja sappitiehytkivien hoidossa. Tutkimusten II ja III perustella suositellaan, että samanaikaisen sappi- ja sappitiehytkivitaudin paras hoito on sappirakkotiehyeen kautta tehtävä toimenpide, silloin kun se on mahdollista toteutttaa.

Tutkimuksessa IV analysoitiin takautuvasti 174 sappikivitautia sairastavaa potilasta, joille oli tehty endoskooppinen sappitiehytkivien poisto ja pidättäydytty sappirakon poistosta

vakavien perussairauksien tai potilaan kieltäytymisen vuoksi. Sappikivitaudin aiheuttamat komplikaatiot ja kuolleisuus olivat matalat 3,9 vuoden mediaaniseuranta-aikana. Tähän vaikutti potilaiden korkea kuolleisuus muihin kuin sappikivitaudista johtuviin syihin.

Yhteenvetona voidaan todeta, että ultraäänimenetelmän käyttö päiväkirurgisessa tähystyksellisessä sappileikkauksessa ei tuo lisäetua verrattuna perinteisen sähkökoukun käyttöön. Samanaikaisen sappi- ja sappitiehytkivitaudin suositeltava hoito on yksivaiheinen laparoskooppinen transkystinen sappitiehytkivien poisto yhdistettynä sappirakon poistoon verrattuna kaksivaiheiseen endolaparoskooppiseen (ERCP + LC) hoitoon. Sappitiehytkivien poisto onnistuu molemmissa ryhmissä yhtä hyvin, vaikka yksivaiheisessa menetelmässä kustannukset ovat vähäisemmät ja sairaalahoito lyhyempi kuin kaksivaiheisessa menetelmässä. Seuranta pelkän endoskooppisen sappitiehytkivien poiston jälkeen iäkkäillä korkean riskin potilailla on hyväksyttävää huolellisen leikkausriskianalyysin jälkeen.

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Yleinen Suomalainen asiasanasto: hoitotulokset; kustannukset; leikkaushoito; lyhytkirurgia; sairaalahoito; sappikivet; sappirakko; sappitiet; tähystysleikkaukset

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IV. Mattila A, Mrena J,Kellokumpu I. Expectant management of gallbladder stones after endoscopic removal of common bile duct stones. International Journal of Surgery 43: 107-111, 2017

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APPENDIX: ORIGINAL PUBLICATIONS

Abbreviations

BIS	Bispectral index
BMI	Body mass index
CBD	Common bile duct
CCI	Charlson Comorbidity Index
CCL	Cholecystocholedocholithiasis
CHD	Common hepatic duct
CT	Computed tomography
DS	Day surgery
EPBD	Endoscopic papillary balloon dilatation
ERCP	Endoscopic retrograde cholangiopancreatography
ES	Endoscopic sphincterotomy
ESWL	Extracorporeal shockwave lithotripsy
EUS	Endoscopic ultrasound
HDL	High density lipoprotein
IQR	Interquartile range
IOC	Intraoperative cholangiography
IOES	Intraoperative ERCP
LC	Laparoscopic cholecystectomy
LCBDE	Laparoscopic common bile duct exploration
LUS	Laparoscopic ultrasound
MRI	Magnetic resonance imaging
MRCP	Magnetic resonance cholangiopancreatography
NOTES	Natural orifice transluminal endoscopic surgery
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
OC	Open cholecystectomy
OS	Overnight stay
PONV	Postoperative nausea and vomiting
QALY	Quality-adjusted life year
SILC	Single incision laparoscopic cholecystectomy
TC	Transcystic
TD	Transductal
TIVA	Total intravenous anesthesia
VAS	Visual analogue scale
US	Ultrasound

1 Introduction

Gallstone disease is one of the most common gastrointestinal disorders, affecting 6% to 22% of adults in the Western world (Aerts and Penninckx 2003). In addition, in Western countries 10%-18% of patients with symptomatic gallbladder stones have secondary common bile duct (CBD) stones (Martin *et al.* 2006).

In Finland, 8478 cholecystectomies were performed in 2015, of which 35 % were operated as day-care surgery. The mean duration of hospital stay after cholecystectomy was two days, the median was one day (www.thl.fi).

Laparoscopic cholecystectomy (LC) and small-incision cholecystectomy have been shown to be alternative methods in handling cholecystolithiasis in comparison with open cholecystectomy (Keus *et al.* 2010). The safety and effectiveness of day-care LC have been confirmed in several studies (Keulemans *et al.* 1998, Hollington *et al.* 1999, Johansson *et al.* 2006, Barthelsson *et al.* 2008, Vaughan *et al.* 2013).

Traditional diathermy hook dissection has been the gold standard in gallbladder surgery since the beginning of laparoscopic era. Ultrasonic dissection in LC has revealed some potential advantages compared to traditional electrocautery in some studies (Power *et al.* 2000, Cengiz *et al.* 2005, 2010).

CBD stones with concomitant gallstones can be managed pre-, intra- or post-operatively depending on the surgical expertise and local resources available (Dasari *et al.* 2013). With increasing experience in advanced laparoscopic surgery, laparoscopic CBD exploration has become an alternative method next to endoscopic clearance of CBD stones. However, the implementation of laparoscopic CBD stone management has not gained popularity in Finland, despite the fact that randomised trials have demonstrated the safety and effectiveness of laparoscopic CBD exploration, e.g. it achieves comparable results with sequential two-stage endolaparoscopic treatment of cholecystocholedocholithiasis (CCL) (Rhodes *et al.* 1998, Cuschieri *et al.* 1999, Sgourakis and Karaliotas 2002, Nathanson *et al.* 2005, Noble *et al.* 2009, Bansal *et al.* 2010, 2014, Rogers *et al.* 2010, Koc *et al.* 2013, Ding *et al.* 2014). In addition, some evidence has emerged in the literature concerning the economical benefits of one-stage laparoscopic CBD stone clearance compared to the two-stage endo-laparoscopic method (Rogers *et al.* 2010, Topal *et al.* 2010, Bansal *et al.* 2014).

Despite the development of laparoscopic techniques and improved perioperative care, cholecystectomy deferral after endoscopic removal of CBD stones in elderly and frail patients may be a tempting alternative to avoid possible high-risk cholecystectomy. However, a wait-and-see-policy after successful endoscopic clearance of CBD stones in patients with intact gallbladder stones is not routinely recommended due to the higher risks of complications connected to stones (McAlister *et al.* 2007, Williams *et al.* 2008).

2 Review of the literature

2.1 ANATOMY OF THE EXTRAHEPATIC BILIARY SYSTEM

The gallbladder is normally 7-10 cm long in adults composing of fundus, body and neck, which continues forming the cystic duct. The gallbladder is separated from the liver by a connective tissue plate. The right and left hepatic ducts unify and form the common hepatic duct (CHD). (Vakili and Pomfret 2008.) After joining with the cystic duct, they form the common bile duct (CBD). In anatomic studies, the average internal diameter of CBD has varied from 4 to 12.5 mm (Kune 1964). The average length of the cystic duct lies in a range between 2 and 4 cm (Figure 1). Lateral insertion of the cystic duct to CHD is the prevailing anatomic pattern (51%-70 %) aside from parallel (15%-20%) and low (4%) medial insertion. (Vakili and Pomfret 2008; Sarawagi *et al.* 2016.) The blood supply of the gallbladder usually arises as a branch from the right hepatic artery forming the cystic artery. Variations in the course of the cystic artery are frequent; there can be a ramification of the cystic artery into several branches before entering at the gallbladder. Appreciation of the biliary anatomy is essential to avoid biliary complications during LC and to evaluate the possibilities of laparoscopic clearance of CBD stones. The difference between Calot´s triangle and hepatocystic triangle is the upper boundary, which is formed by the cystic artery in the former and the lower margin of liver in the latter definition (Figure 1). Clearance of the hepatocystic triangle in LC is essential to gain the "the critical view of safety" for identification of the cystic structures. (Strasberg 2013.)

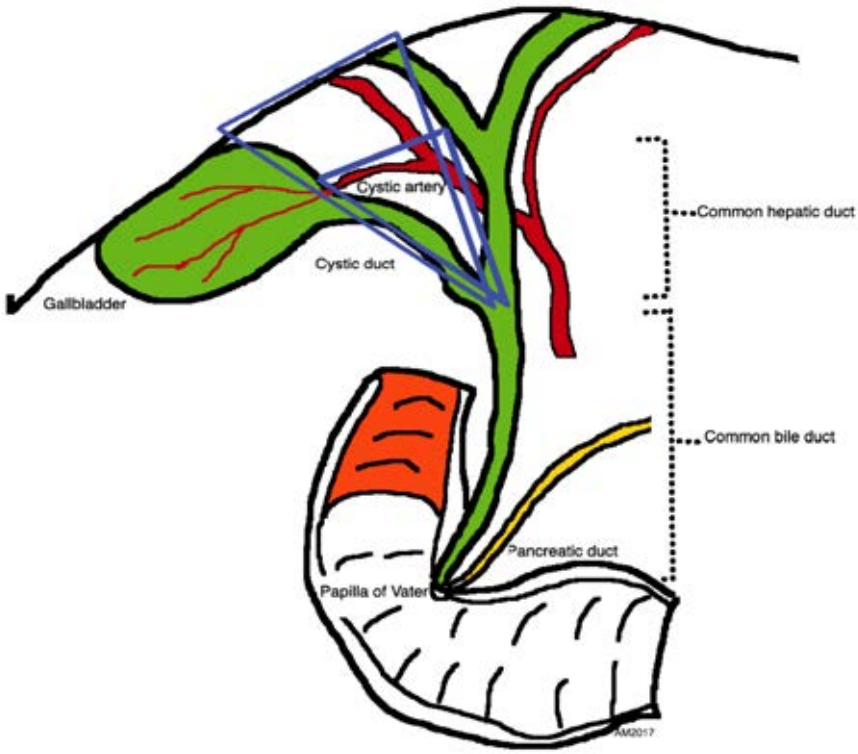


Figure 1. Calot´s triangle (smaller blue triangle) and hepatocystic triangle (larger blue triangle).

2.2 EPIDEMIOLOGY AND PATHOGENESIS

2.2.1 Gallbladder stones

The highest prevalence of gallstone disease (64.1%-73%) has been identified in North American Indians (Sampliner *et al.* 1970; Everhart *et al.* 2002). Intermediate prevalence rates occur in Asian populations (6.2%-21.6%) with the lowest frequencies being found among non-Hispanic blacks (5.3%-13.9%) (Everhart *et al.* 1999).

The prevalence rates are higher in women in Western countries (Aerts and Penninckx, 2003; Stinton *et al*., 2010; D M Shabanzadeh *et al.*, 2016a). However, among Asian patients, the gender-related difference is controversial (Chen *et al.* 2012; Takahashi *et al.* 2014; W. Zhang *et al*. 2015). The higher incidence of gallstones in women is thought to occur via the effect of estrogen on hepatic cholesterol secretion and biosynthesis which increases biliary cholesterol saturation and enhances gallstone formation (Wang *et al.* 2009).

The risk of gallstone disease increases with age in all ethnic groups (Barbara *et al.* 1987, Stinton *et al.* 2010). Cohort studies with repeated ultrasound examinations have estimated the incidence of gallstones to be 0.6%-1.39% per year (Festi *et al.*, 2008; Halldestam *et al.*, 2009; D M Shabanzadeh *et al*., 2016a).

Studies from larger cohorts have revealed that the prevalence of gallstones correlates positively with an increased risk of cardiovascular disease, BMI, non HDL-cholesterol, metabolic syndrome, gallbladder polyps and helicobacter pylori-infection (Takahashi *et al.*, 2014; F. M. Zhang *et al*., 2015; D M Shabanzadeh *et al*., 2016a). Additionally, a rapid weight loss has been postulated to be a risk factor of cholesterol stones (Shiffman ML *et al.* 1991).

The formation of gallstones is multifactorial. The composition of bile is an important factor in gallstone formation. Various conditions such as biliary cholesterol supersaturation, excess pronucleating proteins and hypomotility of gallbladder are thought to affect the crystallization of bile. In the Western world, 70% of gallstones are cholesterol stones (cholesterol content >30 %) and 30% black pigment stones. In contrast, In Eastern Asia, brown pigment stones are associated with chronic bacterial infection of the bile ducts leading to a stone composition mainly consisting of calcium salts of unconjugated bilirubin. (Venneman and van Erpecum 2010.) The formation of cholesterol stones is promoted by cholesterol supersaturation of bile, gallbladder hypomotility and destabilisation of bile by kinetic protein factors. Haemolytic anemias and ileal Crohns disease are the most usual reasons for black pigment stones of polymerized calcium bilirubinate. (Grünhage and Lammert 2006.)

Genetic factors may play a contributory role in cholelithiasis. Thus, several loci in genes that have putative functions in cholesterol metabolism and transport, and sulfonylation of bile acids or hydroxysteroids have been identified. (Buch *et al*. 2007; Joshi *et al.* 2016.)

2.2.2 Common bile duct (CBD) stones

Common bile duct stones (choledocholithiasis) originate from the gallbladder and pass into the bile ducts or develop primarily in the biliary tree. Primary bile duct stones are composed mainly of bilirubin and their frequency is high in Southeast Asian countries. The pathogenesis of primary bile duct stones is associated with bacterial infection, bile stasis and parasitic infections. In addition, primary CBD stones are associated with intrahepatic bile duct stones. (Shoda *et al*. 2003; Tazuma 2006.) Primary CBD stones are either black or brown pigment stones composed of calcium bilirubinate (Wang and Afdhal 2016). Another definition for primary CBD stones after cholecystectomy is at least a two years' symptom free interval (Saharia *et al.* 1977). In some studies, the prevalence of CBD stones found during LC is reported to vary between 1.1% to 22% (Nickkholgh *et al.* 2006, Videhult *et al.* 2011; Lee *et al.* 2016).

2.3 DIAGNOSTICS

2.3.1 Symptoms

Biliary colic presenting as an abruptly beginning pain with increasing intensity is the cardinal symptom of cholelithiasis (Berhane *et al.* 2006). According to a large Italian cohort study, pain in the epigastrium and/or hypochondrium is the main symptom associated with gallstone disease (Festi *et al.* 2008). As a contributory factor, a functional gastrointestinal disorder can be present in the vast majoriy i.e. 80 - 88% of patients, with gallstone disease (Schmidt *et al.* 2012). Confounding symptoms like dyspepsia, blouting, heartburn and flatulence often persist after cholecystectomy (Vetrhus *et al.* 2005).

In a large Danish cohort study (6037 patients), more than 80% of patients with gallstones remained uneventful during the 20-year follow-up time. However, after a 10-year period, predictors of all gallstone related events were found to be female sex, younger age, and having multiple older and larger stones. (D M Shabanzadeh et al., 2016b.) The incidence of developing symptoms or complications from asymptomatic gallstones was 7.6% in a Swedish general population during a 5-year follow-up (Halldestam *et al.* 2004). Some studies have shown that in only 10%- 25 % of asymptomatic individuals will the gallstone disease advance to symptomatic disease (Sakorafas *et al.* 2007, Festi *et al.* 2010).

2.3.2 Laboratory and scoring systems of CBD stones

A Swedish cohort study of 1171 patients operated for gallstone disease over a period of 3 years revealed elevated alkaline phosphatase and bilirubin as the two most reliable predictors of CBD stones (Videhult *et al.* 2011). The strength of this population-based trial was its unselected population and the high frequency of intraoperative cholangiography (95%) to exclude CBD stones. A recent Cochrane analysis concluded that endoscopic ultrasound (US) and liver function tests are not sufficient to exclude CBD stones if the suspicion of CBD stones is high (Gurusamy *et al.* 2015).

Several clinical indicators, biochemical tests and scoring systems based on preoperative data have been suggested for predicting CBD stones. Most of the predictive models have been performed in selected patients with a high risk of CBD stones, e.g. previous biliary pancreatitis or elevated liver function tests. (Huguier *et al.* 1991; Hauer-Jensen *et al.* 1993; Graham *et al.* 1993; Sharma *et al.* 1993; Barkun *et al.* 1994; Onken *et al.* 1996; Menezes *et al.* 2000; Kama *et al.* 2001; Peng *et al.* 2005; Sgourakis *et al.* 2005; van Santvoort *et al.* 2011.) However, the implementation of most tests in daily clinical practice is cumbersome. Sonnenberg et al. devised a decision tree model to compare the costs of imaging modalities when diagnosing CBD stones. They recommended that magnetic resonance cholangiopancreatography (MRCP) should be preferred over endoscopic ultrasound and endoscopic retrograde cholangiopancreatography (ERCP) in patients with low pre-test probability of CBD stones. (Sonnenberg *et al.* 2016.) Topal et al. evaluated a predictive model including five variables for detecting CBD stones. CBD dilatation or stones seen in US, age >60 years, fever, serum amylase level >95 units/l and alkaline phosphatase >670 units/l were the important predictors for CBD stones. They confirmed that additional MRCP is recommended if predicted probability of CBD stones was more than 5 %. (Topal et al. 2003.) Nevertheless, prospective studies have been inconsistent and no single biochemical marker or combination of tests has been identified for detecting CBD stones (Topal *et al.* 2009, Suarez *et al.* 2016).

2.3.3 Imaging

2.3.3.1 Ultrasonography (US)

The historical use of oral cholecystography has limited value in diagnosing gallbladder stones and has been largely replaced by abdominal ultrasonography (Bortoff *et al.* 2000). As a result,

US has been the first line method for the diagnosis of gallstones since the 1970s (Leopold *et al.* 1976). The technique is non-invasive, widely available with a sensitivity of 84%-96% and specificity of 88% - 100%, even when performed by non-radiologists (Schlager *et al.* 1994, Jang *et al.* 2010, Ahmed and Diggory 2011). Tokyo Guidelines for radiological diagnosis of acute cholecystitis include thickening of the gallbladder wall (5 mm or greater), pericholecystic fluid, or direct tenderness when the US probe is pushed against the gallbladder wall. For acute cholecystitis, the diagnostic capability of US possesses a sensitivity of 88% and a specificity of 80%. (Yokoe *et al.* 2013.) Additionally, contrast-enhanced ultrasound is a new method and can be used as a supplemental tool for diagnosing gangrenous cholecystitis (Ripollés *et al.* 2016).

2.3.3.2 Computed tomography (CT)

Primary diagnostics of gallstones with computed tomography is rarely used since most gallstones are poorly calcified and isodense with bile, thus displaying poor visibility in traditional CT (Portincasa *et al.* 2006, Chen *et al.* 2015). However, when using spectral CT imaging, the detection of gallbladder stones can be improved as compared with traditional CT imaging (Chen *et al.* 2015). Additionally, when diagnosing mild cholecystitis, transient focal enhancement of the liver adjacent to the gallbladder can be visualized by arterial phase of dynamic CT (Kim *et al.* 2009).

2.3.3.3 Magnetic resonance imaging (MRI)

Magnetic resonance imaging of gallbladder can be considered as a complimentary imaging modality when US is inadequate, e.g. if the patient is obese (Catalano *et al.* 2008).

A Cochrane review of 18 studies emphasised the high diagnostic accuracy of EUS and MRCP in detecting CBD stones (Giljaca *et al.* 2015). A CT-scan is believed to be inferior compared to MRCP in detecting CBD stones (Moon *et al.* 2005). The benefit of MRCP is the non-invasiveness of the technique while still achieving 85-95% sensitivity and 93%-97% specificity (Romagnuolo *et al.* 2003, Verma *et al.* 2006). A modern multi-detector CT has been used to diagnose CBD stones with 72%-85.4% sensitivity and 96% specificity (Anderson *et al.* 2008, Kim *et al.* 2013).

2.3.3.4 Intraoperative imaging

Intraoperative cholangiography (IOC) has been the standard method for bile duct imaging during cholecystectomy. The purpose of IOC is twofold; to detect choledocholithiasis and to reveal the bile duct anatomy and thus to reduce the incidence of bile duct injury (Buddingh *et al.* 2011, Ford *et al.* 2012). One disadvantage of IOC is the longer operating time (Ding *et al.* 2015), although the time burden is postulated to be only 10-16 minutes (Ford *et al.* 2012, Buddingh *et al.* 2013). The use of selective IOC has been justified by the low incidence of CBD stones (Snow *et al.* 2001, Horwood *et al.* 2010). Randomised studies assessing the benefit of routine IOC for detecting CBD stones have revealed controversial results. Some studies do not support the use of routine IOC (Hauer-Jensen *et al.* 1993;Nies *et al.* 1997; Amott *et al.* 2005; O. A. Khan *et al.* 2011); and some favour the use of IOC for detecting CBD stones (Murison *et al.* 1993, Tusek *et al.* 1997). Nickkholgh et al. conducted a retrospective cohort of 2130 patients with routine versus selective IOC. They concluded that routine use of IOC increased the incidence of detecting CBD stones significantly compared to selective use (3.3% versus 1.1%). (Nickkholgh *et al.* 2006.) However, incidentally found small and silent CBD stones may pass into the duodenum spontaneously, and thus potentially unnecessary interventions can be avoided (Collins *et al.* 2004).

A recent meta-analysis of 11 comparative studies of IOC versus laparoscopic ultrasound (LUS) for detection of CBD stones revealed pooled sensitivity values of 87% and 87% and specificities of 99% and 100%, respectively (Aziz *et al.* 2014). Sun et al. used a decision tree model to devise an optimal diagnostic approach of asymptomatic CBD stones during LC. They found that intraoperative LUS was cost-effective compared to IOC or expectant management of

CBD stones. (Sun *et al.* 2015.) LUS has been reported to be faster, less expensive, and more sensitive at detecting CBD stones. LUS, but not IOC, can detect also sludge. The false negative rate of LUS is equivalent to that of IOC (< 1 %). (Halpin *et al.* 2002.) The disadvantage of LUS is the significant learning curve associated with this approach (Falcone Jr *et al.* 1999). LUS and IOC are considered to be complementary methods during LC. LUS has been advocated as a primary approach in many cases, whereas IOC is performed selectively as a secondary method. IOC is contraindicated in pregnancy and in patients with iodine allergy. In acute cholecystitis, the cystic duct may be obliterated and thus cause cannulation difficulties, favouring the use of LUS. (Catheline *et al*. 2002.)

2.4 TREATMENT OF GALLSTONE DISEASE

The indication for cholecystectomy is symptomatic gallstone disease. When considering cholecystectomy, the risks associated with the operative intervention must be weighed against the risks of gallstone related complications if left untreated. In patients fit for surgery, cholecystectomy should be considered for definitive management of gallstones (Duncan and Riall 2012). A large cohort study from Sweden indicated that the short-term mortality rate after cholecystectomy was near the mortality of the general population, although increasing factors for mortality were co-morbid conditions and perioperative complications (Sandblom *et al.* 2015). No RCTs have been published concerning the benefits of cholecystectomy in asymptomatic patients. According to several guidelines, it is not routinely recommended that asymptomatic gallstones should be operated (Gurusamy and Samraj 2007a, Internal Clinical Guidelines Team 2014, European Association for the Study of the Liver (EASL). Electronic address: easloffice@easloffice.eu 2016).

The risk of developing gallstone related complications is approximately 1-4 % per year (Portincasa *et al.* 2006). In acute cholecystitis, the surgical evaluation should be performed without delay to improve the quality of care as well as reducing the costs of treatment (Campanile *et al.* 2014; Wu *et al.* 2015; Sutton *et al.* 2017). The approach for symptomatic CBD stones necessitates careful judgement because CBD stones can cause life-threatening complications including biliary pancreatitis, acute cholangitis, jaundice, hepatic abscess or chronic obstruction even causing portal hypertension (Costi *et al.* 2014).

Further, a recent review highlighted the low quality of international guidelines on the management of gallbladder and bile duct stones. Most criticism was aimed at the low level of evidence and the lack of any consensus about definitions (van Dijk *et al.* 2017).

2.4.1 Uncomplicated gallstone disease

2.4.1.1 Uncomplicated gallbladder stones

There is some evidence to support early LC for biliary colic (Gurusamy, Davidson, *et al.* 2013). However, timing and indications of cholecystectomy in uncomplicated gallstone disease are controversial (Berger *et al.* 2004). Brazzelli et al carried out a review of two randomized trials comparing conservative management with cholecystectomy in uncomplicated symptomatic gallstone disease. They concluded that in a significant proportion of patients (55%), cholecystectomy could be avoided. (Brazzelli et al. 2015.) Prognostic nomograms have also been developed to predict the 2-year risk of developing gallstone related complications in older patients (Parmar *et al.* 2015). A large randomized trial is intended to start in the Netherlands focusing on identifying those patients who will benefit most from cholecystectomy (de Reuver *et al.* 2016).

According to European guidelines, prophylactic cholecystectomy may be offered simultaneously with restrictive obesity surgery due to the fact that 10-15 % of asymptomatic

gallstones may progress to become symptomatic after bariatric surgery (European Association for the Study of the Liver (EASL). Electronic address: easloffice@easloffice.eu 2016). In contrast to that recommendation, Morais et al claimed that symptomatic gallstones after bariatric surgery are rare and prophylactic cholecystectomy should not be offered at the time of bariatric surgery (Morais *et al.* 2016).

Some earlier studies have revealed some correlation of gallbladder cancer with porcelain gallbladder (Ashur *et al.* 1978). However, this connection is controversial and only a weak recommendation for prophylactic cholecystectomy exists (Khan, Livingston, *et al.* 2011, European Association for the Study of the Liver (EASL). Electronic address: easloffice@easloffice.eu 2016).

2.4.1.2 Uncomplicated CBD stones

Rather few studies have investigated the natural course of asymptomatic CBD stones. Spontaneous passage of CBD stones into the duodenum may occur in 12.9%-21 % of cases (Frossard *et al.* 2000, Pierce *et al.* 2008). Collins et al. performed 997 consecutive LCs and observed filling defects in 4.6 % of intraoperative cholangiographies. A cholangiogram catheter was left in place for 6 weeks, and spontaneous passage of CBD stones was observed in more than half of the patients in repeated contrast studies. No adverse events occurred, and as a result, they recommended expectant management of silent CBD stones (Collins *et al.* 2004).

However, migrating stones may cause biliary pancreatitis and acute cholangitis if they obstruct the ampulla of Vater. This was demonstrated in a retrospective cohort study of 3828 unselected patients with observed CBD stones during cholecystectomy. Unfavourable outcomes were found in 25.3% of patients, when no measures had been adopted to remove CBD stones. As adverse events were detected also with small stones (< 4 mm) , Moller et al points out that attempts should be made to clear the bile ducts thus avoiding possible complications. (Moller *et al.* 2014.)

2.4.2 Complicated gallstone disease

2.4.2.1 Acute cholecystitis

The treatment of choice for acute cholecystitis is cholecystectomy performed as soon as possible after the onset of symptoms (Campanile *et al.* 2014). Urgent cholecystectomy may reduce the number of readmissions and hospital stay and achieve a higher quality of life (Jarvinen and Hastbacka 1980; Lo *et al.* 1998; Kiviluoto *et al.* 1998; Lai *et al.* 1998; Johansson *et al.* 2003; Kolla *et al.* 2004; Macafee *et al.* 2009; Gutt *et al.* 2013; Gurusamy, Davidson, *et al.* 2013; Sutton *et al.* 2017). In a recent prospective randomised trial, early cholecystectomy within 4 days after the onset of symptoms resulted in reduced costs, less morbidity and a shorter hospital stay than delayed cholecystectomy (Roulin *et al.* 2016). Cost utility analyses made in different health care systems also favour early surgical management of acute cholecystitis (Wilson *et al.* 2010, Johner *et al.* 2013, de Mestral *et al.* 2016).

Antibiotic therapy for acute cholecystitis can be seen as support for surgery in many guidelines (Yoshida *et al.* 2007; Miura *et al.* 2013;Campanile *et al.* 2014). However, acute cholecystitis is thought to be an inflammatory rather than an infectious process requiring antibiotics. A recent review showed that there is a lack of convincing evidence to support the use of antibiotics in acute cholecystitis. (van Dijk *et al.* 2016.) Furthermore, the role of antibiotics has been questioned in the only randomised trial published, which compared supportive treatment with antibiotics in mild acute cholecystitis (Mazeh *et al.* 2012).

Percutaneous cholecystostomy is an option for treating acute cholecystitis in high-risk surgical patients (Campanile *et al.* 2014). The conclusion of a Cochrane review of two randomised trials was that there was insufficient data concerning the clinical use of cholecystostomy. Thus, no clear recommendation could be offered. (Gurusamy, Rossi, *et al.* 2013.)

2.4.2.2 Acute biliary pancreatitis

Biliary pancreatitis is a consequence of biliopancreatic obstruction caused by the migration of gallstones (Acosta and Ledesma 1974); especially small gallstones pose an increased risk of developing acute biliary pancreatitis (Venneman *et al.* 2005). According to international guidelines, cholecystectomy is recommended within 2 weeks of the onset of mild pancreatitis or during the index hospital admission to avoid readmission for recurrent biliary events (Working Party of the British Society of Gastroenterology *et al.* 2005, Tenner *et al.* 2013, Yokoe *et al.* 2015). The PONCHO-trial has confirmed that in mild gallstone pancreatitis, cholecystectomy during index admission is associated with reduced costs and lower morbidity compared with interval cholecystectomy (da Costa *et al.* 2016). A Cochrane analysis of 5 randomized controlled trials showed that early routine ERCP had no effect on mortality or complications, regardless of the predicted severity of pancreatitis. However, early ERCP has been recommended in patients with co-existing cholangitis or biliary obstruction. (Tse and Yuan 2012.).

2.4.2.3 Acute cholangitis

An obstruction of the biliary ducts can lead to a stasis of bile, exposing the patient to ascending bacterial infection (Hanau and Steigbigel 2000). The severity of acute cholangitis varies from mild to life-threatening. According to Tokyo guidelines, moderate cholangitis should be drained early and severe cholangitis needs urgent endoscopic decompression. (Kiriyama *et al.* 2013.) However, in a recent study, Schwed et al. pointed out that the timing of endoscopy was not crucial for the prognosis of cholangitis (Schwed *et al.* 2016). Schneider et al. have generated an online risk model for in-hospital mortality, based on thirteen clinical predictors for acute cholangitis but the implementation of this risk model will need further evaluation. (Schneider *et al.* 2016.)

2.5 EVOLUTION OF CHOLECYSTECTOMY TECHNIQUES

Since the first open cholecystectomy, performed by German Carl Langenbuch in 1882 in Berlin (Hardy 1993), cholecystectomy techniques have evolved. One hundred years later, the German surgeon, Erik Muhe, conducted the first laparoscopic cholecystectomy in 1985 (Litynski 1998). The first videolaparoscopic cholecystectomy was done 1987 by a French surgeon, Philippe Mouret (Litynski 1999). Laparoscopy was a surgical revolution allowing the cholecystectomy to be performed with minimal incisions and less surgical trauma. The adoption of LC was fast and within 4 years, LC became extremely popular, accounting for nearly 80 % of all cholecystectomies. (Nair *et al.* 1997.) Interestingly, an increase in cholecystectomy rates was observed after the introduction of LC (Legorreta *et al.* 1993, Johanning and Gruenberg 1998). LC soon became the gold standard for treating cholelithiasis, although initially, reports were published of a higher incidence of bile duct injuries (Connor and Garden 2006). The incidence of bile duct injuries has now been reported to have declined to the level of the open era (Halbert *et al.* 2016).

While LC techniques advanced, some disadvantages of LC led to the simultaneous development of open minilaparotomy cholecystectomy, introduced 1994 by Tyagi et al (Tyagi *et al.* 1994). A Cochrane analysis comparing open cholecystectomy, LC and minilaparotomy cholecystectomy concluded that LC and minilaparotomy cholecystectomy were equally safe and effective. Minilaparotomy cholecystectomy has been associated with less costs and shorter operative time. (Keus *et al.* 2010.) Recent prospective studies comparing MC and LC have shown that they have similar long-term outcomes (Harju, Aspinen, *et al.* 2013, Aspinen *et al.* 2014).

The concept of single incision laparoscopic cholecystectomy (SILC) was presented as well to minimize the surgical trauma while improving the cosmetic outcome. The first descriptions date back to 1997. (Navarra *et al.* 1997.) Altogether 17 randomised studies with 1293 patients

were analysed, with the conclusion that SILC offered no clear advantage compared to conventional LC. The only benefit was the better postoperative cosmesis at the expense of higher costs and more challenging operation. (Lirici *et al*. 2016.)

New approaches have emerged such as NOTES (natural orifice transluminal endoscopic surgery) to further decrease the impact of surgical stress (Dallemagne *et al.* 2009). However, the new technology has been accompanied by unprecedented complications associated with the transvaginal and transgastric access routes (Fisichella *et al.* 2015).

The latest innovation in biliary surgery includes single-site robotic cholecystectomy first performed in 2010 (Konstantinidis *et al.* 2012). However, there are no short and long term studies concerning the benefits of robotic surgery (Vyas *et al.* 2014).

Traditionally, during the open era, the gallbladder was dissected, starting from the gallbladder fundus (fundus-first approach). In contrast, the technique of LC relies upon traction to the fundus of the gallbladder, exposing the triangle of Calot as the starting point of dissection (Reddick and Olsen 1989). However, soon a fundus-first approach was reintroduced to facilitate dissection when anatomy at Calot's triangle was difficult because of adhesions or anatomical abnormalities (Martin *et al.* 1995, Gupta *et al.* 2004).

2.5.1 Ultrasonic dissection in cholecystectomy

Electrocautery is the main energy form used during LC. Alternative energy forms were evaluated early in the beginning of LC era, mainly because of documented risks of monopolar eletrosurgery including burns (Wetter *et al.* 1992, Amaral 1994). Ultrasonic energy is composed of electrical energy which is converted in piezoelectric crystals into high-frequency (55kHz) mechanical vibration. Subsequently, the transferred ultrasonic energy is applied to the tissue, producing cavitation, coaptation/coagulation and a cutting effect. (Sasi 2010.) In vivo studies have shown that ultrasonic dissection causes less lateral thermal damage in human peritoneum than monopolar diathermy (Družijanić *et al.* 2012). Conversely, in pig models using standard power settings, ultrasonic energy generated deeper tissue necrosis than monopolar electrocautery (Homayounfar *et al.* 2012) and higher peak temperatures after deactivativation than electrothermal energy with physical pressure or plasma trisector (Kim *et al.* 2008).

Several randomised studies have evaluated ultrasonic dissection in laparoscopic cholecystectomy. The favourable effects of the ultrasonic dissection compared to electrocautery in LC are reported to be the shorter operative time (Janssen *et al.* 2003; Cengiz *et al.* 2005; Cengiz *et al.* 2010; Kandil *et al.* 2010; Jain *et al.* 2011; Mahabaleshwar *et al.* 2012), less intraoperative bleeding (Cengiz *et al.* 2010, Jain *et al.* 2011) and fewer gallbladder perforations (Janssen *et al.* 2003, Cengiz *et al.* 2010, Kandil *et al.* 2010, Jain *et al.* 2011, Mahabaleshwar *et al.* 2012), as well as quicker recovery and increased same-day discharge (Cengiz *et al.* 2005, 2010, Jain *et al.* 2011). Ultrasonic dissection has also been applied to minilaparotomy cholecystectomy with beneficial results (Harju, Juvonen, *et al.* 2013, Aspinen *et al.* 2016). There are only marginal data in the literature on the economical costs of ultrasonic dissection in LC. In their randomised study, Tempe et al. found that the total costs of ultrasonic dissection in laparoscopic fundus-first method were lower than conventional electrocautery dissection starting from the triangle of Calot. The main reason for lower costs was the shorter operative time and hospital stay in ultrasonic dissection cholecystectomy (Tempe *et al.* 2013).

2.6 DAY-CARE LAPAROSCOPIC CHOLECYSTECTOMY (LC)

Soon after the implementation of LC, several studies showed that same day discharge was possible (Singleton *et al.* 1996, Richardson *et al.* 2001, Leader *et al.* 2004). Reduced convalescence and hospital stay were observed after LC compared to open cholecystectomy (Hendolin *et al.* 2000). In a Cochrane review, Vaughan et al. analysed randomised studies of day-care versus overnight stay LC for symptomatic gallstone disease. Altogether six trials with small sample sizes (492 patients) were analysed with the conclusion that day-care LC did not compromise postoperative patient outcome (Vaughan *et al.* 2013). The outcomes of randomised studies comparing day surgery versus overnight stay in LC are presented in table 1 (Keulemans *et al*. 1998; Hollington *et al.* 1999; Young and O'Connell 2001; Dirksen *et al*. 2001; Johansson *et al.* 2006; Barthelsson *et al.* 2008). Additionally, the same-day discharge rates increased without compromising the safety issues after the implementation of standardised care pathways for day-care LC (Calland *et al.* 2001, Topal *et al.* 2007, Clarke *et al.* 2011).

Delayed discharge after LC is most commonly caused by pain and postoperative nausea and vomiting (PONV). A multimodal approach with total intravenous anesthesia (TIVA), prophylactic intraoperative antiemetics, preoperative dexamethasone and NSAIDs for pain management are thought to be essential for achieving same-day discharge after LC. (J Bisgaard *et al.* 2003; Jensen *et al.* 2007.) On the other hand, intraperitoneal instillation of saline, ketorolac or bupivacaine has conferred no advantages on the postoperative recovery profile (Scheinin *et al.* 1995; Barthelsson *et al.* 2015; Murdoch *et al.* 2016) . As a result, a Cochrane analysis including 25 randomised trials showed inconclusive evidence that NSAIDs, opioids and anticonvulsant agents were able to reduce pain in low anesthetic risk patients (Gurusamy *et al.* 2014).

*Table 1.*Outcome of day-care versus overnight stay RCTs in laparoscopic cholecystectomy. DS= day surgery, OS=overnight stay

Author and year	Country of origin	Number of patients DS	OS	Proportion with prolonged stay DS/OS(%)	Outcome
Keulemans Y 1998	Netherlands	37	37	8.1/0	DS reduced costs
Hollington P 1999	Australia	60	71	18.3/18.3	Equal costs
Dirksen CD 2001	Netherlands	42	44	26.2/54.5	DS reduced costs
Young J 2001	Australia	14	14	21.4/0	Equal recovery
Johansson M 2006	Sweden	52	48	7.7/12.5	DS reduced costs
Barthelsson C 2008	Sweden	41	43	9.8/ 4.7	Equal recovery

2.7 TREATMENT OF CBD STONES

2.7.1 Treatment strategies for gallbladder stones with concomitant CBD stones

No clear consensus concerning the best treatment strategy for CBD stones exists. Surgical CBD clearance during the era of open bile duct surgery seemed superior compared to endoscopy (Dasari *et al.* 2013). The morbidity (5%-24.5%) and mortality (0%-1.7%) of open CBD exploration was acceptable. Successful clearance of bile ducts was achieved in 81.5%-95% of the

patients. (Neoptolemos *et al.* 1987; Moreaux 1995; Hammarstrom *et al.* 1995.) The open era lasted until laparoscopic techniques were introduced in the 1990s.

In 1991, Shapiro et al. published an article devoted to laparoscopic CBD exploration (Shapiro *et al*. 1991). Soon the issue arose of whether CBD stones with concomitant gallbladder stones should be managed more efficiently in a single-stage surgical procedure or as a two-stage endo-laparoscopic approach (Cuschieri *et al.* 1996).

Therapeutic splitting of simultaneous CBD stone management and cholecystectomy have been observed after the implementation of LC. Laparoscopic CBD exploration has not gained widespread popularity because it has been considered time-consuming and demanding (Puhalla, Flint and O'Rourke, 2015). The incidences of open and laparoscopic choledochotomy have declined, while the incidence of ES has increased (Sandzen *et al.* 2012). This was confirmed by another study covering more than 40 years. Despite the advent of laparoscopic techniques, endoscopic procedures have gradually replaced the CBD stone treatment as the primary treatment method. (Stromberg and Nilsson 2011.) However, a cohort study from a tertiary referral center in USA showed that endoscopic bile duct stone treatment has achieved a plateau state during the past 2 decades (Coté *et al.* 2012). According to a survey sent to surgeons in UK and Ireland, in university hospitals, the one-stage strategy was preferred compared to district hospitals where postoperative ERCP was the favoured method (Sanjay *et al.* 2010). Furthermore, in the USA, the main factors restricting the diffusion of laparoscopic CBD exploration in rural areas are lack of equipment and operative time (Bingener and Schwesinger 2006).

In the Cochrane Database Systematic review, Dasari et al. analysed three different techniques of CBD clearance: open, laparoscopic and endoscopic clearance performed either pre-, intra- or post-operatively. Altogether 16 randomised trials with 1758 patients were analysed with mortality being the same between the laparoscopic (0-2.8%) and the endoscopic (0-2.4%) approach. There was also no difference in morbidity between the laparoscopic (9.1-43.2%) and endoscopic (10.5-29.8%) approaches. Single-stage laparoscopic and two-stage endo-laparoscopic methods resulted in similar outcomes regarding retained stones and failure rates. (Dasari *et al.* 2013.)

In certain patient groups, expectant management after endoscopic stone extraction can be considered as a definitive solution. Figure 2 illustrates the numerous therapeutic options for treating CBD stones.

Guidelines for clinical practice have been established both by gastroenterologists and endoscopic surgeons. The chosen strategy for treating CBD stones should be tailored according to the clinical scenario, local expertise and equipment available. (Williams *et al.* 2008; Overby *et al.* 2010; Maple *et al.* 2010; Parra-Membrives *et al.* 2010; Maple *et al.* 2011; Berci *et al.* 2013; Internal Clinical Guidelines Team 2014.)

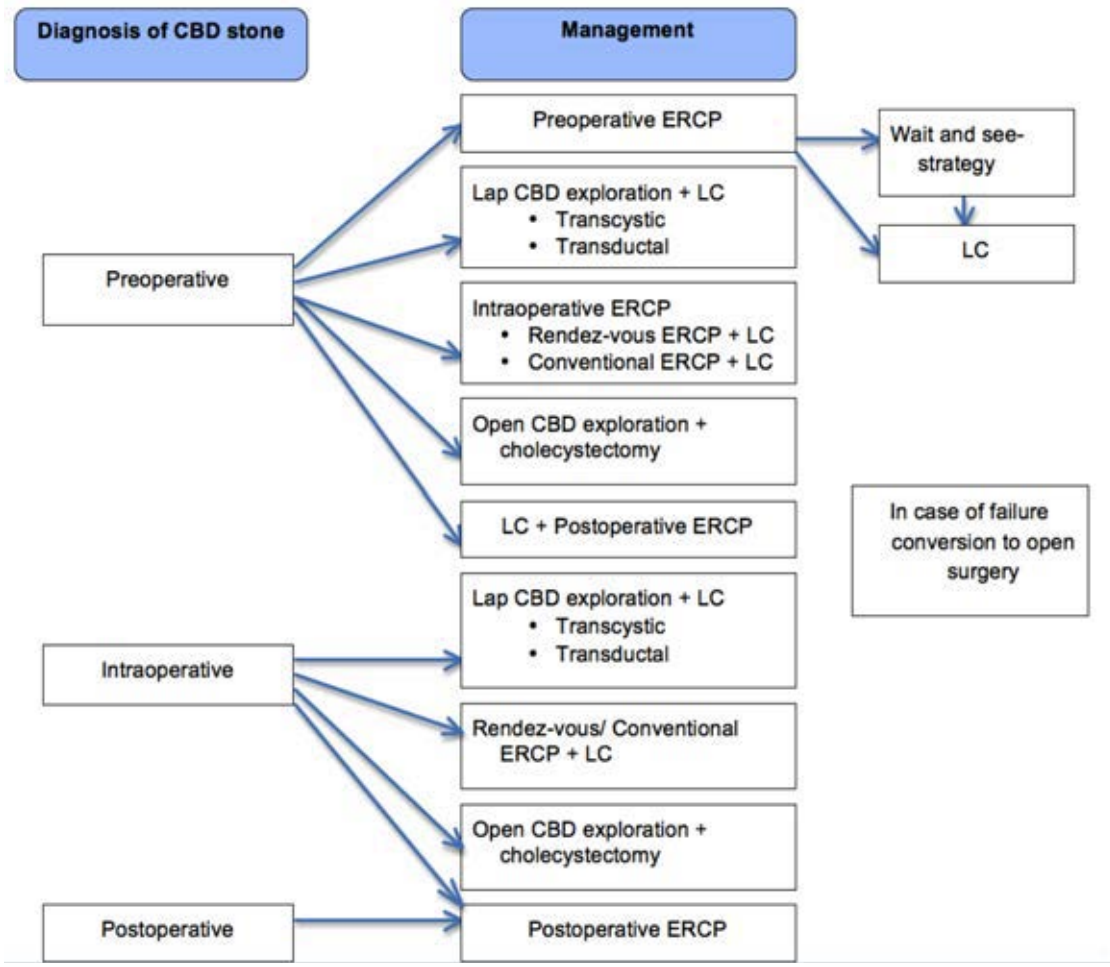


Figure 2. Various options for CBD stone management.

2.7.2 Evolution of open CBD clearance techniques

The first open CBD stone removal was successfully performed by Thornton in 1889 (Thornton 1889). It was not until 1912 that Kehr invented the T-tube and simplified choledochotomy repair and subsequently the use of the T-tube became more popular (Allen and Wallace 1940, Ogilvie 1957, Kehr 1998). The necessity of T-tube insertion was questioned later when lower morbidity after primary closure compared to T-tube drainage was reported (Dawson *et al.* 1957, Payne and Woods 1986). The concerns related to the use of a T-tube were tube migration and bile leaks after T-tube removal (Bernstein *et al.* 1994, Kacker *et al.* 1995). Later, a Cochrane analysis did not recommend the routine use of T-tube after open choledochotomy (Gurusamy and Samraj, 2007b).

After laparoscopic CBD stone removal, bile duct decompression with T-tube was thought to be essential based on the experience from the open era. T-tube drainage serves also for postoperative cholangiography to observe potential residual stones and enables access for stone removal via T-tube tract. (Gurusamy and Samraj 2007b; Gurusamy, Koti, *et al.* 2013.) However, primary suturing of choledochotomy instead of T-tube insertion was implemented soon after the introduction of laparoscopic CBD exploration (Martin *et al.* 1998). Laparoscopic endobiliary stenting is another alternative to decompress the biliary tree after CBD exploration (Gersin and

Fanelli 1998; Kim and Lee 2004). Potential long-term complications after transductal suturing such as bile duct strictures have not been increasingly reported (Waage *et al.* 2003, Yi *et al.* 2015).

Currently, laparoscopic CBDE has superseded the primary open approach for CBD management. Nonetheless, if laparoscopic techniques fail or endoscopy is unsuitable, open removal of CBD stones can be adopted as a rescue method (Williams *et al.* 2008). In cases where impacted stones are unremovable through a choledochotomy incision, a duodenotomy may be sometimes performed with an additional open sphincterotomy or sphincteroplasty (Jones and Soper 1996).

2.7.3 Technique of laparoscopic CBD exploration

Laparoscopic CBD exploration starts with the dissection of cystohepatic triangle following assessment of CBD stones by intraoperative cholangiography or laparoscopic ultrasound (Orenstein *et al.* 2014). Two techniques for laparoscopic CBD stone removal were developed: transcystic exploration and transductal choledochotomy. The techniques are presented in Figures 3a and 3b. (Jones and Soper 1996.) Factors affecting on the optimal choice of laparoscopic exposure have been summarized in Table 2. The choice between transcystic or transductal approach depends on local expertise, choledochal anatomy and stone size. After bile duct exposure, the removal of stones is performed in a similar fashion in both methods. For small stones and sludge, irrigation with saline is preferred. Intravenous glucagon is administered to relax the sphincter of Oddi. Additional instruments like balloon catheters or baskets inserted through the choledochoscope can be used to facilitate the removal of stones. In cases of difficult stones, lithotripsy can be tried. After the procedure, a completion cholangiogram is essential to ensure the ductal clearance. (Petelin 2003; Orenstein *et al.* 2014.) Vindal et al. found that intraoperative choledochoscopy was superior to intraoperative cholangiography for confirming stone clearance after transductal exploration (Vindal *et al.* 2015). Topal et al. demonstrated a similar outcome using intraoperative cholangiography or choledochoscopy (Topal *et al.* 2007). The application of T-tube after transductal exposure is no more routinely recommended (Gurusamy, Koti, *et al.* 2013).

Table 2. Factors affecting to laparoscopic trancystic and transductal approach (Petelin 2003, Santos and Strasberg 2017).

Factor		**Transcystic**	**Transductal**
CBD stone size	<6 mm	+	+
	>6 mm	-	+
Number of CBD stones	limited	+	+
	multiple	-	+
Diameter of cystic duct	<4 mm	-	+
	>4 mm	+	+
Diameter of CBD	<7 mm	+	-
	>7 mm	+	+
Severe inflammation in CBD		+	-
Intrahepatic stones		-	+
Entrance of cystic duct	lateral	+	+
	posterior	-	+
Laparoscopic suturing ability	poor	+	-
	good	+	+

Figure 3a

Figure 3b

Figures 3a and 3b. Laparoscopic common bile duct exploration. Figure 3a depicts transcystic CBD exploration. Figure 3b depicts transductal CBD exploration.

2.7.3.1 Transcystic versus transductal clearance of CBD

From 1998 onwards, thirteen randomised studies have demonstrated the success of laparoscopic CBD clearance to be 53.5% - 100% with the transcystic approach and 58.3% - 100% with the transductal approach (Rhodes *et al.* 1998; Cuschieri *et al.* 1999; Sgourakis and Karaliotas 2002; Nathanson *et al.* 2005; Hong *et al*. 2006; Noble *et al.* 2009; Rogers *et al.* 2010; Bansal *et al.* 2010; ElGeidie, ElShobary, *et al.* 2011; Koc *et al*. 2013; Ding *et al.* 2014; Bansal *et al.* 2014; Poh *et al.* 2016). The transcystic route is preferred for easier access but in the case of failure, a transductal approach can be used when feasible (Puhalla, Flint and O' Rourke, 2015). In a systematic review, Reinders et al. analysed 8 randomised trials on combined endo-laparoscopic and laparoscopic CBD clearance divided into transcystic or transductal approaches. They found that stone clearance was equal between the three methods but the transductal approach was associated with a higher rate of complications than encountered with transcystic stone extraction. (Reinders *et al.* 2014.) The success rate of transcystic approach can be increased with widening the confluence of cystic duct and CBD by microincision (Zhu, Han, *et al.* 2015).

2.7.3.2 Primary closure of choledochotomy versus T-tube drainage

According to Cochrane analysis and a meta-analysis, the routine use of T-tube is not mandatory after CBD exploration. The primary closure of CBD is associated with shorter hospital stay and morbidity. (Yin *et al.* 2012; Gurusamy, Koti, *et al.* 2013.)

2.7.3.3 Adverse events related to laparoscopic CBD exploration

Poor outcome after laparoscopic CBD exploration is associated with increasing age and comorbidity (Noble *et al.* 2011). Additionally, large stones (>5 mm) have been identified to be a risk factor for residual CBD stones after transcystic stone clearance (Stromberg *et al.* 2008). Risk factors for late stone recurrence after transcystic clearance after an average follow-up of two years were reported to be stone number >3 and biliary sludge (Bove *et al.* 2009). Impacted stones in the distal CBD can cause longer operative times, failure and more conversions to open surgery (Noble *et al.* 2011). Postoperative bile leakage is associated with non-dilated CBD and failure in stone clearance (Hua *et al.* 2016).

2.7.4 Endoscopic treatment of CBD stones

The first diagnostic endoscopic retrograde cholangiopancreatography (ERCP) was performed in 1968 by William McCune followed by Itaru Oi from Japan in 1970 (McCune *et al.* 1968, Oi 1970). The procedure evolved rapidly and the first therapeutic ERCP with sphincterotomy and transpapillary CBD stone extraction was independently introduced in 1974 by Classen in Germany and Kawai in Japan (Classen and Demling 1974, Kawai *et al.* 1974). Endoscopic ductal clearance can be achieved in over 90 % of patients, although additional ERCPs are needed in up to 25 % of cases (Rhodes *et al.* 1998; Suc *et al.* 1998; Tzovaras *et al.* 2012; Nathanson *et al.* 2005).

2.7.4.1 Endoscopic sphincterotomy versus endoscopic papillary balloon dilatation

As an improvement, Staritz et al. introduced endoscopic papillary balloon dilatation (EPBD) in 1982. In EPBD, the sphincter of Oddi is partly conserved compared to endoscopic sphincterotomy which cuts the sphincter system. (Staritz *et al.* 1982.) Some reports described an increase of post-procedure pancreatitis (Staritz *et al.* 1982, Disario *et al.* 2004), while not being confirmed in some others (Bergman *et al.* 1997). Accordingly, some guidelines recommend to avoid the use of EPBD (Williams *et al.* 2008) or restrict its use to patients with coagulopathy or at risk of infection (Weinberg *et al.* 2006; Maple et al. 2011). Several studies have shown that combined use of EPBD with endoscopic sphincterotomy has been associated with lower recurrence of stones (1.9%-10%) than conventional endoscopic sphincterotomy (3.0%-17.4%) (Bergman *et al.* 1997; Ochi *et al.* 1999; Yasuda *et al.* 2001; Natsui *et al.* 2002; Vlavianos *et al.* 2003; Yasuda *et al.* 2010; Lu *et al.* 2014; Sakai *et al.* 2016). Another amendment of the balloon dilatation-

technique was adding the combined endoscopic sphincterotomy with a large balloon dilatation (Ersoz *et al.* 2003, Paik *et al.* 2014).

For difficult stones, extracorporeal shock wave lithotripsy (ESWL), electrohydraulic or laser lithotripsy can be used in selected patients with reported success rates of 83%-90% (Meyenberger *et al.* 1996, Sackmann *et al.* 2001), 83%-100% (Adamek *et al.* 1996, Farrell *et al.* 2005) and 100% (Patel *et al.* 2014), respectively. However, most of these published studies are small in number and subject to bias. Additionally, high-risk patients with incomplete CBD clearance may require endoprothesis as a bridging therapy to prevent acute cholangitis (Chopra *et al.* 1996, Williams *et al.* 2008).

2.7.4.2 Intraoperative rendez-vous endoscopic retrograde cholangiopancreatography (ERCP)

Intraoperative endoscopic sphincterotomy with the rendez-vous technique was first published in a case series in 1993 (Deslandres *et al.* 1993). However, the technique did not gain acceptance until La Greca et al. reported that there were pathologically higher levels of pancreatic amylase present after conventional intraoperative ERCP compared to rendez-vouz ERCP (La Greca *et al.* 2007). Likewise, Swahn et al. conducted a prospective case-control study with similar results (Swahn, Regner, *et al.* 2013). The reduction of post-ERCP pancreatitis in rendez-vous bile duct cannulation was confirmed in a large Swedish nationwide population-based study of 12 718 ERCP procedures (Swahn, Nilsson, *et al.* 2013).

The laparoscopic phase of intraoperative rendez-vous ERCP involves an antegrade inserted guidewire, sphincterotome or retrieving basket, which is passed through the cystic duct to duodenum by the laparoscopic surgeon. This facilitates the cannulation of the papilla by the endoscopist and a sphincterotome can be inserted to perform sphincterotomy and CBD stone removal. As a result, the inadvertent cannulation of pancreatic duct can be avoided especially in cases with a difficult anatomy. (Nakajima *et al.* 1996; Cavina *et al.* 1998.) On the other hand, the main disadvantage of intraoperative ERCP is the requirement of simultaneous surgical and endoscopic teams in the operative theatre (Baloyiannis and Tzovaras 2015, March *et al.* 2016).

2.7.4.3 Adverse events related to ERCP

Large series have shown that ERCP carries a moderate risk of morbidity (5%-15%) and mortality (0.3%-3.6%), mostly due to post-procedure pancreatitis, bleeding and perforation (Rhodes *et al.* 1998; Ong *et al.* 2005; Stromberg and Nilsson 2011; Bansal et al. 2014). Currently noninvasive diagnostic methods like MRCP and EUS are highly effective in confirming the presence of CBD stones, thus ERCP is used solely as a therapeutic intervention (Williams *et al.* 2008).

The incidence of long-term recurrence of CBD stones after ES occurs in some 4.1%-11.3% of patients (Pereira-Lima *et al.* 1998, Costamagna *et al.* 2002, Sugiyama and Atomi 2002, Ando *et al.* 2003, Langerth *et al.* 2014). The reason for CBD stone recurrence is multifactorial. Several risk factors have been identified such as large diameter of CBD, periampullary diverticulum and bacterobilia after ES. (Boerma and Schwartz 2006; Cai *et al*. 2016.)

2.7.5 Single-stage versus two-stage management of CBD stones

CBD stones can be removed as a single-stage procedure during LC by laparoscopic transcystic or transductal approach. Other options for single-stage treatment are intraoperative endoscopic sphincterotomy and bile duct clearance or open CBD exploration as a primary procedure or after conversion of LC. The two-stage approach includes pre-or postoperative endoscopic sphincterotomy with concomitant LC. (Williams *et al.* 2008; Overby *et al.* 2010; Internal Clinical Guidelines Team 2014.)

Several attempts have been made to evaluate the outcome after one-stage and two-stage CBD stone management. One major criticism concerns the small sample size of the RCTs (Clayton *et al.* 2006). A Cochrane review of 16 RCTs addressed the heterogeneity among the trials. The risk of bias was high, due to the fact that the distinction between suspected and confirmed bile duct

stones was not adequately defined at the time of randomisation. As a consequence, no significant difference in the safety and efficacy was observed between laparoscopic or pre-and intraoperative ERCP groups. (Dasari *et al.* 2013.) A similar outcome with no difference in morbidity, mortality or ductal clearance has been reported in some meta-analyses comparing one-stage versus two-stage management of CBD stones (Clayton *et al.* 2006, Alexakis and Connor 2012, Lu *et al.* 2012). Zhu et al also observed no difference in morbidity or mortality between one-stage or two-stage strategies. However, in their meta-analysis, the single-stage treatment was better in terms of ductal clearance, shorter hospital stay and reduced operative time. (H. Y. Zhu *et al.* 2015.) Another meta-analysis showed more complications with the two-stage management with preoperative endoscopic CBD clearance than with the one-stage method or the postoperative endoscopic procedure (Nagaraja *et al.* 2014).

Overall, the advantage of single-stage surgical approach for patient seems to be lower interventional burden and a shorter hospital stay (Reinders *et al.* 2014). Several drawbacks have been identified with the two-stage strategy, mainly related to complications of endoscopy and sphincterotomy (Costi *et al.* 2014). Furthermore, new gallstones can migrate from gallbladder to CBD and cause recurrent biliary events despite the performed sphincterotomy. This was addressed in one randomised study regarding the timing of LC after preoperative ERCP. Reinders et al. found that biliary related events occurred more often (36.2%) in patients with delayed LC after endoscopic sphincterotomy than in patients with early LC (within 72 hours). (Reinders *et al.* 2010.) Recently, similar results were reproduced in another randomised study, suggesting that a one month delay in LC after ERCP predisposes to recurrent biliary events (El Nakeeb *et al.* 2016). However, endoscopic clearance rates have been reported to be similar (80%-97%) prior to or after cholecystectomy (Chang *et al.* 2000).

2.7.5.1 Randomised studies of preoperative ERCP + LC versus laparoscopic CBD exploration

Since 1998 eight randomised trials have evaluated the results of preoperative two-stage versus one-stage laparoscopic CBD exploration. The details of one-stage versus two-stage studies are shown in Table 3. It is noteworthy that three of these studies had fewer than 50 patients in each arm and were most likely underpowered.

The first published randomised trial was so far the largest multicenter European study carried out in 1999 (Cuschieri *et al.* 1999). In this study (n=300), one-stage ductal clearance resulted in shorter hospital stay, but success and patient morbidity were similar between the study groups.

Sgourakis et al. analysed 78 patients receiving either transcystic or transductal approach compared to preoperative ERCP + LC. They concluded that ductal clearance was similar in both study groups. However, inclusion criteria of the patients were more or less unclear and study groups small. (Sgourakis and Karaliotas 2002.)

Noble et al. conducted a small randomised study (n=91), where they compared higher-risk patients receiving either preoperative ERCP + LC or transcystic /transductal approach according to the surgeon's preference. Laparoscopic clearance was more effective with fewer procedures in spite of higher morbidity. (Noble *et al.* 2009.)

Bansal et al. conducted two trials. The first study was a pilot study with a small sample size (n=30). The conclusion was that single-stage management had similar success with a shorter hospital stay than the two-stage method.(Bansal *et al.* 2010.) The second study of Bansal et al. confirmed the previous results with a larger sample size (n=168). The one-stage group had fewer procedures and was more cost effective than the two-stage group. (Bansal *et al.* 2014.)

Rogers et al. randomised 122 patients with ASA grade I or II to preoperative ERCP + LC or transcystic laparoscopic CBD clearance. The clearance rate, overall costs and patient acceptance were equal between the study groups. However, hospital stay was shorter in the one-stage group. (Rogers *et al.* 2010.)

Koc et al. randomised 120 patients to preoperative ERCP + LC or transductal laparoscopic clearance. The ductal clearance was similar with less morbidity in the one-stage group. (Koc *et al.* 2013.)

Ding et al. reported similarly low morbidity in both ERCP + LC and laparoscopic CBD exploration groups. A bias of the study was that all the procedures were performed by only one experienced surgeon familiar with both procedures. (Ding *et al.* 2014.)

Table 3. Outcomes of RCTs of (A) one-stage (LCBDE) versus (B) two-stage (preoperative ERCP+ LC) treatment of CBD stones.

References	Year	Number of patients	CBD Stone clearance (%)		Postoperative morbidity (%)		Mortality (%)		Length of hospital stay (median, days)		Conversion to other procedures(%)		Hospitalization charges	
			A	B	A	B	A	B	A	B	A	B	A	B
Cuschieri	1999	300	84.0	84.0	12.8	15.8	0.75	1.5	6	9	12.8	6.0	nm	nm
Sgourakis	2002	78	85.7	84.3	17.8	18.7	2.8	2.4	7.4	9	14.3	15.7	nm	nm
Noble	2009	91	100	61.7	43.2	29.8	0	2.1	3	5	0	38.3	nm	nm
Bansal	2010	30	93.5	86.7	26.7	26.7	0	0	4.2	4	6.7	15.3	nm	nm
Rogers	2010	122	96.8	88.2	9.1	10.5	0	0	4	5	3.6	1.8	22 603[a]	25 348[a]
Koc	2013	120	96.5	94.4	7	11.1	0	0	3	6	1.8	7.4	nm	nm
Ding	2014	221	93.6	94.6	3.6	5.1	0	0	nm	nm	6.4	3.6	nm	nm
Bansal	2014	168	91.7	88.1	23.8	22.6	0	3.6	4.6	5.3	11.9	7.1	394[b]	507[b]

[a] mean hospital service charge ($)
[b] average cost per patient ($)
nm =not mentioned

Table 4. Outcomes of RCTs of (A) one-stage (LCBDE) versus (B) two-stage (LC + postoperative ERCP) treatment of CBD stones.

References	Year	Number of patients	CBD Stone clearance (%)		Postoperative morbidity (%)		Mortality (%)		Length of hospital stay (median, days)		Conversion to other procedures(%)		Hospitalization charges	
			A	B	A	B	A	B	A	B	A	B	A	B
Rhodes	1998	80	75	75	17.5	15	0	0	1	3.5	25	25	nm	nm
Nathanson [a]	2005	86	97.6	95.6	17	13	0	0	6.4	7.7	7.3	6.7	nm	nm

[a] randomisation after failed TC clearance to choledochotomy or postoperative ERCP
nm =not mentioned

Table 5. Outcomes of randomised trials of (A)one-stage (LC+ intraoperative ERCP) versus (B)two-stage (preoperative ERCP +LC) treatment of CBD stones.

References	Year	Rendez-vous ERCP (yes,no)	Number of patients	CBD Stone clearance (%)		Postoperative morbidity (%)		Mortality (%)		Length of hospital stay (days)		Conversion to other procedures (%)		Hospitalization charges ,C	
				A	B	A	B	A	B	A	B	A	B	A	B
Morino	2006	yes	91	95.7	80	10.9	8.9	0	0	4.3[b]	8[b]	4.3	33.3	2829	3834
Rabago	2006	yes	123	90.2	96.6	8.5	23	0	0	5[b]	8[b]	5.2	10.2	2414	2708
Lella	2006	yes	120	96.7	96.7	3.3	10	0	0	3[a]	6[a]	5	0	nm	nm
ElGeidie	2011	no	198	97.8	95.3	4.5	3	0	0	1.3[b]	3[b]	2.6	2.2	nm	nm
Tzovaras	2012	yes	99	94	91.8	14	12	2	0	4[a]	5.5[a]	12	20.4	nm	nm
Sahoo	2014	yes	83	70.7	90.5	0	12	nm	nm	10.9[b]	6.8[b]	9.5	29	nm	nm

[a] median, [b] mean, nm =not mentioned

Table 6. Outcomes of randomised trials of (A)one-stage (LC +LCBDE) versus (B)one-stage (LC +intraoperative ERCP) treatment of CBD stones.

References	Year	Rendez-vous ERCP (yes,no)	Number of patients	CBD Stone clearance (%)		Postoperative morbidity (%)		Mortality (%)		Length of hospital stay (mean, days)		Conversion to other procedures (%)		Hospitalization charges	
				A	B	A	B	A	B	A	B	A	B	A	B
Hong	2006	no	234	89.4	91.4	5.6	9.4	0	0	4.7	4.3	10.7	8.6	13 560[c]	17 280[c]
ElGeidie	2011	no	226	92	97.2	7.1	9.3	0	0	2.2[a]	3.1[a]	5.2	2.7	nm	nm
Poh	2016	no	104	69	87	38	27	0	0	2[b]	3[b]	2	15	nm	nm

[a] mean, [b] median, [c] RMB (= chinese renminbi), nm =not mentioned

2.7.5.2 Randomised studies of LC + postoperative ERCP versus laparoscopic CBD exploration

Randomised studies with LC + postoperative ERCP versus laparoscopic CBD exploration are shown in Table 4. Rhodes et al. conducted a small series (n=80) with a transcystic approach as a first option in the laparoscopy group. In case of failure, choledochotomy was performed without a T-tube but an antegrade pigtail catheter was applied. Subsequently, 25 % of the patients in the LC + postoperative ERCP group needed an additional ERCP for bile duct clearance. They concluded that the one-stage method was as effective as the two-stage method in clearing the bile ducts but associated with a shorter hospital stay. (Rhodes *et al.* 1998.)

Nathanson et al. randomised 86 patients after unsuccessful transcystic bile duct clearance to either the transductal approach or postoperative ERCP. There was no significant difference in postoperative retained stones, reoperations or morbidity between the study groups. The authors suggested that choledochotomy was a good choice after failed ERCP or for unfavourable logistics for postoperative ERCP. (Nathanson *et al.* 2005.)

2.7.6 Intraoperative ERCP

2.7.6.1 Randomised studies of intraoperative ERCP +LC versus preoperative ERCP+ LC

Randomised studies of one-stage (intraoperative ERCP +LC) vs. two-stage (preoperative ERCP + LC) treatment of CBD stones are shown in Table 5. Morino et al. randomised 91 patients to either one-stage or two-stage treatment for concomitant gallbladder and CBD stones. LC was performed within 24-72 hours after ERCP. The rendez-vous intraoperative ERCP achieved a higher rate of bile duct clearance with a shorter hospital stay and lower costs. (Morino *et al.* 2006.) Lella et al. did not observe any post-ERCP pancreatitis in the single-step rendez-vous intraoperative ERCP group, while in the preoperative ERCP+ LC group, post-ERCP pancreatitis was observed in 10 % of patients (Lella *et al.* 2006). Rabago et al. analysed 123 patients with an intermediate risk of choledocholithiasis to preoperative ERCP followed by LC within 8 weeks or to the intraoperative ERCP +LC approach. They found both methods equally effective but the intraoperative ERCP+LC group was cheaper, had less morbidity and a shorter hospital stay. (Rabago *et al.* 2006.) ElGeidie et al. randomised 198 patients with preoperative confirmed choledocholithiasis to intraoperative ERCP + LC or preoperative ERCP + LC. They could not find any difference in the surgical outcomes or ductal clearance between the study groups, despite the fact that intraoperative ERCP was performed in the traditional way, not as rendez-vous. However, the hospital stay was significantly shorter in the one-stage treatment. (ElGeidie, ElEbidy, *et al.* 2011.) Tzovaras et al. included also emergency patients in their randomised trial (n=100). The conclusion was that rendez-vous intraoperative ERCP+ LC was associated with shorter hospital stay, similar morbidity and as good a bile duct clearance rate as the two-stage approach. (Tzovaras *et al.* 2012.) Sahoo et al. enrolled 83 patients to preoperative ERCP + LC or rendez-vous intraoperative ERCP + LC treatment. They observed severe pancreatitis in 12 % of the two-stage group but none in the rendez-vous ERCP. Bile duct clearance was better in the one-stage arm, although the outcome data was incompletely presented in the study. (Sahoo *et al.* 2014.)

As a conclusion, three different meta-analyses of RCTS evaluated short-term outcomes of intraoperative ERCP + LC versus two-stage preoperative ERCP + LC. All the studies were single-center studies with low bias. The conclusion in both meta-analyses was that intraoperative ERCP+ LC led to equal CBD stone clearance rates with reduced post-ERCP pancreatitis and shorter hospital stay compared to two-stage treatment of CBD stones. (Gurusamy *et al.* 2011.;Wang *et al.* 2013; Tan *et al.* 2017.)

2.7.6.2 Randomised studies of intraoperative ERCP+LC versus laparoscopic CBD exploration

So far, three randomised studies of single-stage management between laparoscopic CBD exploration + LC and intraoperative ERCP+ LC treatment of CBD stones have been published. The studies are presented in Table 6. Hong and colleagues operated 234 patients with preoperatively or intraoperatively diagnosed CBD stones. They found similar clearance rates in laparoscopic CBD exploration and intraoperative ERCP groups. However, the study had some methodological weaknesses in terms of randomisation and disparities between the study groups. (Hong *et al.* 2006.)

ElGeidie et al. randomised 226 patients with preoperatively suspected bile duct stones. They found no difference in ductal clearance between the groups. Interestingly, laparoscopic clearance was performed under fluoroscopic guidance without choledochoscopy. (ElGeidie, ElShobary, *et al.* 2011.)

Poh et al. randomised 104 emergency patients with LC to either intraoperative ERCP or the transcystic / transductal approach at the attending surgeon´s discretion. The rate of retained stones was significantly higher and postoperative duration of stay longer in the laparoscopic CBD exploration group than in the intraoperative ERCP group. The authors concluded that the acute presentation of all cases might have hampered the transcystic approach and led to inferior results. (Poh *et al.* 2016.)

2.7.7 Expectant management after ERCP + endoscopic sphincterotomy (ES)

The management of gallbladder stones after CBD stone clearance with ES in fragile high surgical risk patients is debatable. The initial reports of early and late results after ES as the final treatment of CBD stones in patients with a high operative risk for cholecystectomy were encouraging with a late complication rate of 12 %. It was reported that recurrent biliary tract complications may appear after ES in patients with intact gallbladder. (Escourrou *et al.* 1984.)

Five randomised studies comparing elective cholecystectomy with a wait-and-see policy after successful ES and stone extraction are summarized in Table 7. Hammarström et al. compared open cholecystectomy with expectant management after ES with equal long term results in both groups. However, the mortality from heart disease was significantly higher in the ES treatment arm. (Hammarstrom *et al.* 1995.) One open cholecystectomy and two laparoscopic cholecystectomy trials preferred surgery to ES (Targarona *et al.* 1996, Boerma *et al.* 2002, Lau *et al.* 2006). Recurrent biliary events occurred more often in the ES patients requiring further endoscopy or surgical intervention (Targarona *et al.* 1996; Boerma *et al.* 2002; Lau *et al.* 2006; Heo *et al.* 2015). There are guidelines suggesting that in patients with CBD and gallbladder stones, ES as a sole treatment should be avoided (McAlister *et al.* 2007, Williams *et al.* 2008).

Costi et al. published a case-control study with a wait-and-see policy after ES and found that octogenarians developed biliary related complications in 48 % of cases. They recommended sequential treatment also for patients over 80 years old. (Costi *et al.* 2007.) In contrast, Yasui et al. analysed retrospectively a total of 1728 patients with gallbladder in situ who underwent ES and stone extraction for choledocholithiasis over a 10 year period. They found that patients over 80 years had a lower incidence of acute cholecystitis than patients under 80 years after ES with a similar risk of CBD stone recurrence. (Yasui *et al.* 2012.) A large cohort study from USA showed that during one year follow up after ES, cholecystectomy was offered for only half of the patients (Huang *et al.* 2017).

Several studies have also been published suggesting higher incidence of cholangitis and pancreatitis as delayed adverse events after ES (Langerth *et al*. 2014; Langerth *et al.* 2015). Wide common bile duct (> 15-22 mm), duodenal diverticula, bacterobilia and brown pigment stones have been recognized as risk factors for late choledochal stone recurrence after ES (Pereira-Lima *et al.* 1998, Costamagna *et al.* 2002, Sugiyama and Atomi 2002, Cai *et al.* 2016).

Studies of long-term risk for biliary tract cancer after ES have proved inconclusive (Karlson *et al.* 1997, Mortensen *et al.* 2008, Langerth *et al.* 2015). In a Swedish population-based cohort study of 27708 patients undergoing ERCP for benign disease, the risk for biliary tract malignancy was

elevated but this was irrespective of ES. Instead, the gallstone disease itself could be the carcinogenic factor. (Stromberg *et al.* 2008.)

Table 7. Outcomes of randomised trials of wait-and-see policy (A) versus cholecystectomy after endoscopic sphincterotomy (B) for treating common bile duct stones.

References	Year	Number of patients		Surgery	Actual cholecystectomy rate (%)		Follow-up time (years)		Recurrent biliary symptoms (%)	
		A	B	B	A	B	A	B	A	B
Hammarström	1995	39	44	open	35.9	93.2	7.6	6.8	28	5
Targarona	1996	50	48	open	22	100	3.3	3.3	21	6
Boerma	2002	59	49	lap	37.3	89.8	2	2	47	2
Lau	2006	88	82	lap	13.5	100	4.9	5.5	24	7
Heo	2015	45	45	lap	28.9	60.5	3.2	3.5	20	18.6

2.8 HOSPITAL COST

2.8.1 Economic evaluation of CBD stone management

Several attempts have been made to evaluate the costs between different types of CBD stone management. Some retrospective analyses from USA have shown that hospital charges in laparoscopic transcystic CBD exploration were lower compared to pre- or post-operative ERCP (Liberman *et al.* 1996; Schroeppel *et al.* 2007). A retrospective study from China reported similar results, but the source of cost calculations was not mentioned (Lu *et al.* 2013). Another study from Belgium favoured also laparoscopic CBD clearance compared to ERCP. However, the study was limited by its small size (Topal *et al.* 2010).

Most of the previous randomised studies on costs are byproducts of studies comparing the outcome between one-stage versus two-stage methods. Rogers et al reported no difference in total costs, but physician fee charges were lower with the one-stage treatment (Rogers *et al.* 2010). Only one RCT has compared cost-effectiveness of laparoscopic CBD exploration and two-stage (preoperative ERCP + LC) management of CBD stones with short-term outcomes. The one-stage transductal method was shown to be more effective and less costly than the two-stage method (Bansal *et al.* 2014). In two randomised studies, one-stage intraoperative ERCP was evaluated to be less costly than the two-stage (preoperative ERCP + LC) treatment (Morino *et al.* 2006, Rabago *et al.* 2006). Additionally, one-stage intraoperative ERCP was less costly than one-stage laparoscopic CBD exploration in a randomised study originating from China (Hong *et al.* 2006).

Four different treatment pathways of CBD stones were compared in a cost-decision analysis from the USA. Laparoscopic CBD exploration was considered the most cost-effective way of managing CBD stones, likewise intraoperative cholangiography with selective postoperative ERCP was more cost-effective than routine preoperative ERCP. (Urbach *et al.* 2001.) Poulose et al. compared ERCP with laparoscopic CBD exploration + routine intraoperative cholangiography for incidentally discovered CBD stones in a decision tree model. They concluded that postoperative ERCP was less costly and more effective than laparoscopic CBD

exploration. (Poulose *et al.* 2007.) Another cost-effectiveness analysis, from the perspective of a third-party payer stated that if CBD stones were detected intraoperatively; then postoperative ERCP should be preferred (Brown *et al.* 2011). On the whole, when estimating the value of cost-effectiveness analyses one must consider the possible sources of variability in the models. All of the above-mentioned studies reflect the situation in USA health-care systems.

A quality-adjusted life year (QALY) equals 1 year of life in perfect health. The calculation of QALY is an estimation of remaining years of life after a certain medical intervention with weighting each year with a quality-of-life score (0-1 scale). A cost-utility study from UK reported that intraoperative ERCP was superior to preoperative ERCP in treating CBD stones with both achieving similar qualities of life. If £20,000 /QALY was used as a threshold, then there was a 92.9% probability that intraoperative ERCP would be cost-effective compared to preoperative ERCP. The estimated savings mainly originated from the shorter hospital stay including that appropriate scheduled synchronous endoscopic and surgical teams would be available. (Gurusamy *et al.* 2012.)

To evaluate better all strategies for treating CBD stones, a Markov model was developed in UK 2014 for health economic evaluation of the cost effectiveness of different inteventions in symptomatic CBD stones. The model compared laparoscopic CBD exploration with pre-, intra- and post-operative ERCP for managing CBD stones. Surprisingly, intraoperative ERCP was less costly and produced more QALYs than either of the other treatments. The analysis also supported early intervention in order to gain maximum utility. As a result, after 1000 replications, probabilistic sensitivity analysis showed that at £20,000 /QALY as the threshold, LC + intraoperative ERCP was cost effective in 84.6% of replications. (Internal Clinical Guidelines Team (UK) 2014.) The generalizability of these results to healthcare settings outside the UK depends on the local resourses, socio-economic aspects, insurance policies and the availability of different treatment pathways.

3 Aims of the Study

The general aim of this study was to examine the day-care laparoscopic cholecystectomy dissection techniques and the different treatment options for concomitant gallbladder and common bile duct stones.

The specific aims were:

1. To evaluate the feasibility of ultrasonic scissors compared to diathermy hook in day-care laparoscopic cholecystectomy within evidence-based perioperative care pathway (I).

2. To examine the short and long-term results of laparoscopic bile duct exploration for common bile duct stones (II).

3. To estimate the success, morbidity and hospital stay after one-stage versus two-stage management of common bile duct stones (III).

4. To determine hospital costs of one-stage versus two-stage management of common bile duct stones (III).

5. To evaluate the short- and long-term outcome of expectant management of gallbladder stones after endoscopic sphincterotomy for common bile duct stones (IV).

4 Patients and Methods

The overview of patients in each study is presented in Table 8. The local ethics committee approved the study protocol of study I. All other studies were approved by the hospital administration. All causes of death were collected from hospital records or from the National Cause of Death Registry. Preoperative and short-term outcome data were collected prospectively in studies II and III. In studies II, III and IV, the long-term outcome was investigated retrospectively using data from hospital records and a mailed questionnaire.

Table 8. Patients included in studies I-IV.

Study	Patients	Surgical method	Enrolment period	Length of follow up (median)	Type of study
I	88	Laparoscopic ultracision	2012-2014	30 days	RCT
	79	Laparoscopic diathermy hook			
II	288	Laparoscopic CBD exploration	1999-2011	5.1 years	Short-term outcome : prospective Long-term outcome: retrospective
III	97	One-stage LCBDE			Short-term outcome: prospective Long-term outcome: retrospective
			1999-2014	6.9 years	
	120	Two-stage ERCP+ LC			Short and long-term outcome: retrospective
IV	181	Endoscopic sphincterotomy	1999-2014	3.9 years	Retrospective series

4.1 STUDY I: DAY-CARE LAPAROSCOPIC CHOLECYSTECTOMY WITH DIATHERMY HOOK VERSUS FUNDUS-FIRST ULTRASONIC DISSECTION: A RANDOMISED STUDY

Study I was a prospective, randomised study, which consisted of 169 elective patients who underwent laparoscopic cholecystectomy in the day-care unit of Central Hospital of Central Finland during April 2012 to September 2014. Only adult patients (ASA I-II) were included with written informed consent being obtained prior to inclusion.

Patients were randomised to two different treatment groups; laparoscopic ultracision or the laparoscopic diathermy hook dissection method. Computerized randomisation with sealed opaque envelopes was undertaken by a third party, not participating in the treatment of patients. The randomisation into two treatment groups took place by a staff nurse at the operation theater after the induction of anesthesia. Patients and recovery room personnel were blinded to the study design.

A flow chart of study I is shown in Figure 4.

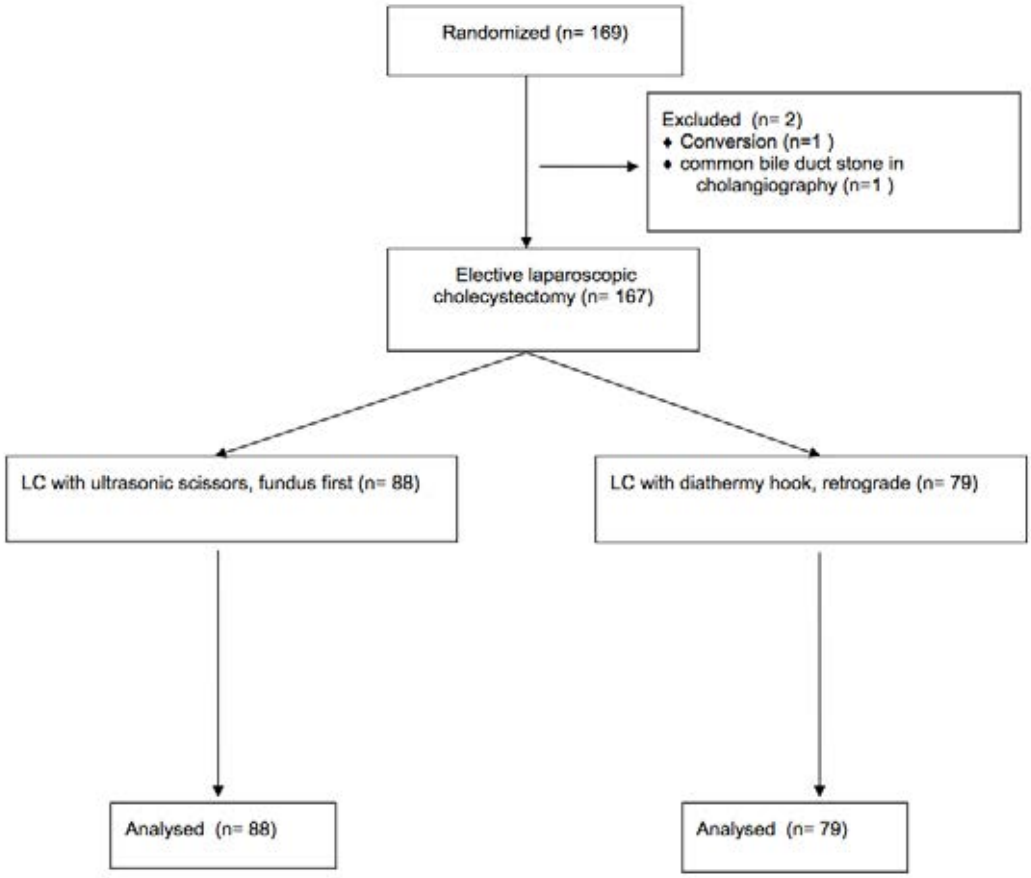


Figure 4. Flow chart of study I

4.2 STUDY II: AN AUDIT OF SHORT- AND LONG-TERM OUTCOMES AFTER LAPAROSCOPIC REMOVAL OF CBD STONES IN FINLAND

Short-and long-term outcomes after laparoscopic removal of CBD stones were examined in 288 patients admitted to Central Hospital of Central Finland and Hyvinkää Hospital between January 1999 and December 2011. The patients underwent elective or emergency LC + laparoscopic CBD exploration after preoperative or intraoperative diagnosis of choledocholithiasis. Patients with an intact gallbladder and verified residual CBD stones after preoperative ERCP + ES were also included. Exclusion criteria were severe pancreatitis, cholangitis and significant comorbidity.

4.3 STUDY III: COST ANALYSIS AND EFFECTIVENESS OF ONE-STAGE VERSUS TWO-STAGE ENDOLAPAROSCOPIC TREATMENT OF CHOLECYSTOCHOLEDOCHOLITHIASIS

Altogether 97 patients underwent one-stage CBD clearance + LC and 120 patients two-stage procedure (ERCP+ ES and subsequent LC) for CBD stones between January 1999 and December 2014 at the Central Hospital of Central Finland. Patients with gallbladder stones and concomitant CBD stones were included but patients treated with urgent laparoscopic CBD exploration + LC, acute cholecystitis or cholecystectomy deferral-policy after endoscopic sphincterotomy were excluded. A flow chart of study III is shown in Figure 5.

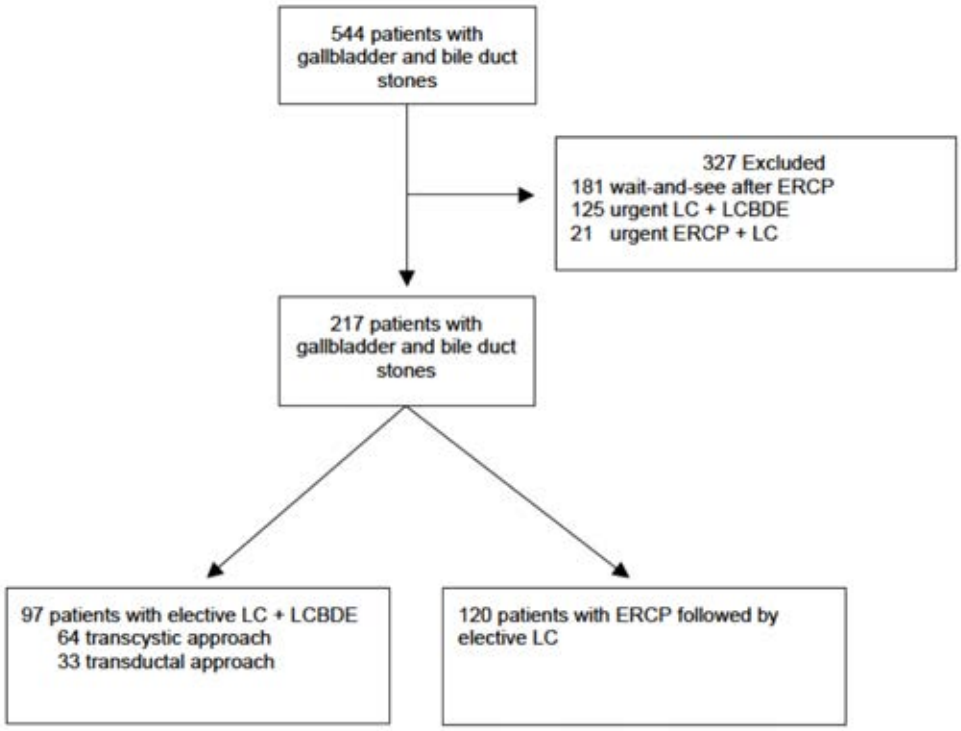


Figure 5. Flow chart of study III.

4.4 STUDY IV: EXPECTANT MANAGEMENT OF GALLBLADDER STONES AFTER ENDOSCOPIC REMOVAL OF CBD STONES

Some 181 consecutive patients with intact gallbladder underwent endoscopic sphincterotomy for CBD stones between January 1999 and December 2014. Patients who were not scheduled for elective cholecystectomy after endoscopic sphincterotomy, patients evaluated to be a high-risk patient for anesthesia and surgery, or if the patient refused the offered cholecystectomy were included in this study. Biliary tract or pancreatic malignancy was an exclusion criterion.

4.5 SURGICAL TECHNIQUE

4.5.1 Technique of cholecystectomy

The laparoscopic cholecystectomy in study I was performed after randomisation either by diathermy hook starting from the triangle of Calot or by ultrasonic scissors starting from the gallbladder fundus downward. The trocar set-up was similar in both dissection methods. The cystic duct was sealed with metallic clips. Intraoperative cholangiography was performed when feasible. The amount of intraoperative blood loss was measured by the scrub nurse. Patients and recovery room personnel were blinded to the surgical technique used. All operations were performed by one of two consultant surgeons.

In studies II, III and IV, laparoscopic cholecystectomy was performed using a four trocar set-up with traditional diathermy hook dissection starting from the triangle of Calot. Primary open cholecystectomies and conversions to open surgery in laparoscopic cholecystectomy were performed through a right subcostal incision. In study III, in the two-stage group, elective LC was performed later after ERCP+ ES by either a senior or registrar surgeon.

4.5.2 Laparoscopic CBD exploration

In studies II and III, laparoscopic CBD exploration was performed either transcystically or by choledochotomy. CBD stones were removed transcystically when feasible. Indications for transcystic exposure were stone size less than 7-8 mm, stone number ≤ 3 and lateral insertion of cystic duct. A transductal approach was chosen for multiple CBD stones, large stones (<7-8 mm) causing ductal dilatation, CBD stones proximal to cystic duct insertion, posterior entrance of cystic duct or in case of a failed transcystic approach. Dilatation of the cystic duct was not used routinely. Stones were extracted with a Dormia basket, Fogarty balloon catheter or flushing and pushing techniques. The clearance of CBD was confirmed with choledochoscopy and/or cholangiography. Conversion to open surgery was done if laparoscopic CBD exploration was unsuccessful or in cases where there were impacted CBD stones. After choledochotomy, a T-tube was inserted in the beginning of series, later only in cases with a risk of bile leakage. The choledochotomy site was sutured with absorbable sutures. One-stage procedures were performed by senior surgeons.

4.6 ERCP + ES

ERCP in studies II, III and IV was performed in either inpatient or as an ambulatory setting. All procedures were performed by senior consultants. Endoscopic sphincterotomies were performed under propofol sedation using a wire-guided sphincterotome. Clearance of CBD was achieved with Dormia basket, balloon or mechanical lithotripsy. After incomplete CBD stone

removal, a biliary stent was inserted and redo-endoscopy was programmed. A biliary stent was also inserted in case of postoperative bile leakage followed by repeated endoscopy and stent removal after 3-4 weeks.

4.7 DAY-CARE TREATMENT

Multimodal anesthestic regime was used based on recent evidence from the literature (Table 9). Postoperative pain assessment was measured using a numeric rating scale (NRS) (0=no pain; 10= most pain). The postoperative pain (NRS), nausea and vomiting (PONV) were registered at one, two and four hours postoperatively in the day surgery unit. The consumption of opioids in the recovery room was registered. Thirty-day morbidity and readmissions were recorded using mailed questionnaire and hospital records.

Table 9. Multimodal regime for day-care LC randomised trial.

Intervention	
Premedication	Paracetamol 2 g po
	Etoricoxib 120 mg po (unless contraindicated)
	No sedatives
	No anxiolytics
Induction and maintenance	Propofol 5 mg/kg/h
	Remifentanil 0.75 ug/kg/min
	Cisatracurium 0.1 mg/kg
	Dexamethasone 10 mg iv
	Ondansetron 4 mg iv
	Ketoprofen 100 mg iv (unless contraindicated)
	No antibiotics
	Bis ™-monitoring
Pneumoperitoneum	10 mmHg CO_2
Trocar site infiltration	
(After skin closure)	Ropivacaine 7.5 mg/ml 20 ml
Postoperative care in recovery room	Fentanyl 25-50 ug iv on demand (maximum dose 200 ug)
	Oxycodone 5 mg po on demand (maximum dose 30 mg)
	Metoclopramide 10-30 mg iv on demand
	Ondansetron 4 mg iv on demand
	Dehydrobenzperidol 0.5 mg iv on demand

4.8 COST CALCULATION

In the economic evaluation, all costs were calculated using the year 2014 prices (€). The numbers of surgical procedures, surgical department days, ICU days and readmissions were recorded. Personnel expenses including correction coefficient (0.82 for ERCP without the presence of anesthesiologist) were obtained from the hospital administration. The allocated operating room costs included time spent in the operating room (basic costs 197.72€) and recovery room (0.50 € per minute), duration of surgery (8.5 € per minute for LC, 0.82 x 8.5 € per minute for ERCP), expertise of the operating team (0.6045 € per minute for senior consultant, 0.403 € per minute for resident) and disposable equipment for ERCP and laparoscopic CBD exploration. Postprocedural costs included the price of ward days (602 € per day), intensive care unit days (1973 € per day), radiological examinations (CT 135 €, MRCP 258 €, US 102 €, T-tube cholangiography 234 €), histological analysis of gallbladder (350 €) and reoperations. The costs of readmissions to outpatient clinic (176 € outpatient physician consultation), radiological examinations and readmissions to surgical ward were separately calculated. Capital costs of reusable instruments and standard laparoscope and duodenoscope equipment were excluded.

4.9 STATISTICAL METHODS

The results are presented as means (SD) and medians (IQR). In the statistical analysis, ANOVA, Chi-square test, Mann-Whitney U test and Fisher´s exact test were used. p values < 0.05 were considered significant. Binary logistic analyses were used to assess factors affecting the success of laparoscopy in study II. In study III, analysis of variance (ANOVA) or Kruskal-Wallis test was used when appropriate. As the data for costs were highly skewed, a bias corrected and accelerated bootstrap estimation was used to derive 95% confidence intervals and differences between the means were tested by a bootstrap-type ANOVA, and post hoc testing of several univariate comparisons were made with Hochberg's adjustment at significance level 0.05. Statistical analyses were performed using STATA statistical software (study I) and SPSS (study II, III, IV). Cumulative recurrence rates (study II) and cumulative mortality and long-term complication rates (study IV) were calculated using the Kaplan-Meier method.

5 Results

5.1 STUDY I: DAY-CARE LAPAROSCOPIC CHOLECYSTECTOMY WITH DIATHERMY HOOK VERSUS FUNDUS-FIRST ULTRASONIC DISSECTION: A RANDOMISED STUDY

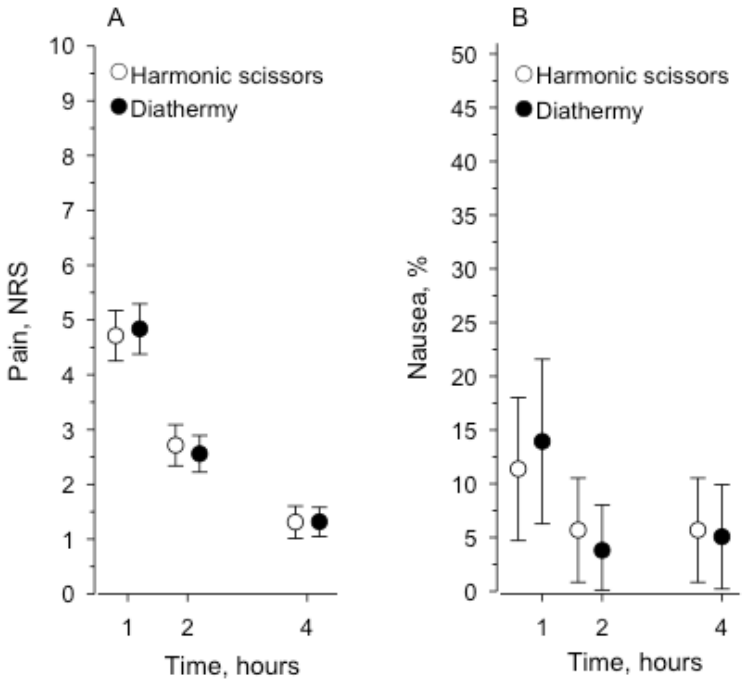
5.1.1 Preoperative and intraoperative factors

Baseline demographic characteristics did not differ significantly between the study groups. Both study groups represented individuals who were overweight, with mean BMI (kg/m^2) being over 27.

The median operative time (45 min) for diathermy hook LC and ultrasonic scissors LC did not differ between the study groups. Intraoperative gallbladder perforations and bleeding were also similar. Intraoperative cholangiography was performed in 74 (32 ultrasonic/42 diathermy hook) patients (44.3%), with a median procedure time of 5 minutes.

5.1.2 Postoperative outcome

Recovery room time, 30-day morbidity and readmissions were similar between the study groups. Same-day discharge (87%) did not differ between the diathermy hook and the ultrasonic scissors group, (p=0.98). Postoperative pain and PONV were equal during recovery room time between the study groups (Figure 6).



Figures 6A and 6B. Figure 6A depicts postoperative pain score (p=0.96) and Figure 6B depicts PONV in diathermy and ultrasonic scisssors group (p=0.78).

5.2 STUDY II: AN AUDIT OF SHORT- AND LONG-TERM OUTCOMES AFTER LAPAROSCOPIC REMOVAL OF CBD STONES IN FINLAND

5.2.1 Baseline characteristics

Between January 1999 to December 2011, altogether 288 patients were operated on with laparoscopic CBD exploration + LC in Hyvinkää Hospital (n=90) and Central Hospital of Central Finland (n=198). Patients undergoing elective or emergency operation with proven pre- or intraoperative choledocholithiasis were included. Also patients with intact gallbladder stones and residual CBD stones after endoscopic sphincterotomy were included. One third of patients were categorised as ASA III-IV. Acute cholecystitis was diagnosed in 13.3% of patients.

All patients underwent intraoperative choledochoscopy. In nine patients, the preoperative suspicion of CBD stones could not be confirmed during choledochoscopy. Intraoperative cholangiography was performed in 92.8% of patients.

5.2.2 Primary success of laparoscopic CBD exploration and early outcome

Laparoscopic CBD clearance was accomplished in 232 of the 279 patients (83.2%). The clearance rate increased by an additional 10 % after conversion to open surgery. Retained CBD stones were removed in an additional 19 (6.8%) patients by postoperative ERCP. In elective operations, the primary clearance rate was significantly better than in emergency operations (85.1% versus 70.3%, p=0.025).

The multivariate analysis revealed that failed laparoscopic CBD clearance was associated with stone size > 7 mm [OR 3.51 (95% CI 1.53-8.03), p=0.003], difficult anatomy [OR 18.01 (95% CI 15.03-64.49), p<0.001], and a transductal approach [OR 2.98 (95% CI 1.37-4.47), p=0.006]. Impacted stones at ampulla of Vater were the reason for failure in 11 patients. The 30-day morbidity was 12.2% with severe Dindo-Clavien complications in 4.3% of patients.

Median postoperative stay was significantly shorter after the transcystic (2 days, IQR 1-3) than after the transductal (4 days, IQR 3-7 days) approach, (p< 0.001).

5.2.3 Long-term outcome

Median follow-up time was 5.1 years. The cumulative CBD stone recurrence rates after 5 and 10-years were 3.6% and 6.0%, respectively. The crude incidence of stone recurrence was 3.5%.

5.3 STUDY III: COST ANALYSIS AND EFFECTIVENESS OF ONE-STAGE VERSUS TWO-STAGE ENDOLAPAROSCOPIC TREATMENT OF CHOLECYSTOCHOLEDOCHOLITHIASIS

5.3.1 Baseline characteristics

The mean age of patients in the one-stage group was 59.1 years (SD 19.0) and in the two-stage group 64.8 years (SD 15.3),(p=0.016). The proportion of patients > 75 years was 26.8 % in the one-stage compared to 32.5 % in the two-stage group,(p=0.474). The one-stage group had a female predominance (80.4%) compared to the two-stage group (53.3%) with no statistical difference. Over 70 % of the patients in both study groups had minor comorbidities (ASA I-II).

5.3.2 Operative details and surgical outcome

Primary success of CBD clearance in the one-stage group was 88.7% (86/97 patients) and in the two-stage group 85.0% (102/120 patients). After conversion, the clearance rate increased in the one-stage and in the two-stage group to 96.9% and 98.3%, respectively,($p=0.36$). Total operative time was significantly longer in the one-stage group than in the two-stage group (150 min vs. 112 min),($p<0.001$). The 30-day surgical outcome is presented in Table 10.

Table 10. 30-d surgical outcome

	One-stage		**One-stage**	**Two-stage**	
	N=97		**N=97**	**N =120**	
	TC approach N=64	TD approach N=33	Total		p- value total one-stage vs two-stage
Successful CBD stone clearance, n (%)					
LC + LCBDE /Index ERCP [a]	59 (92.2)	27 (81.8)	86 (88.7)	102 (85.0)	0.66
After conversion to open surgery	3 (4.7)	5 (15.2)	8 (8.2)	16 (13.3)	0.36
After ERCP for residual stones	2 (3.1)	1 (3.0)	3 (3.1)	2 (1.7)	0.15
Total operative time, median (IQR) min [b]	140 (69.3)	165 (52.5)	150 (61.0)	112 (64.0)	<0.001
30-d mortality, n (%) [c]	0 (0)	1 (3.0)	1 (1.0)	0 (0)	0.27
30-d overall morbidity, n(%) [d]	6 (9.4)	9 (27.2)	15 (15.5)	9 (7.5)	0.64
Surgical morbidity, n (%)	5 (7.8)	4 (12.1)	9 (9.3)	5 (4.2)	0.13
Bile leak	2	3	5	0	
Postoperative bleeding	1	0	1	2	
Wound infection	1	0	1	1	
Intra-abdominal abscess	0	1	1	0	
Post-ERCP pancreatitis	1	0	1	0	
Bleeding after ERCP	0	0	0	2	
General morbidity, n (%)	1 (1.6)	5 (15.2)	6 (6.2)	5 (4.2)	0.50
Renal insufficiency	0	1	1	0	
Fever, unknown origin	0	0	0	1	
Vocal cord injury from intubation	0	1	1	0	
Myocardial infarction	0	0	0	1	
Heart insufficiency	1	0	1	1	
Pneumonia	0	3	3	2	
Dindo-Clavien gr IIIb-V, n (%)	2 (3.1)	3 (9.1)	5 (5.2)	2 (1.7)	0.25
Postoperative stay, median (IQR) days [b]	2 (1-3)	5 (2-8)	2 (2-5)	4.5 (3-7)	<0.001
Reoperation, n (%)	2 (3.1)	2 (6.1)	4 (4.1)	1 (0.8)	0.11
Readmission, n(%)	3 (4.7)	16 (48.5)[e]	19 (19.6)	7 (5.8)	0.002

a Two-stage group
b Two-stage: ERCP and LC time
c Clostridium perfringens sepsis
d Figures in the columns are not additive because some patients had more than one complication
e ambulatory cholangiography and T-tube removal in 14 patients
TC = transcystic, TD=transductal

5.3.3 Economical evaluation

The mean costs of disposable equipment were significantly lower in the one-stage group (526 €) compared to the two-stage group (739€), (p<0.001). Ambulatory T-tube removal increased the readmission costs in the one-stage group. Mean hospital costs were similar in both treatment groups (6785 € in the one-stage, 6913 € in the two-stage), p=0.806. However, when mean hospital costs were subdivided between the transcystic and transductal groups, the former method was less costly than either transductal or two-stage management. The economical results are presented in Table 11. When subtracting patients with a complicated postprocedural course, the mean difference in total costs was 1000 € lower in the one-stage group [5487 € (95 % CI:5164 € to 5809 €)] compared to patients in the two-stage group [6487 € (95 % CI : 6019 € to 6956 €)], (p<0.001).

Table 11. Mean differences (95% CI) in hospital costs between one-stage and two-stage groups.

Costs	One-stage N=97		Two-stage N=120	P-value (Multiple comparison)*
	Transcystic (TC) N=46 Mean (95% CI)	Transductal (TD) N=33 Mean (95% CI)	ERCP + LC N=120 Mean (95% CI)	
Operation room, €	2806 (2680 to 2931)	3191 (3006 to 3377)	3025 (2898 to 3151)	TC/ TD 0.013 TC/ Two 0.071 TD/ Two 0.438
Postoperative, €	2572 (2200 to 2944)	5835 (3580 to 8089)	3825 (3309 to 4342)	TC/ TD <0.001 TC/ Two 0.049 TD/ Two 0.08
Readmission, €	77 (38 to 192)	339 (6 to 672)	63 (4 to 121)	TC/ TD 0.048 TC/ Two 0.018 TD/ Two 0.997
Total costs, €	5455 (4971 to 5938)	9364 (7048 to 11 681)	6913 (6340 to 7486)	TC/ TD <0.001 TC/ Two 0.029 TD/ Two 0.02

* Bias corrected and accelerated bootstrap estimation was used to derive 95% confidence intervals.

CI: Confidence interval

TC: Transcystic

TD: Transductal

5.4 STUDY IV: EXPECTANT MANAGEMENT OF GALLBLADDER STONES AFTER ENDOSCOPIC REMOVAL OF CBD STONES

5.4.1 Baseline characteristics

The mean age of patients was 79.6 years (SD 9.2) with an equal gender distribution (female 49.7%). The majority of patients had significant comorbidities. The numbers of patients with ASA III and IV was 87.8% and the mean Charlson Comorbidity Index (CCI) was 5.4 (SD 2.8). CCI was significantly higher in the elderly (>75 years) patient group,($p<0.001$).

5.4.2 Follow-up

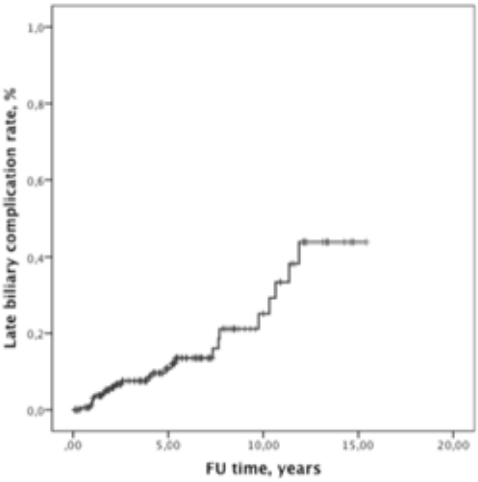
In the study group, 30-day mortality after endoscopic sphincterotomy was 3.9 % and 30–day morbidity 9.4 %. CBD stone clearance was achieved in 92.8% of patients at the first attempt. Some 7.2 % of patients needed ≥2 ERCP procedures to gain 100 % clearance rate.

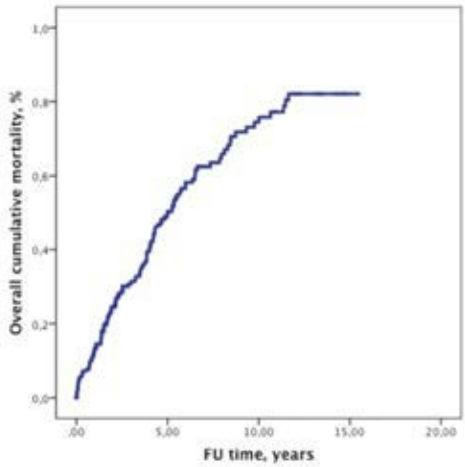
During the study period, 3 and 5 year cumulative mortality was 31.4% and 49.7%, respectively (Figure 7B). The late cumulative biliary related morbidity at 3 and 5 years was 7.6% and 10.8%, respectively (Figure 7A). The crude incidence of long-term biliary related outcome is presented in Table 12. The distribution of long-term complications was similar between younger and older patients ($p=0.458$). Long-term surgical interventions were performed in 17 (9.8%) patients as follows; additional ERCPs in 9 (5.2%), on-demand cholecystectomy in 7 (3.9%) patients and enterolithotomy for gallstone ileus in one (0.6%) patient.

Table 12. Long-term outcome in study IV.

Variable	**N=174 (%)**
Morbidity	24 (13.8)
Acute cholecystitis	10 (5.7)
CBD stone recurrence	9 (5.2)
Sine materia- cholangitis [a]	2 (1.1)
Acute biliary pancreatitis	2 (1.1)
Gallstone ileus	1 (0.6)
Biliary-related mortality	3 (1.7)

[a] cholangitis without evidence of stones or sludge





7A 7B

Figure 7A and 7B. Figure 7A depicts late cumulative biliary related morbidity and 7B depicts overall cumulative mortality.

6 Discussion

6.1 GENERAL DISCUSSION

The purpose of this study was to investigate and improve the contemporary management of cholecystocholedocholithiasis. Study I investigated day-care laparoscopic cholecystectomy using a standardised treatment protocol with two different surgical techniques. Patients presenting with concomitant CBD stones have several treatment options available; pre-, intra- or post-operative ERCP, open or laparoscopic exploration of CBD with stone removal or conservative management with or without endoscopic sphincterotomy for stone clearance. Studies II and III evaluated the success of CBD stone clearance with endoscopic and laparoscopic methods. In Study III, we investigated also the economical impact of CBD stone management comparing one-stage laparoscopic and two-stage endo-laparoscopic strategies. Study IV focused exclusively on observing the sequelae of endoscopic CBD stone clearance in patients with a cholecystectomy deferral-policy.

The impact of this thesis is twofold; firstly, to substantiate the good outcome of day care management of uncomplicated gallstone disease and to reveal that this is not dependent on the operative method itself, and secondly, to highlight the issue of laparoscopic CBD stone management in Finland with special reference to hospital costs. Furthermore, this thesis complements the findings of earlier studies on the wait-and-see management of gallbladder stones after endoscopic clearance of CBD stones.

6.2 STUDY I: DAY-CARE LAPAROSCOPIC CHOLECYSTECTOMY

Study I focuses on the modern day-care LC with special reference to the evaluation of two different dissection methods. Previous studies have suggested that ultrasonic dissection is superior to the traditional diathermy hook dissection in day-care LC (Cengiz *et al.* 2005, 2010). Contrary to expectations, we could not find any difference between the mean operative time associated with the ultrasonic dissection and diathermy hook methods. The total mean operative time in our study was in agreement with that reported in other trials (Janssen *et al.* 2003, Cengiz *et al.* 2005, 2010), with the exception of one study (Mahabaleshwar *et al.* 2012) which had a small sample size and did not report any statistical power calculations. In our study, the two dissecting methods resulted in similar and high same-day discharge rates. Implementing an evidence-based pre-emptive anesthetic regimen was the crucial step in our research frame. Consequently, postoperative pain scores and the incidence of nausea reached acceptable criteria for home discharge already 2 hours after surgery irrespective of surgical technique.

The rates of intraoperative complications as well as postoperative 30-day morbidity were low in both study groups, in line with previously published results (Cengiz *et al.* 2005, 2010, Gurusamy *et al.* 2008, Vaughan *et al.* 2013). We observed a higher rate of intraoperative gallbladder perforations in the ultrasonic dissection group, although the subsequent bile spillage without escaped stones did not affect the surgical outcome. Intraoperative blood loss has been reported to be lower when using ultrasonic dissection than monopolar diathermy, even in cases of acute cholecystitis (Cengiz *et al.* 2010; Catena *et al.* 2014). In our study, blood loss was minmal in both study groups. Our 30-day morbidity and readmission rates were low

and are in line with previous results (Cengiz *et al.* 2005; Cengiz *et al.* 2010; Enochsson *et al.* 2013).

Our selection of different dissection methods (fundus-first versus conventional retrograde method starting from the triangle of Calot) and energy sources (ultrasonic scissors versus monopolar diathermy hook) was based on previous trial designs (Cengiz *et al.* 2005, 2010). In these trials, the ultrasonic dissection itself was the key factor in achieving a better surgical outcome contributing to less blood loss, fewer intraoperative gallbladder perforations and faster surgery. Some studies with a traditional starting point (triangle of Calot) had already demonstrated that ultrasonic dissection resulted in a better outcome than electrocautery (Tsimoyiannis *et al.* 1998, Janssen *et al.* 2003).

Only one study has evaluated the economic impact of ultrasonic dissection versus conventional diathermy in LC. It found that the costs of conventional electrocautery LC were higher than those of ultrasonic dissection method, the main reason being longer operation time and more prolonged convalescence from work. (Tempe *et al.* 2013.)

In our study, the potential advantages of ultrasonic dissection over diathermy dissection in LC could not be confirmed. As the perioperative pathway was identical in both study groups, and the only difference was the use of an expensive disposable ultrasonic device in ultrasonic dissection group, in-hospital costs may be lower in the diathermy group.

6.3 STUDY II AND III: FEASIBILITY OF ONE-STAGE AND TWO-STAGE MANAGEMENT OF CBD STONES

The optimum treatment for gallbladder stones and concomitant CBD stones is still debated. During the open era, surgical clearance of CBD stones was routine. With the development of laparoscopic techniques in the 1990s, laparoscopic CBD exploration challenged the previously accepted doctrine that there should be endoscopic removal of CBD stones (Rhodes *et al.* 1998, Cuschieri *et al.* 1999). The single-stage approach for concomitant gallbladder and CBD stones provides the ability to treat the patient in one session for both problems instead of the two-stage endo-laparoscopic approach.

The clearance rates of laparoscopic CBD exploration have been reported to be between 75%-100%, with a morbidity of 11%-43% (Rhodes *et al.* 1998, Cuschieri *et al.* 1999, Sgourakis and Karaliotas 2002, Nathanson *et al.* 2005, Noble *et al.* 2009, Bansal *et al.* 2010, 2014, Rogers *et al.* 2010, Koc *et al.* 2013, Ding *et al.* 2014). It is noteworthy that a significant proportion of these studies included only patients with minimal morbidity or insufficient preoperative risk assessment (Rhodes *et al.* 1998; Cuschieri *et al.* 1999; Sgourakis and Karaliotas 2002; Rogers *et al.* 2010; Bansal *et al.* 2010; Koc *et al.* 2013; Ding *et al.* 2014). Despite the observation that one third of the patients included in Study II were suffering from severe systemic diseases (ASA III, IV), our CBD clearance rates and postoperative morbidity were consistent with the previous reports. Successful clearance rates after two-stage management of CBD stones have been reported to be between 61.7%-94.6%, with morbidity in the range 5.1%-29.8% (Rhodes *et al.* 1998, Cuschieri *et al.* 1999, Sgourakis and Karaliotas 2002, Nathanson *et al.* 2005, Noble *et al.* 2009, Bansal *et al.* 2010, 2014, Rogers *et al.* 2010, Koc *et al.* 2013, Ding *et al.* 2014). In study III, the ductal clearance rate (96.9%) and postoperative morbidity (15.5%) of elective patients in the one-stage management group were consistent with the published reports. Likewise, the two-stage management group displayed apparently similar ductal clearance (98.3%) and postoperative morbidity (7.5%).

Several studies and meta-analyses have showed convincing results favouring the use of transcystic approach instead of a transductal approach in laparoscopic CBD exploration (Paganini *et al.* 2007; Reinders *et al.* 2014; W. Zhang *et al.* 2015; Feng *et al.* 2016). The transcystic

approach offers easier access to CBD without damaging the integrity of CBD, even though the transcystic approach necessitates that certain anatomical landmarks should be ideal (cystic duct entrance and bifurcation angle to CBD, diameter of cystic duct, location, number and size of stones) (Feng *et al.* 2016). In addition, widening the transcystic approach with a microincision can even enhance the success rate of CBD clearance (Chen *et al.* 2013). Residual stones after transcystic clearance have been associated with large and multiple stones and biliary sludge (Stromberg *et al.* 2008, Bove *et al.* 2009). In study II, several factors associated with failed stone clearance were identified; stone size > 7 mm (OR 3.51), difficult anatomy (OR 18.01) and transductal approach (OR 2.98). In addition, stone clearance rates were significantly higher in elective laparoscopic CBD surgery (85.1%) than in emergency operations (70.3%). In study III, transcystic removal resulted in a significantly shorter hospital stay (2 vs 4 days) than a transductal approach. Likewise, overall morbidity, severe complications and the reoperation rate were higher with the transductal approach compared to transcystic or two-stage approach, although not statistically significantly. Previous studies have found a reduced hospital stay after one-stage CBD stone clearance compared to two-stage endo-laparoscopic management (Alexakis and Connor 2012, Zhu, Xu, *et al.* 2015). Similarly, in study II, the postoperative stay was 3 days, and in study III, it was 2.5 days shorter in the one-stage than in the two-stage approach.

The time frame for differentiating between a residual or recurrent stone is somewhat inconclusive in the literature, varying from 6 months to 2 years after primary intervention (Saharia *et al.* 1977, Jackson and Evans 2017, Konstantakis *et al.* 2017, Paspatis *et al.* 2017). Another form of definition is to categorize the stones as primary or secondary according to whether they have a lamellar or muddy appearance (Cox *et al.* 2015). The cut-off date for residual and recurrent stones in our study was set to 1 year after laparoscopic CBD exploration. More importantly, the low incidence of recurrent stones after 5-years (3.6%) and 10-years (6.0%) of follow-up as detected in study II seems to be consistent with earlier observations. Long-term recurrence rates of 0%-6.7% after laparoscopic CBD clearance (Waage *et al.* 2003; Paganini *et al.* 2007; Berthou *et al.* 2007; Quaresima *et al.* 2017) are comparable to recurrence rates of 5.8%-11% after ERCP (Pereira-Lima *et al.* 1998; Ando *et al.* 2003; Kim *et al.* 2012).

Additional disadvantages of the two-stage clearance method are associated with the potential risks of endoscopic sphincterotomy (Dasari *et al.* 2013, Costi *et al.* 2014), and the time interval after endoscopic sphincterotomy to subsequent LC, which predisposes the patient to migrating CBD stones (Reinders *et al.* 2010, El Nakeeb *et al.* 2016). Another concern is the appearance of inflammation in the Calot´s triangle after endoscopic sphincterotomy, which is thought to be a risk factor for difficult LC and a higher rate of conversions (Allen *et al.* 2006, Donkervoort *et al.* 2010, Bansal *et al.* 2014). On the other hand, intraoperative ERCP during LC is an extension of the one-stage CBD clearance method. When performed as a rendez-vous – technique, the risk of ERCP induced pancreatitis can be minimized (Swahn, Nilsson, *et al.* 2013). However, RCTs with conflicting results have been published only concerning traditional intraoperative ERCP versus laparoscopic CBD exploration (Hong *et al.* 2006, ElGeidie, ElShobary, *et al.* 2011, Poh *et al.* 2016).

In conclusion, management of gallbladder and common bile duct stones can be achieved with excellent results with both one-stage and two-stage strategies. In our study, the favoured method for one-stage CBD clearance proved to be the transcystic approach, when feasible.

6.4 STUDY III: COSTS OF ONE-STAGE VERSUS TWO-STAGE CBD STONE MANAGEMENT

According to previous trials and meta-analysis, the advantages of one-stage laparoscopic CBD clearance, when compared with the two-stage endolaparoscopic approach, are the lower number of procedures, lower costs, shorter hospital stay all achieved with no difference in morbidity and mortality (Cuschieri *et al.* 1999; Sgourakis and Karaliotas 2002; Noble *et al.* 2009; Rogers *et al.* 2010; Bansal *et al.* 2010; Koc *et al.* 2013; Bansal *et al.* 2014; Ding *et al.* 2014). The results from study III are mostly in line with previous reports. Contrary to expectations, the mean hospital costs of one-stage (laparoscopic CBD exploration + LC) management were similar with the costs of two-stage (ERCP+ LC) management. It is somewhat surprising that the significantly shorter postoperative stay did not have any major effect on hospital expenses. The reason for this is not clear, but the discrepancy can be explained by the higher incidence of postoperative morbidity in the transductal group, thus increasing the hospital expenses in the one-stage group. However, when dividing the one-stage group into transcystic and transductal categories, a more favourable economical effect of transcystic clearance could be observed, as the transcystic approach represents a more straightforward operative technique. Likewise, some of the transductal operations were consequences of failed transcystic attempts, resulting in a longer operating time and higher expenditure. Similar results of lower costs associated with the transcystic approach compared to transductal exposure have been reported from China (Zhang, Xu, *et al.* 2015). However, the large diversities between healthcare systems in different countries limit the comparison of absolute expenditures.

A small cost-analysis study from Belgium showed that the one-stage procedure was less costly in patients with an uneventful post-procedural course (Topal *et al.* 2010). The same phenomenon could also be seen in our study when postoperative complications were excluded. The main source of hospital expenses during operation theatre visit originated from staff costs, not the use of disposable equipment. Similarly, postoperative personnel and overhead costs of surgical ward were the principal factors accounting for the total expenses in both one-stage and two-stage treatment groups. By minimizing the time spent in the operating theatre and in the surgical ward after CBD stone management, the total expenses could be reduced in the future.

Recently, costs of intraoperative ERCP have also been evaluated. A decision-tree model analysis indicated that traditional intraoperative ERCP seemed to be less costly than preoperative ERCP in the UK setting (Gurusamy *et al.* 2012). Another improvement in CBD stone clearance appeared with the one-stage rendez-vous intraoperative ERCP, which has challenged the one-stage laparoscopic CBD exploration (Swahn, Nilsson, *et al.* 2013). The rendez-vous ERCP has been associated with minimal rates of post-ERCP pancreatitis, although the accomplishment of the procedure means that an endoscopy team has to be available. Additionally, some evidence exists favouring rendez-vous ERCP as being more economical than a sequential two-stage treatment (Garbarini *et al.* 2016).

6.5 STUDY IV: EXPECTANT MANAGEMENT AFTER ENDOSCOPIC SPHINCTEROTOMY

There is a debate about the role of cholecystectomy after ES and watchful waiting in elderly patients. Some authors advocate a wait and see-policy (Bignell *et al.* 2011, Yasui *et al.* 2012), while others prefer planned cholecystectomy (Costi *et al.* 2007). According to previous studies, adopting a wait and see-policy after endoscopic removal of CBD stones in patients with calculous gallbladder is not recommended as a standard treatment (McAlister *et al.* 2007). Biliary tract complications after endoscopic removal of CBD stones has been reported in 20%-

47% of patients with expectant management compared to planned cholecystectomy in randomised studies (Hammarstrom *et al.* 1995, Targarona *et al.* 1996, Boerma *et al.* 2002, Lau *et al.* 2006, Heo *et al.* 2015).

In this study, the incidence of long-term biliary complications was low. These findings are in accordance with the results of other retrospective cohort studies (Costamagna *et al.* 2002; Bignell *et al.* 2011; Yasui *et al.* 2012). The high proportion of elderly and frail patients with relatively low life expectancy explains the relatively high number of non-biliary related deaths in our study. During the follow-up, only three biliary originated deaths occurred, all of them in elderly subjects.

The incidence of acute cholecystitis in the wait and see-group has varied in previous randomised trials between 5.6%-12% (Targarona *et al.* 1996, Boerma *et al.* 2002, Lau *et al.* 2006). In our study, the incidence of acute cholecystitis was in line with previous reports, although the incidence of on-demand cholecystectomy was lower than in randomised trials.

Previous endoscopic sphincterotomy has been associated with a higher risk of conversion to open surgery in elective LC, the increase being substantially higher when cholecystectomy is scheduled as an on-demand procedure. The etiology is thought to involve scarring in the area of the hepatoduodenal ligament. (Boerma *et al.* 2002; Lau *et al.* 2006.) In our study, the conversion rate of LC after endoscopic sphincterotomy was lower than that reported in the literature.

The incidences of retained CBD stones and CBD stone recurrence in this study were slightly lower compared with previous reports (Suc *et al.* 1998, Boerma *et al.* 2002, Lau *et al.* 2006). Here, the biliary related events occurred throughout the 3.9 years median follow-up, while in randomised studies, the highest incidence has been encountered within two years after ES (Targarona *et al.* 1996, Lau *et al.* 2006).

In our study, 30-day mortality was low (3.9%), with the main contributing factors being the presence of cardiac illness and severe cholangitis. This is in line with previous studies (Targarona *et al.* 1996; Suc *et al.* 1998; Boerma *et al.* 2002). The 30-day morbidity was low (9.9%), in accordance with published results (Boerma *et al.* 2002; Lau *et al.* 2006; Dasari *et al.* 2013),

Recurrent cholangitis after endoscopic sphincterotomy in an Asian population has been associated with pigment stones (Lau *et al.* 2006), in contrast to Western reports of pancreatitis and cholangitis without concomitant CBD stones (Costamagna *et al.* 2002, Langerth *et al.* 2014). Likewise, our long-term cholangitis was categorized as "sine materia"–cholangitis. The relationship of late biliary malignancy associated with cholangitis is still a matter of debate. Some reports with long follow-up times have not confirmed the association of biliary tract cancer (Karlson *et al.* 1997, Langerth *et al.* 2015), while in some studies, a cancer risk was detected (Søgaard *et al.* 2014). We did not observe any biliary tract cancer in our study population.

In conclusion, endoscopic sphincterotomy does not protect against biliary related events. In our study population, adverse events occurred evenly throughout the follow-up period. Nonetheless, late cumulative biliary related morbidity was relatively low (10.8%) after 5 years. With this in mind, in elderly and frail patients, a wait-and-see policy is an acceptable option. However, cholecystectomy deferral after endoscopic sphincterotomy cannot be routinely recommended. Thus, careful evaluation of surgical risk factors and comorbidities is essential when making the decision of whether or not to operate.

6.6 LIMITATIONS AND STRENGTHS OF THE STUDY

There are some limitations in this study. In study I, the main limitation was the lack of hospital cost evaluation and a postoperative quality-of–life measurement. Another limitation was that

the study was not a multicenter study, but conducted in a single surgical unit by experienced surgeons.

In studies II and III, the learning curve effect and the advances in laparoscopic equipment may also have influenced the results. Zhu et al. stated that the plateau of the learning curve for transcystic clearance was estimated to be reached after 250 procedures (Zhu, Han, *et al.* 2015). In contrast, procedural competency in mastering ERCP has been suggested to be achieved with a lower threshold (Shahidi *et al.* 2015). Analysing our laparoscopic CBD exploration results after the learning period might have enhanced the results of our cost calculations in study III. The lack of randomisation may have caused some selection bias, as some high-risk and elderly patients may have been scheduled for two-stage endolaparoscopic or a cholecystectomy deferral –policy after endoscopy instead of one-stage treatment. Another disadvantage is that the results of the economical evaluation in study III may not be applied outwith the Finnish healthcare system. One potential criticism lies in the fact, that we did not calculate the cost-effectiveness of different CBD stone management options.

Study IV was retrospective in nature. As retrospective studies rely on the meticulousness of medical records, some minor symptoms like biliary pain attacks may have been ignored in the medical registers.

However, the study also had several strengths. Study I was a randomised study conducted with strict perioperative regimens and standardised operative steps. The benefit of studies II and III was that the role of laparoscopic CBD exploration in Finland has not been previously evaluated. Our analysis included also long-term outcome with good compliance. In situations, when therapeutic strategies are widely available, the results of this study can help to select the appropriate workup and management of cholecystocholedocholithiasis. Another strength is that cost calculations in study III were based on detailed accounting of personnel expenditure, major resources, disposable instruments, operating room, recovery room and surgical ward expenses, not as a diagnosis related group linked to a fixed payment amount based on the average treatment cost per patient in the group. Despite the retrospective nature of study IV, it has distinctive advantages since it involves all patients treated with expectant management in one hospital during a period of sixteen years.

6.7 PERSPECTIVES FOR THE FUTURE

Studies concerning the benefits of intraoperative ERCP compared to a two-stage approach in the management of concomitant gallbladder and CBD stones are being increasingly published (Tan *et al.* 2017). If common bile duct stones are preoperatively confirmed by preoperative MRCP or intraoperative cholangiography, the treatment strategy should be directed towards intraoperative one-stage management. RCTs of success and costs between intraoperative rendez-vous ERCP and transcystic clearance of CBD stones need to be thoroughly investigated.

Extensive implementation of intraoperative cholangiography during LC is crucial when considering one-stage management of concomitant gallbladder and CBD stones. A recent data from Sweden illustrated that intraoperative cholangiography had been performed in 88% of cholecystectomies and the incidence of CBD stones was 11.6 % (Moller *et al.* 2014), contrary to Finland, where the incidence of intraoperative cholangiography was 6.8% of all cholecystectomies performed in 2015 (www.thl.fi). The data on the true incidence of intraoperativelly treated CBD stones in Finland is not available. Further studies concerning the management of concomitant gallbladder and CBD stones and the economic impact of different treatment strategies would be beneficial, especially concerning the improvements in endo-laparoscopic day-care management. More information is needed about the spontaneous passage of small (<5 mm) CBD stones. It would be enlightening to conduct an RCT of intraoperatively observed small (< 5 mm) CBD stones treated with any peroperative method

compared to leaving the CBD stones in situ since this could provide knowledge if there is a critical stone size that should be cleared.

Preoperative risk assessment in elderly and frail patients is important when considering surgical management of concomitant gallbladder and CBD stones. Although guidelines of preoperative risk evaluation have been published, the final decision to operate is left to the health professional and patient itself (Kristensen *et al.* 2014). Preoperative frailty screening tests have been demonstrated to improve surgical outcome (Hall *et al.* 2017) and identify patients with a high risk of mortality (Johnson *et al.* 2014, Melin *et al.* 2015). However, only a few studies have been published concerning preoperative geriatric risk assessment of laparoscopic cholecystectomy (Lasithiotakis *et al*. 2013; Kenig *et al*. 2016). Further studies in this field will be needed to determine the most accurate and efficient method of frailty assessment to ultimately improve surgical outcome of gallstone disease in elderly patients.

7 Conclusions

Based on these studies, the following conclusions regarding gallstone and common bile duct stone treatment can be drawn:

1) Laparoscopic cholecystectomy in day-care practice resulted in excellent same-day discharge by applying either diathermy hook or ultrasonic dissection

2) Laparoscopic CBD stone exploration was a feasible method for treating CBD stones with low short- and long-term recurrence rates

3) One-stage laparoscopic CBD exploration resulted in a similar CBD clearance rate and postoperative morbidity as encountered with the two-stage ERCP +LC method, but it was associated with a shorter postoperative hospital stay

4) One-stage laparoscopic transcystic CBD exploration resulted in lower hospital costs than the two-stage ERCP +LC method or the one-stage transductal approach.

5) Adoption of a wait-and-see policy after endoscopic sphincterotomy resulted in low and acceptable short-and long-term biliary related mortality and morbidity, without any difference between patients <75 or ≥ 75 years of age. Most biliary related events occurred evenly throughout the follow–up time.

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ORIGINAL PUBLICATIONS (I-IV)

I

Day-care laparoscopic cholecystectomy with diathermy hook versus fundus-first ultrasonic dissection: a randomized study

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Day-care laparoscopic cholecystectomy with diathermy hook versus fundus-first ultrasonic dissection: a randomized study

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Abstract
Background and aim To examine the impact of day-care laparoscopic cholecystectomy (LC) with ultrasonic scissors dissection versus diathermy hook dissection method in a randomized setting.
Methods From April 2012 to September 2014, a total of 169 elective day-care patients were randomized to undergo either laparoscopic cholecystectomy with ultrasonic scissors using fundus-first approach ($n = 88$) or diathermy hook dissection starting from the triangle of Calot ($n = 79$). Main measures of outcome were operative time, same-day discharge and intraoperative complications. Secondary outcome measures were postoperative pain (numeric rating scale), postoperative nausea and vomiting (PONV), readmissions and 30-day morbidity.
Results Median operative time was similar in the ultrasonic dissection and diathermy hook dissection groups (45 vs 45 min, $p = 0.95$). Same-day discharge was possible in 77 patients (87 %) in the ultrasonic dissection group and in 69 patients (87 %) in the diathermy group, $p = 0.98$. Intraoperative gallbladder perforations, mean intraoperative bleeding, postoperative pain and PONV at 1, 2 and 4 h ($p = 0.78$) did not differ significantly between the study groups.
Conclusion Day-care LC using either diathermy hook or ultrasonic dissection resulted in excellent same-day discharge in both groups (87 %). LC with ultrasonic dissection does not offer any clinical advantages compared to diathermy dissection.

Keywords Laparoscopy · Day surgery · Cholecystectomy · Ultrasonic dissection

Previous meta-analysis and randomized trials have confirmed the safety and effectiveness of day-care laparoscopic cholecystectomy (LC) compared to overnight-stay LC with no significant differences in morbidity, pain control, quality of life, patient satisfaction or return to normal daily activities [1–5]. Traditional LC with diathermy hook dissection starting from the triangle of Calot has been the gold standard. However, ultrasonic dissection of the gallbladder has been shown to cause less thermal injury in the surrounding tissues than diathermy hook [6]. Previous randomized studies using the fundus-first approach and ultrasonic dissection have shown less pain, intraoperative bleeding and intraoperative gallbladder perforations, and shorter sick leave than LC with traditional diathermy dissection [7, 8]. Moreover, the fundus-first approach has been described to shorten operative time, reduce postoperative PONV and increase same-day discharge [7, 8].

Adequate pain relief is an essential part of short-stay surgery. Postoperative nausea and vomiting may also delay postoperative discharge. To improve our day-care laparoscopic cholecystectomy pathway and same-day discharge, an evidence-based approach was adopted to optimize the perioperative care [9, 10]. This study examined the impact of laparoscopic cholecystectomy with ultrasonic scissors

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and fundus-first approach or diathermy hook dissection starting from the triangle of Calot on operative time, same-day discharge and intraoperative complications.

Patients and methods

From April 2012 to September 2014, a total of 169 patients were randomly assigned to undergo either a standard LC with diathermy hook dissection or fundus-first LC using ultrasonic dissection in the day-care unit of Central Hospital of Central Finland. Main measures of outcome were operative time, same-day discharge and intraoperative complications. Secondary outcome measures were postoperative use of analgetics, postoperative nausea and vomiting (PONV), readmissions and 30-day morbidity.

Patients were examined in the outpatient department by the operating surgeons and scheduled for day-care surgery. If the inclusion criteria were fulfilled, patients were offered to take part in the ongoing study. Included were elective patients aged from 18 to 65 years having symptomatic cholelithiasis and normal liver enzymes, American Society of Anesthesiologists (ASA) score I or II, body mass index (BMI) under 35 and no bile duct dilatation in ultrasound. Excluded were patients with NSAID allergy, ASA score III or IV, previous upper GI surgery, common bile duct stones in preoperative imaging or history of severe acute pancreatitis. Computerized randomization with sealed opaque envelopes was done by a third party. The envelopes were stored in the operating theater. A sealed envelope was opened by a staff nurse after initiation of anesthesia. The study was approved by the Ethics Committee of Central Hospital of Central Finland (Dnro 3U/2012, ClinicalTrials.gov NCT01553331). Written informed consent was obtained from each patient before enrollment.

Day-care laparoscopic cholecystectomy pathway

Premedication with 2 g oral paracetamol and 120 mg etoricoxib was given 1 h before the surgery. No opioids, sedatives or anxiolytes were administered routinely. Knee-length compression stockings were used routinely to prevent deep vein thrombosis. Induction and maintenance of anesthesia were achieved with propofol and remifentanil infusion. The depth of anesthesia was bispectral index-guided (BIS). Cis-atracurium was administered for muscle relaxation. During anesthesia, dexamethasone 10 mg and ondansetron 4 mg were given intravenously to reduce postoperative nausea and vomiting (PONV). Ketoprofen 100 mg iv was administered for pain relief. Neuromuscular blockade was monitored with NMT module. At the end of the operation, all port sites were infiltrated with total amount of 20 ml of ropivacaine 7.5 mg/ml. During recovery room period, patients received 25–50 μg iv fentanyl for breakthrough to pain, up to a maximum total dose of 200 μg. Oxycodone 5 mg orally was administered repeatedly up to maximum of 30 mg if necessary. Metoclopramide 10–30 mg iv, ondansetron 4 mg iv or dehydrobenzperidol 0.5 mg iv was used as anti-emetic drugs when appropriate.

All operations were performed by two senior surgeons with over 10-year experience of conventional LC. The ultrasonic dissection technique was familiar to both surgeons from other gastrointestinal surgeries. Fundus-first LC with ultrasonic dissection technique was implemented by operating 15 patients before starting the randomized trial. Patient positioning was standard supine position with the surgeon and assisting nurse standing at the patient's left and monitors at the head of the bed. A standard 4-trocar setup with intra-abdominal pressure of 10 mmHg was used. The decision to do intraoperative cholangiography was left to the discretion of the operating surgeon. Cholangiography time was measured in both operating methods from the placement of first cystic duct clip until the last clip was placed after completion of C-arm cholangiography.

In the diathermy hook dissection method, the cystic artery and cystic duct were closed with metallic clips. The gallbladder was dissected from the liver bed with retrograde manner using diathermy hook. Ultrasonic dissection with Harmonic scissors (Harmonic ACE, Ethicon Endo-Surgery, Ohio, USA) was initiated by opening the serosa of gallbladder fundus, and the dissection proceeded toward the triangle of Calot. The cystic artery was divided with ultrasonic scissors. The cystic duct was closed with metallic clips.

Intraoperative gallbladder perforations were managed temporarily with graspers, and after the dissection of gallbladder from liver bed, the area was rinsed with saline solution. The operative time was measured from first skin incision to last stitch placement after infiltration of local anesthetic. The amount of procedural blood loss was estimated. The specimen was removed in a plastic bag through umbilicus in both surgical methods.

Patients and recovery room nurses were blinded to the surgical technique used in the operation. The operating surgeons and the operating room staff were excluded from postoperative treatment and evaluation. Postoperative pain was recorded at 1, 2 and 4 h after surgery using numeric rating scale (NRS) from 0 = no pain to 10 = worst possible pain. Postoperative nausea was registered at 1, 2 and 4 h after surgery. Postoperative pain medication at home included etoricoxib 60 mg and paracetamol 1 g t.i.d advised to take if needed. As a rescue medication, 5 mg oxycodone tablets were given to the patient.

Patients were discharged by a recovery room nurse after they were nausea and pain free (NRS ≤ 4) with oral analgesics, fully mobilized, able to drink and urinate. Reasons for overnight stay were assessed. Patients were followed up for 30 days. Thirty-day morbidity and readmissions were recorded.

Statistical methods

The data are presented as means with standard deviations (SD), medians with interquartile range (IQR) or counts with percentages. The 95 percent confidence intervals (95 % CI) are given for the most important outcomes. Results were analyzed by the ANOVA, Chi-square test, Mann–Whitney *U* test and by Fisher's exact test. p values of <0.05 were considered to be significant. Statistical analyses were performed using STATA statistical software. For a difference in same-day discharge of 20 % between the study groups and a test power of 85 % ($\alpha = 0.05$), 71 patients were required in each study arm.

Results

The flowchart of the study patients is presented in Fig. 1. Baseline characteristics were similar between the study groups (Table 1). Two patients (1.2 %) were excluded: one had conversion to open surgery because of severe adhesions and the other had common bile duct stones in intraoperative cholangiography, which were removed by transcystic technique. A total of 169 patients in day-care surgery unit met the inclusion criteria for day-care LC.

Surgical outcome is presented in Table 2. Median operative time was similar in the diathermy dissection and ultrasonic dissection group [45 min (SD 20) versus 45 min (SD 20), $p = 0.95$]. Same-day discharge was possible in 69 patients (87 %) and in 77 patients (87 %) in the diathermy and ultrasonic group, respectively ($p = 0.98$). Pain, PONV, and 30-day morbidity and readmission rates were low with no significant difference between the study groups. Postoperative pain scores and PONV after 1, 2 and 4 h in the recovery room did not differ significantly between the study groups (Fig. 2A, B).

Postoperative intravenous fentanyl was administered in the diathermy group to 61 patients (77 %) and in the ultrasonic dissection group to 68 patients (77 %) [mean postoperative consumption 66 mg (SD 53) versus 67 mg (SD 59), respectively, $p = 0.93$]. During the recovery room period, oxycodone was used in 70 (89 %) patients in the diathermy group and in 84 patients (95 %) in the ultrasonic dissection group [mean consumption 9.3 mg (SD 7.0) versus 10.4 mg (SD 11.4), respectively, $p = 0.48$].

Discussion

Previous studies and meta-analyses have shown that same-day discharge after day-care LC using diathermy hook dissection can be achieved in some 60–81 % of cases [3, 11–14]. However, some studies have demonstrated an improved same-day discharge rate after LC using ultrasonic dissection (73–95 %) than after LC with conventional diathermy dissection LC (66–76 %) [7, 8]. This study shows that using an optimized perioperative pathway in day-care LC including modern pain management, both diathermy and ultrasonic dissection techniques, is effective in treating cholelithiasis without compromising patient safety and resulting in similar outcome. Particularly, the same-day discharge rate was similar (87 %) in the study groups. Mean operative time in previous randomized studies comparing ultrasonic dissection method and diathermy dissection seems to be lower in ultrasonic dissection method (27–60 vs 34–65 min) in contrast to our study showing similar operating time in both study groups [7, 8, 15, 16].

Effective, evidence-based anesthetic management and multimodal analgesia are a prerequisite to decrease surgical stress response and to enhance same-day discharge in day-care gallbladder surgery [9, 17]. In order to optimize anesthesia and pain management of day-care LC according to modern guidelines, we used pre-emptive anesthesia which has been shown to reduce the need of postoperative opioids after LC [9, 17]. Consequently, we could not find any significant difference between the study groups with regard to postoperative analgetic use, pain score or time spent in postoperative care unit. Previously, postoperative nausea and vomiting and pain scores during the first postoperative 24 h have been observed to be reduced after LC with ultrasonic dissection than after LC with diathermy dissection [7, 8]. There is also some evidence that ultrasonic dissection may reduce intraoperative bleeding [7], but this was not confirmed in our study.

Several studies have reported an overall complication rate from 3.9 to 6.1 % after traditional LC for gallstone disease [18–22]. Day-care LC-related complications have been documented to be low, and no significant difference has been observed compared to overnight stay [3, 23]. Our postoperative morbidity was low and in line with the 1.2–5 % postoperative morbidity rate reported in randomized trials comparing day-care LC with ultrasonic dissection versus traditional day-care LC with diathermy dissection [7, 8] Particularly, the incidence of bile duct injury after traditional diathermy LC has been around 0.2–1.5 [18, 21, 24] and was here 0.6 %: In our study, a bile leak from cystic stump occurred in one patient in the electrocautery group, which was treated by ERCP and

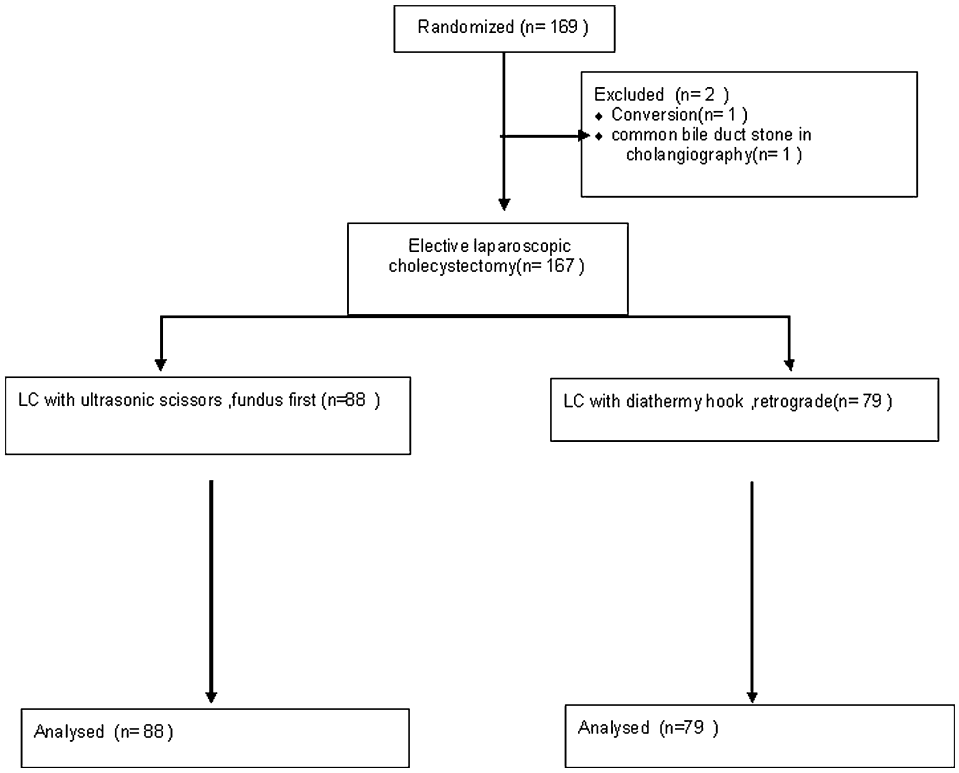

Fig. 1 Flowchart

Table 1 Baseline demographic characteristics

	Diathermy hook ($n = 79$)	Ultrasonic scissors ($n = 88$)	p value
Age, mean (SD) years	45.0 (13)	47.0 (11)	0.22
Female sex, n (%)	59 (75)	59 (67)	0.28
BMI (kg/m^2), mean (SD)	27.6 (3.8)	27.2 (3.7)	0.54
ASA I, n (%)	63 (80)	75 (85)	
ASA II, n (%)	16 (20)	13 (15)	

stenting. The bile leak was not associated to the dissection method itself. Our 30-day readmission rate was 5 versus 3 % in the diathermy and ultrasonic dissection groups and in agreement with the reported range of 2.0–7.0 % after day-care LC worldwide [3, 13].

Overall, intraoperative gallbladder perforations occur in 8.6–20 % during conventional diathermy dissection [25, 26]. However, in randomized series comparing diathermy and ultrasonic dissection gallbladder perforations (40–51 vs 16–26 %) seems to occur less often with ultrasonic dissection [7, 15, 16]. In our study, intraoperative perforations occurred more often in the ultrasonic group (27 vs. 20 %), although the difference was not statistically significant. Small perforations without stone spillage can be managed with rinsing and suction combined with temporary closure of the perforation site with a grasper or clip. Hence, the impact of small perforation without stone spillage on the surgical outcome is minimal, as shown here.

Our study should be interpreted with some caution, however. The major limitation is the lack of quality-of-life measurement. In addition, we did not examine the return to work and normal daily activities. Economical direct in-hospital costs have been reported to be lower after ultrasonic fundus-first LC than after conventional diathermy LC

Table 2 Surgical outcome

	Diathermy hook (n = 79)	Ultrasonic scissors (n = 88)	*p* value
Operation time, min (SD)	45 (20)	45 (19)	0.95
Gallbladder perforation, *n* (%)	16 (20)	24 (27)	0.29
Intraoperative bleeding, mean, ml (SD)	16 (26)	13 (15)	0.45
30-day morbidity	4 (5)	3 (3)	0.71
Bile duct injury, *n* (%)	0 (0)	0 (0)	
Port-site infection	2	2	
Port-site hematoma	1	0	
Deep vein thrombosis	0	1	
Bile leak form cystic stump[a]	1	0	
Recovery room time, min (SD)	283 (78)	264(70)	0.081
Readmission rate, *n* (%)	4 (5)	3(3)	0.81

[a] Bile leak was treated by ERCP and stenting

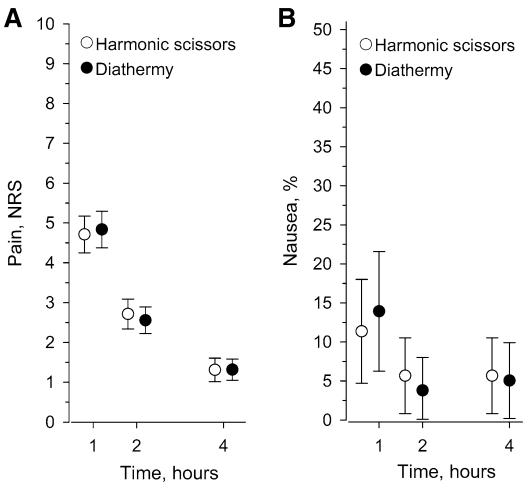

Fig. 2 **A**, **B** postoperative pain score in diathermy and ultrasonic scissors group. $p = 0.96$ and postoperative nausea in diathermy and ultrasonic scissors group. $p = 0.78$

[27]. However, the difference was mainly related to the shorter operative time in the fundus-first ultrasonic technique not found in our study. Consequently, in-hospital costs of the ultrasonic dissection technique may be higher due to the price of single-use ultrasonic scissors.

Conclusion

The fundus-first LC with ultrasonic dissection results in similar operative time, blood loss and postoperative recovery profile as LC with conventional diathermy dissection and therefore does not offer any significant advantages compared to conventional LC diathermy hook dissection.

Compliance with ethical standards

Disclosures A. Mattila, J. Mrena, I. Kellokumpu, J. Nevantaus and H. Kautiainen have no conflicts of interest or financial ties to disclose.

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II

An audit of short- and long-term outcomes after laparoscopic removal of common bile duct stones in Finland

Mattila A, Luhtala J, Mrena J, Kautiainen H and Kellokumpu I

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An audit of short- and long-term outcomes after laparoscopic removal of common bile duct stones in Finland

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Abstract
Background and aim To audit short- and long-term outcomes after laparoscopic common bile duct exploration (LCBDE) and factors influencing the success of the laparoscopic treatment.
Methods From January 1999 to December 2011, 288 patients (93 males) underwent a single-stage laparoscopic cholecystectomy combined with LCBDE in two Finnish Hospitals. Short-term outcome data were collected prospectively. Long-term outcomes were examined retrospectively. The main measures of outcome were the success of laparoscopic CBD stone clearance and recurrence of CBD stones in the long-term, with 30-day mortality, morbidity, and the length of postoperative hospital stay as secondary outcome measures.
Results CBD stones were successfully removed by one-stage laparoscopic procedure in 232 of the 279 patients (83.2 %) with verified CBD stones and after conversion to open surgery in additional 28 patients (93.2 %). Nineteen patients (6.8 %) having residual stones after surgery were successfully treated with postoperative ERCP. On multivariate analysis, the independent factors associated with a failed laparoscopic stone clearance were stone size over 7 mm [OR 3.51 (95 % CI 1.53–8.03), $p = 0.003$], difficult anatomy [OR 18.01 (5.03–64.49), $p < 0.001$] and transcholedochal approach [OR 2.98 (1.37–4.47), $p = 0.006$]. Laparoscopic stone clearance also failed in all 11 patients having impacted stones at the ampulla of Vater. Cumulative long-term recurrence rate was 3.6 % at 5 years and 6.0 % at 10 years. Thirty-day mortality was 0.3 % and morbidity 12.2 %. Postoperative hospital stay was median 2 (IQR 1–3) days after transcystic CBD removal and 4 (IQR 3–7) days after transcholedochal CBD removal, $p < 0.001$.
Conclusion Our results show that one-stage LC combined with LCBDE stone clearance is safe and effective in most patients thus reducing the number of additional, potentially dangerous endoscopic procedures. Moreover, large or impacted stones are a risk factor for failed stone clearance.

Keywords Laparoscopy · Bile duct stone · Choledochoscopy

In the era of open cholecystectomy, open bile duct surgery was superior to preoperative endoscopic retrograde cholangiography (ERCP) in achieving common bile duct (CBD) stone clearance [1–5]. The introduction of laparoscopic cholecystectomy in the early 90's was associated with increased use of ERCP and endoscopic sphincterotomy (ES) to treat CBD stones because operative clearance of CBD stones along with laparoscopic cholecystectomy was not considered technically possible [6]. Today, patients with CBD stones undergoing laparoscopic cholecystectomy can be managed by laparoscopic CBD exploration and stone removal at the time of surgery, or by pre-, intra or postoperative ERCP [7, 8].

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The goal of therapy in choledocholithiasis is to achieve ductal clearance with the fewest number of interventions, least morbidity and lowest costs. Current evidence suggests that laparoscopic CBD stone clearance is as efficient as pre- or postoperative ERCP/ES resulting in a reduced number of total procedures, shorter hospital stay and similar mortality and morbidity [9–15]. Despite good short-term outcomes after laparoscopic CBD stone removal the management of CBD stones in patients who need to undergo cholecystectomy is still controversial and most surgeons prefer two-stage treatment strategy.

Long-term complications after laparoscopic CBD stone removal such as bile duct strictures and recurrent stones are scantily reported in the literature [16–18]. We therefore examined short and long-term results of one-stage laparoscopic cholecystectomy and CBD stone removal and factors influencing the success of the laparoscopic treatment.

Materials and methods

From January 1999 to December 2011, 288 patients with gallbladder stones and suspected CBD stones underwent laparoscopic cholecystectomy combined with laparoscopic CBD exploration (LCBDE) at the Central Hospital of Central Finland ($N = 198$) and at Hyvinkää Hospital in Hospital District of Helsinki and Uusimaa ($N = 90$). Central Hospital of Central Finland is a university affiliated to large teaching hospital. The technique of LCBDE was first adopted by IK after an appropriate training course in 1995. The study patients were operated by four experienced laparoscopic upper GI-surgeons trained by IK and having large experience in open and laparoscopic cholecystectomies. Included were patients undergoing elective or emergency laparoscopic cholecystectomy with preoperative or intraoperative confirmation of choledocholithiasis, as well as patients with gallbladder in situ having residual CBD stones after preoperative ERCP/ES. Excluded were patients with severe pancreatitis or cholangitis, as well as patients with significant comorbidity in whom a prolonged laparoscopic procedure would have been potentially harmful. Common bile duct stones were suspected on the basis of clinical, laboratory, ultrasonographic and since 2002 preoperative magnetic resonance cholangiopancreaticography (MRCP) findings in 288 patients and verified in 279 patients by intraoperative cholangiography (IOC) and choledochoscopy. Before the MRCP era ERCP was occasionally used to diagnose and treat CBD stones.

Preoperative and short-term outcome data were collected prospectively. Long-term outcome was investigated retrospectively using a mailed, self-completed questionnaire about jaundice, diagnosis and treatment of recurrent CBD stones, as well as the date of diagnosis of recurrent stones. Missing data were completed by phone calls. Hospital records were also carefully reviewed. The causes of death were obtained from the National Cause of Death Registry. The study was approved by the hospital administration.

Surgical technique

A standard operative technique was used as described earlier [19]. A 4-trocar technique was used for laparoscopic cholecystectomy. After verification of CBD stones by intraoperative cholangiography, a fifth 5 mm trocar was introduced under the right costal margin in midclavicular position for the choledochoscope. Transcystic (TC) CBD exploration was preferred for stones less than 7–8 mm in diameter, stone number ≤ 3, and if the cystic junction was lateral. Choledochotomy was chosen for large stones (>7–8 mm) causing ductal dilatation, multiple stones, if the CBD stones were situated above the cystic duct junction or the cystic junction was posterior, or if the TC approach failed. Stones were removed using Dormia basket, Fogarty balloon catheter or flushing and pushing techniques as described in the literature [20]. The cystic duct was not routinely dilated. Hyoscine butylbromide (Buscopan) was used to relax the sphincter of Oddi. The clearance of CBD was confirmed with choledochoscopy and/or cholangiography. If residual stones were detected intraoperatively they were removed by repeated choledochoscopy or conversion to open procedure in order to achieve one-stage clearance of the CBD stones. Choledochotomy was closed using 4-0 or 5-0 absorbable interrupted monofilament sutures. In the beginning of our series, T-tube was inserted routinely after choledochotomy. Later on T-tube was used selectively and the decision to insert a T-tube or to do a primary choledochotomy closure was left to the discretion of the operating surgeon. The cystic duct was closed by clips or sutured. Cholecystectomy was performed after laparoscopic CBD clearance with a diathermy hook in a retrograde manner. An abdominal drain was placed in the sub-hepatic space and removed postoperatively if no bilious drainage was detected. T-tube was removed 8–10 days after surgery in the outpatient department. The indications for postoperative ERCP were uncertainty about complete CBD stone clearance during the index operation, residual stones shown by postoperative T-tube cholangiography, or postoperative bile leakage or jaundice.

Definitions

Conversion to open surgery was defined as a necessity to interrupt the laparoscopic procedure and to proceed with open technique. Postoperative 30-day complications were classified according to the Dindo-Clavien classification

Table 1 Baseline characteristics

	$N = 279$
Age, mean (SD) (years)	57.2 (19.3)
Male sex, *n* (%)	91 (32.6)
BMI (kg/m^2), mean (SD)	27.0 (4.8)
ASA I-II, *n* (%)	186 (66.7)
ASA III-IV, *n* (%)	93 (33.3)
Diagnostic workup, *n* (%)	
Preoperative ERCP	27 (9.7)
Preoperative MRCP	153 (54.8)
Intraoperative cholangiography	259 (92.8)
Choledochoscopy	279 (100.0)
Clinical symptoms[a]	
Acute cholecystitis, *n* (%)	37 (13.3)
Clinical jaundice, *n* (%)	61 (21.9)
Biliary pain, *n* (%)	228 (81.7)
Previous biliary pancreatitis, *n* (%)	29 (10.4)
Abnormal liver tests, *n* (%)	168 (60.2)
Histopathological diagnosis	
Acute cholecystitis	37 (13.3 %)
Chronic cholecystitis	219 (78.5 %)
Normal gallbladder	23 (8.2 %)

[a] Figures in the column are not additive because many patients had more than one symptom

[21]. Primary treatment failure was defined as a failure of CBD stone clearance by laparoscopic means and necessity to do a conversion to open surgery or postoperative ERCP in order to complete duct clearance. Retained CBD stones were defined as stones detected within 1 year after the index operation, and recurrent stones were defined as stones found 1 year after the index operation. Difficult anatomy was defined as an unclear anatomy in the hepatocystic triangle due to severe adhesions, fibrotic scarring, posterior insertion of the cystic duct to CBD or if the patient had a Mirizzi syndrome.

Statistical analysis

The data are presented as means with standard deviations (SD), medians with interquartile range (IQR) or counts with percentages. The 95 % confidence intervals (95 % CI) are given for the most important outcomes. The groups were compared using the Mann–Whitney *U*-test or the χ^2-test. Cumulative recurrence rate analysis was based on the product limit estimate (Kaplan–Meier) of the cumulative "survival "function. Binary logistic regression analysis was used to assess factors affecting the success of laparoscopic CBD clearance. Statistical analyses were performed using SPSS statistical software.

Table 2 Operative data in the 279 patients with verified CBD stones

	$N = 279$
Operation time, median (IQR) (min)	145.0 (114.0–180.0)
Intraoperative diagnosis of CBD stones	
Cholangiography, *n* (%)	259 (92.8)
Choledochoscopy, *n* (%)	279 (100.0)
Conversion to open surgery, *n* (%)	37 (13.3)
Reasons for conversion	
Difficult or unclear anatomy[a]	17
Suspicion of CBD perforation[b]	2
Failed clearance of impacted stone at ampulla of Vater	11
Failed clearance of large CBD stones	2
Mirizzi syndrome	1
Obesity	1
Technical problem	1
Posterior insertion of cystic duct, narrow CBD	1
Intraoperative bleeding	1
Successful CBD stone clearance, *n* (%)	279 (100.0)
Laparoscopic CBD stone clearance	232 (83.2)
After conversion to open surgery	28 (10.0)
After postoperative ERCP for retained stones	19 (6.8)
Stone size, median (IQR) (mm)	6.0 (5–8)
Transcystic removal[c]	5.0 (4–7)
Transcholedochal removal	8.0 (5.7–11.3)
Stone number, median (IQR)	2 (1–3)
Transcystic removal	1 (1–3)
Transcholedochal removal	2 (1–4)

[a] Adhesions, chronic inflammation, Mirizzi syndrome

[b] No perforation found at exploration

[c] Transcystic versus transcholedochal, $p < 0.001$

Results

Baseline characteristics of the 279 patients are shown in Table 1. The diagnostic work-up included preoperative MRCP in 153 (54.8 %), intraoperative cholangiography in 259 patients (92.8 %), and choledochoscopy in all patients. In addition, preoperative ERCP with CBD stone removal was done in 27 patients (9.7 %) still having CBD stones at the time of LC. Biliary pain was the most common presenting symptom (81.7 %) followed by jaundice (21.9 %), signs of acute cholecystitis (13.3 %), and history of previous biliary pancreatitis (10.4 %). Histopathological findings of the gallbladder are shown in Table 1.

Intraoperative data are shown in Table 2. Common bile duct exploration was performed via the cystic duct in 177 of the 279 patients (63.4 %) and through a choledochotomy in 102 patients (36.6 %). Conversion to open surgery was necessary in 37 patients (13.3 %) because of failed

Table 3 Short-term outcome ($N = 279$)

30-day mortality, *n* (%)[a]	1 (0.3)
30-day overall morbidity, *n* (%)	34 (12.2)
General	16 (5.7)
Myocardial infarction	1 (0.4)
Heart insufficiency	2 (0.7)
Asthma worsening	1 (0.4)
Atelectasis	2 (0.7)
Renal insufficiency	1 (0.4)
Urinary tract infection	3 (1.1)
Postoperative dizziness	1 (0.4)
Fever, unknown origin	5 (1.8)
Surgical	18 (6.5)
Sepsis (Clostridium. perfringens)	1 (0.4)
Bile leak[b]	7 (2.5)
Hemorrhage	3 (1.1)
Trocar site hernia	2 (0.7)
Abscess	2 (0.7)
Wound infection	3 (1.1)
Dindo-Clavien severity grade IIIb-V, *n* (%)	12 (4.3)
Reoperations, *n* (%)	3 (1.1)
Readmissions, *n* (%)	1 (0.4)
Postoperative stay, median (IQR) d	3 (2–5)
Transcystic method[c]	2 (1–3)
Transcholedochal method	4 (3–7)
postoperative ERCP	28 (10.0)
Retained stones	19 (6.8)
Bile leak	4 (1.4)
Bile duct stricture	1 (0.36)
Suspicion of residual stones	4(1.43)

[a] Severe Clostridium Perfringens sepsis

[b] Bile leak: ERCP and stenting 4, reoperation and T-tube 2, prolonged T-tube drainage 1

[c] Transcystic versus transcholedochal $p < 0.001$

laparoscopic stone clearance in 13 patients (35.1 %) and other causes (64.9 %) making the laparoscopic operation difficult (Table 2). In the emergency operations, the conversion rate to open surgery was significantly higher than conversion in the elective operations: 29.7 % (11 of 37 patients) versus 10.7 % (26 of 242 patients), $p = 0.005$, the main reason being difficult or unclear anatomy. Short-term outcome is shown in Table 3.

Success of laparoscopic CBD stone removal

Successful laparoscopic CBD stone clearance was achieved in 232 of the 279 (83.2 %) patients, and after conversion to open surgery in additional 28 patients with an overall success rate of 93.2 % for one-stage procedure. In elective operations, laparoscopic CBD stone clearance was successful in 206 of the 242 patients (85.1 %) and in emergency operations in 26 of the 37 patients (70.3 %), $p = 0.025$, and after conversion to open surgery in 93.8 versus 89.2 %, $p = 0.300$. T-tube was inserted in 57 patients. Retained stones after surgery were found in 19 of 279 patients (6.8 %) either by postoperative T-tube cholangiography in 10 patients (3.6 %) or ERCP in 9 patients (3.2 %). On multivariate analysis, the independent factors associated with a failed laparoscopic stone clearance were stone size over 7 mm [OR 3.51 (95 % CI 1.53–8.03), $p = 0.003$], difficult anatomy [OR 18.01 (5.03–64.49), $p < 0.001$], and transcholededochal approach [OR 2.98 (1.37 to 4.47), $p = 0.006$]. Laparoscopic CBD stone removal also failed in all 11 patients having impacted stones at the ampulla of Vater. All retained stones were removed by ERCP.

Postoperative ERCP was also performed in additional nine patients to confirm the complete clearance of CBD (four patients), and to treat bile leak (four patients) or to dilate a CBD stricture (one patient).

Long-term outcome

Long-term outcome data were available in 259 of 279 patients (response rate 92.8 %) having a median follow-up time 5.1 years (IQR 2.9–7.8 years). Of the 279 patients, 19 patients had died of the following reasons: coronary heart disease (10), pneumonia (3), ovarian cancer (1), herpes encephalitis (1), traffic accident (1), colon cancer (1), sepsis of unknown origin (1), and gallbladder cancer (1) in an 80-year-elderly patient having comorbid conditions and a with an incidental finding of T2 gallbladder cancer in the histopathological examination. One CBD stricture was observed during the index operation and was successfully treated with ERCP and balloon dilatation. The crude incidence of recurrent stones was 3.5 % (9 of 259 patients: one patient had cholangitis and 8 other had biliary pain with elevated liver tests). Recurrent ductal stones were verified with MRCP and successfully removed by ERCP. The cumulative 5-year and 10-year recurrence rates of CBD stones was 3.6 % (95 %CI 1.8–7.3 %) at 5 years and 6.0 % (2.5–14.0 %) at 10 years (Fig. 1). Median time to recurrence was 1.4 years (IQR 1.0–4.2 years).

Secondary outcome measures

The 30-day morbidity was 12.2 %: surgical complications occurred in 18 patients (6.5 %) and general complications in 16 patients (5.7 %). There were no ERCP-related complications. Reoperation was done in 3 (1.1 %) patients: 2 for bile leak and 1 for hemorrhage. Severe (Dindo-Clavien IIIb-V) complications were observed in 12 patients (4.3 %). Bile leaks were observed in 7 (2.5 %) patients. One 73 -year-old female patient died of Clostridium

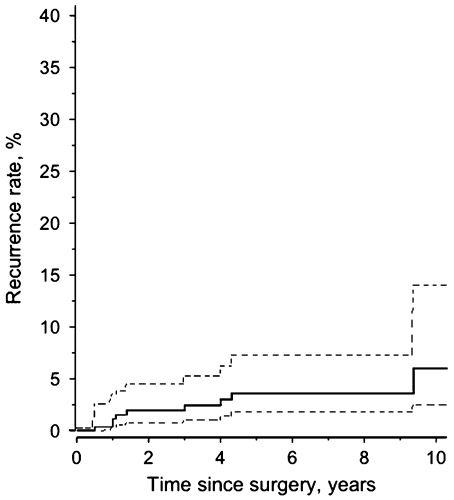

Fig. 1 Cumulative long-term recurrence rate of CBD stones. (95 % CI) 162 × 180 mm (72 × 72 DPI)

perfringens sepsis. Postoperative hospital stay was median 3 days (IQR 2–5): transcystic group 2 days (IQR 1–3) and choledochotomy group 4 days (IQR 3–7). $p < 0.001$. One patient was readmitted because of fever of unknown origin.

Discussion

The ideal treatment for CBD stones is still controversial [8]. At present, CBD stones are commonly managed with preoperative or postoperative ERCP although one-stage laparoscopic cholecystectomy combined with laparoscopic CBD stone clearance is increasingly reported in the literature. According to a recent meta-analysis and randomized controlled trials successful laparoscopic CBD stone clearance has been reported in 75–100 % of the patients with an associated morbidity from 11 to 43 % [9–15, 22, 23]. In line with that our success rate of CBD stone removal was 83.2 % after laparoscopy alone and 93.2 % after conversion to open surgery. This was achieved with low 30-day morbidity (12.2 %), reoperation (1.1 %) and readmission (0.4 %) rates, short hospital stay (median 3 days), and a low incidence of retained stones (6.8 %) which were removed by postoperative ERCP. Independent determinants for failed laparoscopic CBD stone removal were stone size ≥7 mm, transductal approach and difficult anatomy of the cystohepatic triangle due to adhesions, scarring, and fibrosis. Moreover, the success rate of laparoscopic CBD stone clearance was lower in the emergency operations than in the elective operations.

It is well known that the success or failure of laparoscopic CBD stone clearance is related to patient selection, surgeon's experience, and quality of surgery. Our conversion rate of 13.3 % is in agreement with previous studies reporting conversion rates from 3.5 to 25 % [9–13]. Of note, the main reasons for conversion in our study were severe adhesions and chronic inflammation in the cystohepatic triangle making laparoscopic surgery difficult. The high rate of acute and chronic cholecystitis in this study may explain the reason for conversion in the difficult anatomy group. Only 13 of the 37 patients (35.1 %) were converted because of an unsuccessful CBD removal. Patients with impacted stones at ampulla of Vater were all converted to open surgery because no mechanical, electrohydraulic, or laser lithotripsy was available. An improvement for CBD stone clearance has been reported when using electrohydraulic lithotripsy [24]. Moreover, it was our aim to do one-stage surgical procedure either laparoscopically or after conversion to avoid postoperative ERCPs, which also have a known morbidity and treatment failure rate [23].

Long-term ductal stone recurrence rates after laparoscopic CBD stone clearance are scantily reported in the literature [16, 17, 25, 26]. Our 5-year (3.6 %) and 10-year (6.0 %) recurrence rates compare favorably to previous long-term results reporting stone recurrence rates from 0 to 6.7 % [16, 17, 25, 26]. In comparison, long-term results after ERCP and ES have shown recurrent choledocholithiasis in 5.8–11 % [27–30]. Whether CBD stones detected after the index operation were retained or recurrent stones are uncertain. In our study retained CBD stones were diagnosed by a completion cholangiography and choledochoscopy during the index operation, and postoperative T-tube cholangiography or occasionally postoperative ERCP after surgery.

According to meta-analysis and randomized clinical trials [9–15, 22], the advantages of one-stage laparoscopic cholecystectomy and CBD stone clearance are a reduced number of total procedures, lower costs, shorter hospital stay, and similar morbidity and mortality when compared with 2-stage endo-laparoscopic approach [7, 23, 31–33]. In our series, the 30-day mortality and overall morbidity rates were low in agreement with previous studies [9–12, 15]. The number of major postoperative bile leaks (2.2 %) necessitating endoscopic ($N = 4$) or operative treatment ($N = 2$), as well as reoperation and readmission rates was very low. Similar outcomes and even greater bile leak rates have been published [13, 17, 24]. Thus, laparoscopic cholecystectomy combined with laparoscopic CBD stone clearance can be done without major risks in daily clinical practice. This finding is also supported by a large, Swedish population-based study comparing different management strategies for CBD stones during five decades [34].

Potential disadvantages of ERCP/ES include the risk of serious complications, costs, and the inconvenience of undergoing a subsequent laparoscopic cholecystectomy for gallbladder stones. Besides, about 2–15 % of patients who undergo preoperative ERCP and sphincterotomy have residual ductal stones at intraoperative cholangiogram as shown also here. Post-procedural mortality is <1 % and morbidity from 5 to 11 % including post-ERCP pancreatitis, duodenal perforation, sepsis, and bleeding [8]. Endoscopic sphincterotomy also causes bacterobilia in all patients and predisposes the CBD to the increased risk of recurrent bilirubinate stones in the long term. An advantage of surgical CBD exploration is that the sphincter anatomy is not distorted. Moreover, the incidence of postoperative pancreatitis after LCBDE is rare (0.4–0.5 %) [16, 25] and was here 0 %. Postoperative recovery after transcystic CBD stone clearance was similar to that reported after laparoscopic cholecystectomy alone [16, 35] and significantly shorter than after transcholedochal clearance.

A major challenge with this study and other similar studies was the lack of randomization which may have caused some selection bias. For logistic reasons, some patients with CBD stones, as well as elderly high-risk patients with comorbidities have been managed by 2-stage endo-laparoscopic approach instead of one-stage laparoscopic approach or by ERCP alone leaving the gallbladder in situ. The learning curve and evolving laparoscopic technique may have played a role as well. On the other hand, the long-term outcome was investigated in 259 of the 279 eligible patients. The compliance in this study compares favorably with earlier studies with some 93 % of the patients returning the questionnaire for long-term evaluation. The economical impact of laparoscopic CBD stone clearance compared to 2-stage endo-laparoscopic treatment remains to be analyzed in the future.

Conclusion

Our results show that laparoscopic cholecystectomy combined with laparoscopic CBD stone clearance is safe and effective method of treating CBD stones in most patients both in elective and emergency situations, thus reducing the number of additional, potentially dangerous endoscopic procedures. Moreover, large or impacted stones at the ampulla of Vater are risk factors for failed stone clearance.

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III

Cost analysis and effectiveness of one-stage versus two-stage endolaparoscopic treatment of cholecystocholedocholithiasis: a retrospective cohort study

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Cost-analysis and effectiveness of one-stage laparoscopic versus two-stage endolaparoscopic management of cholecystocholedocholithiasis: a retrospective cohort study

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Abstract

Background: One–stage laparoscopic common bile duct (CBD) stone clearance and laparoscopic cholecystectomy (LCBDE+LC) for cholecystocholedocholithiasis (CCL) can be performed with similar short and long-term outcomes than two-stage endoscopic retrograde cholangiography followed by subsequent LC (ERCP+LC). This study examined retrospectively the outcome and hospital costs of one-stage versus two-stage treatment of CBD stones.

Methods: From January 1999 and December 2014, 217 consecutive, elective patients underwent one-stage (LCBDE + LC) or two-stage (ERCP + subsequent LC) treatment for CBD stones. The data from the one-stage management was collected prospectively, and from the two-stage management retrospectively. The main measure of outcome was hospital costs, with the success of one-stage versus two-stage management, postoperative morbidity and postoperative stay as secondary outcome measures.

Results: One-stage laparoscopic transcystic management was the least costly option compared to laparoscopic one-stage transductal approach (TC 5455€ versus TD 9364, $p < 0.001$) or two-stage management (6913 €, $p = 0.02$). Overall success rate of primary intervention (including conversions to open surgery) for CBD stone clearance was 96.9%, 97.0% and 98.3% after transcystic one-stage, transductal one-stage and two-stage approach, $p = 0.79$. Postoperative morbidity was 15.5% versus 7.5%, $p = 0.64$, and postoperative hospital stay median 2 days (IQR 2–5) versus 4.5 days (IQR 3–7), $p < 0.001$ in the one-stage and two-stage management groups.

Conclusions: Our study shows that laparoscopic one-stage transcystic management of CCL results in high rate of CBD clearance, fewer procedures per patient, shorter hospital and lower costs than the two-stage management. Therefore the one-stage transcystic management seems to be an attractive strategy for the treatment of CCL depending on local resources and surgical expertise .

Keywords: Laparoscopy, Choledocholithiasis, Cost-analysis

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Background

CBD stones are commonly managed with pre-, intra or post-operative ERCP although laparoscopic common bile duct exploration (LCBDE) has gained wide acceptance over the last 20 years [1].

Current evidence demonstrates similar CBD stone clearance rate for LCBDE (75% -100%) and ERCP (62% -96%) [2–10].The advantages of LCBDE + LC include a reduced number of procedures and shorter hospital stay [3, 9, 10].

Two- stage treatment is currently the most commonly used strategy for of CCL. Costs of one-stage versus two-stage treatment of CBD stones, however, are scantily reported in the literature. Two randomized studies have reported in-hospital costs in favour of one –stage method [3, 10]. Non-randomized studies using propensity score or cost analysis have also shown lower total in-hospital costs for one-stage than for two-stage method [11–15].

In order to rationalize the treatment of CCL the aim of this study was to compare the success and costs of one-stage versus traditional two-stage management for CCL. Based on previous studies (3,10) our hypothesis was that the laparoscopic one-stage treatment is more cost-efficient, and is associated with an improved outcome and shorter hospital stay.

Methods

Finland offers its residents government-subsidised public-sector specialised healthcare. Central Hospital of Central Finland hospital is a university-affiliated secondary referral center, and the only hospital offering surgical and advanced endoscopic service in the catchment area of 276,000 inhabitants.

From January 1999 to December 2014, alltogether 217 consecutive, elective patients with gallbladder stones and concomitant CBD stones were treated in our hospital. The one-stage group consisted of 97 consecutive patients who underwent LCBD exploration and concomitant LC in elective setting, with preoperative or intraoperative confirmation of choledocholithiasis. The two-stage group consisted of 120 consecutive patients with CCL who underwent preoperative ERCP + ES followed by elective LC. The flow chart of patients is presented in Fig. 1. Excluded from the study were patients who were scheduled for emergency LC due to acute cholecystitis, patients considered unfit for surgery or those few who refused cholecystectomy after ERCP and EST, and patients needing urgent ERCP for acute cholangitis.

CBD stones were diagnosed on the basis of clinical, laboratory, ultrasonographic, intraoperative cholangiography (IOC), choledochoscopy and since 2002 preoperative magnetic resonance cholangiopancreaticography (MRCP) findings. Before the MRCP era ERCP was occasionally used to diagnose and treat CBD stones.

The main measure of outcome was hospital costs per patient including readmissions. The cost analysis was undertaken from the perspective of healthcare providers view. The secondary measures of outcome were the success of CBD clearance, 30-day morbidity, mortality and length of postoperative hospital stay. Preoperative and short term outcome data of the one-stage group were collected prospectively, and similar data of the two-stage group retrospectively from hospital records. Patients from both study groups were evenly distributed during the observation period. Long-term outcome was investigated retrospectively using a mailed, self-completed questionnaire about jaundice, diagnosis and treatment of

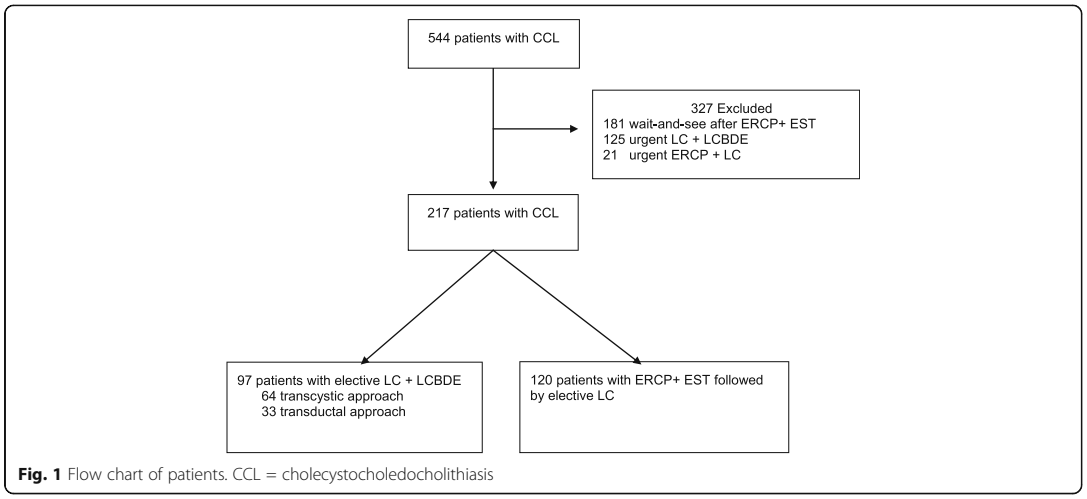

Fig. 1 Flow chart of patients. CCL = cholecystocholedocholithiasis

recurrent CBD stones as well as the date of diagnosis of recurrent stones. The causes of death were obtained from the National Cause of Death Registry. The study was approved by Ethics Committee of the Central Hospital of Central Finland. Informed consent was obtained from the prospective part of the study population. The need for informed consent from the retrospective patient cohort was waived. The aims and content of this study are in accordance with the Helsinki Declaration.

Surgical and endoscopic technique

The decision to do one-stage or two-stage procedure was made according to surgeons experience and preference. Technique of LCBD exploration has been described in previous publications [16, 17] . In the one-stage group the primary aim was to do transcystic CBD stone clearance, when feasible. Transductal approach was chosen for large stones (>7–8 mm), multiple stones, if the CBD stones were situated above the cystic duct junction, if the cystic junction was posterior, or if the TC approach failed. Conversion to open surgery was made, if the laparoscopic one-stage CBD stone clearance failed, to avoid postoperative ERCPs, which also have a known morbidity and treatment failure rate [18]. LCBD explorations and LC were performed by senior surgeons or residents under senior guidance. All ERCP procedures were performed by senior surgeons familiar with the procedure. Patients underwent EST and clearance of CBD with balloon or Dormia basket. Laser lithotripsy was not available. In the case of residual CBD stones after primary ERCP clearance, a plastic stent was introduced and a new ERCP was scheduled.

Cost analysis

Costs were calculated according to the year 2014 prices (€). Pre-existing data on some major resources and their allocated costs in 2014 were obtained from the hospital administration (Table 1). Costs of operative room resources (basic costs, anesthesia and nurses, surgical team, instrument use) and recovery room services were calculated according to the time spent in the operating and recovery rooms, duration of surgery, and the level of training required. The costs of disposable instruments including Dormia baskets, sphincterotomes, cannulas, extraction balloons, guidewires, stents, contrast agents, cholangiography catheters, trocars, drains, hemostatic agents, hemostatic sealing devices, and hemostatic clips for LCBD exploration in LC and ERCP were calculated according to the use. Excluded were costs of preoperative waiting time for the operation or ERCP, capital costs of reusable instruments, standard laparoscopic equipment, duodenoscopes, administration and societal costs. The correction coefficient of 0.82 for ERCP procedure price was based on the use of intravenous sedation without the presence of an anesthesiologist, permitting the ERCP time to be less costly than LC despite the same qualification of the attending surgeon.

Statistical analysis

The data are presented as means with standard deviations (SD) or as medians with interquartile range (IQR) or as counts with percentages. Statistical comparison between the study groups was made by independent T-test, Mann-Whitney U test, Chi-Square test, the analysis of variance (ANOVA) or Kruskal-Wallis test, when appropriate. As the data for costs were highly skewed, bias corrected and accelerated bootstrap estimation was used to derive 95% confidence intervals and differences between the means were tested by bootstrap- type ANOVA, and post hoc testing of several univariate comparisons were made with Hochberg's adjustment at significance level 0.05. The 95% confidence intervals (95%CI) are given for the most important outcomes. Statistical significance was defined as a p value <0.05. Statisical analyses were performed using SPSS statistical software (version 24.0 for Windows, SPSS Inc., Chicago IL, United States).

Results

The flow chart of the patients is shown in Fig. 1. Alltogether 97 patients underwent one-stage and 120 patients two-stage treatment for CCL in the elective setting. Baseline characteristics are shown in Table 2. Patients in the two-stage group were slightly older with male predominance. Elderly patients ≥75 years and ASA –scores were evenly distributed in the study groups.

Cost analysis

Overall, mean hospital costs per patient in the one-stage group were similar to the two-stage treatment group (6785 € versus 6913 €, $p = 0.806$) (Table 3). Additionally, when comparing patients with uncomplicated postprocedural course, the mean total costs were significantly lower in the one-stage group [5487 € (95% CI: 5164 € to 5809 €)] than in the two-stage group [6487 € (95% CI: 6019 € to 6956 €)], $p < 0.001$.

One-stage laparoscopic management using transcystic approach was the least costly option compared to laparoscopic one-stage transductal approach (TC 5455 € versus TD 9364 €, $p < 0.001$) or two-stage management (6913 €, $p = 0.02$) (Table 3). The per-patient operation room costs, postoperative expenses and readmission costs were lower in the one-stage transcystic group compared to one-stage transductal group. However, operation room and postoperative costs were similar, and readmission cost lower in two-stage treatment compared to one-stage laparoscopic transcystic treatment. Costs of disposable equipment were significantly higher in the

Table 1 Major resources and their allocated costs

	Units costs (€)	
1. Operating rooms costs		
Basic costs (cleaning,electricity,sterilization,etc.)	197.72	
Total operating room time for LC (1 anesthesiologist +3 nurses)	8.5	per min
Total operating room time for ERCP (3 nurses without anesthesiologist)	0.82 × 8.5	per min
Operating time for specialist surgeon (LC)	0.6045	per min
Operating time for resident surgeon (LC)	0.403	per min
Recovery room time (LC)	0.50	per min
ERCP time for specialist surgeon	0.6045	per min
Recovery room time (ERCP)	0.50	per min
Equipment for LC and ERCP[a]		
2. Postprocedural costs		
Surgical ward after LC and ERCP[b]	602.00	per day
Intensive care unit[b]	1973.00	per day
T-tube cholangiography	234.00	
CT	135.00	
MRCP	258.00	
US	102.00	
Reoperation price[c]		
ReERCP price[c]		
Histology analysis (gallbladder)	350	
3. Readmission		
Outpatient physician consultation	176	
Readmission to surgical ward	602.00	
T-tube cholangiography	234	
CT	135.00	
MRCP	258.00	
US	102.00	
Reoperation price[c]		
ReERCP price[c]		

ERCP Endoscopic retrograde cholangiopancreatography, *MRCP* Magnetic-resonance cholangiopancreatography, *CT* Computed tomography, *US* Ultrasound
[a]Disposable instruments
[b]Personnel and overhead costs of surgical ward/ intensive care unit included
[c]Calculated separately depending on total operating room costs (paragraph 1)

Table 2 Baseline characteristics

	One stage *N* = 97	Two stage *N* = 120	*P* value
Age, mean (SD) years	59.1 (19.0)	64.8 (15.3)	0.016
Age > 75, %	26 (26.8)	39 (32.5)	0.474
Male sex, n (%)	19 (19.6)	56 (46.7)	<0.001
BMI (kg/m^2), mean (SD)	26.3 (3.9)	27.3 (5.4)	0.131
ASA, n (%)			
I -II	71 (73.2)	90 (75.0)	0.763

Table 3 Mean differences (95% CI) in hospital costs between one-stage and two-stage groups

Costs	One-stage $N = 97$		Two-stage $N = 120$	P-value (Multiple comparison)*
	Transcystic (TC) $N = 46$ Mean (95% CI)	Transductal (TD) $N = 33$ Mean (95% CI)	ERCP + LC $N = 120$ Mean (95% CI)	
Operation room, €	2806 (2680 to 2931)	3191 (3006 to 3377)	3025 (2898 to 3151)	TC/ TD 0.013 TC/ Two 0.071 TD/ Two 0.438
Postoperative, €	2572 (2200 to 2944)	5835 (3580 to 8089)	3825 (3309 to 4342)	TC/ TD <0.001 TC/ Two 0.049 TD/ Two 0.08
Readmission, €	77 (38 to 192)	339 (6 to 672)	63 (4 to 121)	TC/ TD 0.048 TC/ Two 0.018 TD/ Two 0.997
Total costs, €	5455 (4971 to 5938)	9364 (7048 to 11,681)	6913 (6340 to 7486)	TC/ TD <0.001 TC/ Two 0.029 TD/ Two 0.02

CI Confidence interval, *TC* Transcystic, *TD* Transductal
*Bias- corrected and accelerated bootstrap estimation was used to derive 95% confidence intervals

two-stage group (739 €) compared to the one-stage group (526 €) due to a higher price of ERCP disposables, $p < 0.001$.

Effectiveness of one-stage versus two-stage management

Short term outcome is shown in Table 4. Overall success rate of primary intervention (including conversions to open surgery) for CBD stone clearance was 96.9%, 97.0% and 98.3% after one-stage transcystic, one-stage transductal and two-stage approaches, $p = 0.79$. Conversion rate to open surgery was similar in the two study groups: one-stage group 8.2% (inflammation or insufficient visualization of the cystohepatic triangle 3, impacted stone in the ampulla 3, suspicion of CBD perforation 1 and residual CBD stones 1), two-stage group 13.3% (adhesions 14, intra-operative bleeding 1, and impacted stone 1). T-tube was inserted in 22 of the 33 patients (66.7%) who underwent transcholedochal stone clearance. The median total operative time was significantly shorter in the two-stage group compared to the one-stage group, $p < 0.001$. The 30-day morbidity was similar in the two study groups, with no difference in severe (Dindo-Clavien IIIb-V) complications. One patient died in the one-stage group due to Clostridium perfringens-sepsis. Postoperative hospital stay was median 2 days (IQR 2–5) versus 4.5 days (IQR 3–7), $p < 0.001$ in the one-stage and two-stage management groups. Reoperation rates were 4.1% in the one-stage group (intra-abdominal sepsis 2, bile leak from choledochotomy site 1 and duodenotomy leak after removal of impacted ampullary CBD stone 1), and 0.8% in the two-stage group (postoperative hemorrhage 1). The 30-day readmission rate was significantly higher in the one-stage group (19.6%) than in the two-stage group (5.8%), $p = 0.002$, due to more frequent ambulatory T-tube removal,and postoperative ERCPs (stent removal, suspicion of residual CBD stones and cystic stump leakage). In the two-stage group reasons for readmissions were ambulatory T-tube removal, postoperative wound infection, ERP for residual CBD stone and intractable postoperative pain (Table 4).

Discussion

From a health economics point of view, two randomized trials from USA and India have demonstrated lower costs in the one-stage than in the two-stage management of CCL [3, 10] . This is in line to our study where transcystic approach resulted in lowest total costs. In the randomized trials [3, 10] patients had a good health status and younger age (median < 50 years) whereas in our study some 30% of the patients were older than 75 years and 25% of the patients had severe health problems (ASA III-IV), thus potentially increasing postoperative morbidity. It is well known that the clinical outcome and costs of surgery are dependant on surgeon's experience and the quality of treatment. Some evidence of reduced hospital costs of one-stage treatment compared to two-stage treatment has also been reported in patients having uneventful post-procedural recovery [19]. When patients with postoperative complications were excluded in our study, the mean total difference was −1000 € in favor of the one-stage management.

Previous randomized trials and meta-analyses have demonstrated the safety and efficacy of one-stage management for CCL with a success rate of 75% to 96.8%, and with an associated postoperative morbidity of 3.6% to 43.2% [2–8, 10, 20]. Overall success of two −stage management has been 61.7% to 94.6%, with an associated postoperative morbidity of 5.1% to 29.8% [2–4, 7, 8, 10]. Our overall success rate for CBD stone removal and postoperative morbidity after one-stage and two-stage management are in accordance with these results. This was achieved with apparently similar surgical and ERCP-related morbidity.

Table 4 Short-term (30-day) surgical outcome after one-stage and two-stage management

	One-stage *N* = 97		One-stage *N* = 97	Two-stage *N* = 120	*p*- value total one-stage vs two-stage
	TC approach *N* = 64	TD approach *N* = 33	Total		
Successful CBD stone clearance, n (%)					
LC + LCBDE /Index ERCP [a]	59 (92.2)	27(81.8)	86 (88.7)	102 (85.0)	0.66
After conversion to open surgery	3(4.7)	5 (15.2)	8 (8.2)	16 (13.3)	0.36
After ERCP for residual stones	2 (3.1)	1 (3.0)	3 (3.1)	2 (1.7)	0.15
Total operative time, median (IQR) min [b]	140 (69.3)	165 (52.5)	150 (61.0)	112 (64.0)	<0.001
30-d mortality, n (%) [c]	0 (0)	1 (3.0)	1 (1.0)	0 (0)	0.27
30-d overall morbidity, n(%) [d]	6 (9.4)	9 (27.2)	15 (15.5)	9 (7.5)	0.64
Surgical morbidity, n (%)	5(7.8)	4 (12.1)	9 (9.3)	5 (4.2)	0.13
Bile leak	2	3	5	0	
Postoperative bleeding	1	0	1	2	
Wound infection	1	0	1	1	
Intra-abdominal abscess	0	1	1	0	
Post-ERCP pancreatitis	1	0	1	0	
Bleeding after ERCP	0	0	0	2	
General morbidity, n (%)	1 (1.6)	5 (15.2)	6 (6.2)	5 (4.2)	0.50
Renal insufficiency	0	1	1	0	
Fever, unknown origin	0	0	0	1	
Vocal cord injury from intubation	0	1	1	0	
Myocardial infarction	0	0	0	1	
Heart insufficiency	1	0	1	1	
Pneumonia	0	3	3	2	
Dindo-Clavien gr IIIb-V, n (%)	2 (3.1)	3 (9.1)	5 (5.2)	2 (1.7)	0.25
Postoperative stay, median (IQR) days [b]	2 (1–3)	5 (2–8)	2 (2–5)	4.5 (3–7)	<0.001
Reoperation, n (%)	2 (3.1)	2 (6.1)	4 (4.1)	1 (0.8)	0.11
Readmission, n(%)	3 (4.7)	16 (48.5)	19 (19.6)	7 (5.8)	0.002

TC transcystic, *TD* transductal
[a]Two-stage group
[b]Two-stage: ERCP and LC time
[c]Clostridium perfringens sepsis
[d]Figures in the columns are not additive because some patients had more than one complication

Three of the 4 randomized trials reported longer total operative times in the two-stage management group [3, 7, 9, 10] in contrast to our study showing that one-stage management resulted in significantly longer operative time than the two-stage management. Conversion to transcholedochal approach after failed attempt of transcystic clearance increased the operative time in our study. Despite shorter total operative time in the two-stage management group, the operating room costs nested mainly from personnel expenditure of two separate procedures and disposable equipment used in ERCP.

Several studies have reported a significant reduction of hospital stay in patients receiving one-stage management compared with two-stage management of CBD stones [2–4, 7, 9, 10]. In accordance with these studies, the median postoperative hospital stay in our series was 2.5 days shorter in the one-stage group compared to the two-stage group. Postoperative hospital expenses originated mainly from basic surgical ward care accounting some 50% of the total costs of CBD stone management in both treatment groups. With this in mind, future efforts to improve hospital logistics and quality-of care are important to obtain shorter transit time and more profitable results. Accomplishing CBD stone treatment during single hospital visit should be a goal worth considering. Intraoperative ERCP (IOES) performed with rendez-vouz and assisted insertion of transcystic guidewire is considered as an improvement over standard ERCP techniques with lower rate of post-ERCP pancreatitis [21] So far, in randomised studies of one-stage management of CCL, only traditional IOES + LC versus

LCBDE + LC have been compared with controversial results [22–24] A limitation of IOES is the requirement of simultaneous endoscopy team performing ERCP during laparoscopy in the operating theatre.

The proportion of readmission costs within total expenses were higher in the transductal group mainly due to ambulatory T- removal. However, the use of T-tube was dramatically reduced after reports on the safety of choledochotomy closure without T-tube [25].

Limitations and possible biases in this study are the lack of randomization which may have caused some selection bias, and the small number of patients making the detection of small differences between the study groups unreliable. The study design was retrospective and therefore cost-analysis instead of cost-benefit analysis was undertaken. Capital costs of laparoscopic equipment were excluded because laparoscopic equipment is nowadays considered standard operating room equipment used in many different operations. Costs in the Finnish healthcare are not applicable to every country, since the pricing of goods and services vary between healthcare systems. However, the share-out of the one-stage and two-stage management costs reflects the relative distribution of expenses between the the one-stage and two-stage management. Also the success rate of laparoscopic CBD stone clearance and hospital stay are in line with previous studies, suggesting that the quality of surgery has been as good as elsewhere.

Conclusion

Our study shows that laparoscopic one-stage transcystic management of CCL results in high rate of CBD clearance, fewer procedures per patient, shorter hospital and lower costs than the two-stage management. Therefore the one-stage transcystic management seems to be an attractive strategy for the treatment of CCL depending on local resources and surgical expertise.

Abbreviations

CBD: Common bile duct; CCL: Cholecystocholedocholithiasis; CI: Confidence interval; ERCP: Endoscopic retrograde cholangiopancreatography; IOES: Intraoperative endoscopic sphincterotomy; LC: Laparoscopic cholecystectomy; LCBDE: Laparoscopic common bile duct exploration; OR: Operating room; TC: Transcystic; TD: Transductal

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None.

Authors ' contributions

AM, JM and IK designed the study. AM, JM and IK performed data acquisition and analysis. AM, JM and IK prepared the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by Ethics Committee of Central Hospital of Central Finland. Written informed consent was obtained from the prospective part of the study population. The need for informed consent from the retrospective patient cohort was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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IV

Expectant management of gallbladder stones after endoscopic removal of common bile duct stones

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Original Research

Expectant management of gallbladder stones after endoscopic removal of common bile duct stones

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HIGHLIGHTS

- Wait-and −see policy after endoscopic sphincterotomy can not be recommended as a standard treatment.
- Biliary-related events occur throughout the follow-up time.
- Short-term mortality after endoscopic sphincterotomy is mainly due to cholangitis.
- Long-term mortality is mostly non-biliary related.

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ABSTRACT

Background: Wait-and-see policy after endoscopic sphincterotomy (ES) for common bile duct (CBD) stones in patients with concomitant gallbladder stones may lead to recurrent biliary complications. The aim of this study was to assess the short and long-term results of wait-and-see policy in patients with intact gallbladder after endoscopic clearance of CBD stones.

Materials and methods: From January 1999 to December 2014 a total of 181 consecutive patients with intact gallbladder underwent ES for CBD stones. The main measures of outcome were long-term biliary complications, biliary related mortality, CBD stone recurrence and need for surgical interventions. Secondary outcomes were 30-day mortality and 30-day morbidity. Clinical data were retrospectively collected from hospital records and from the National Registry of Death.

Results: During the median follow-up of 3.9 years (IQR 1.6–6.6) late biliary complications were observed in 24 (13.8%) patients. Cumulative biliary related morbidity at 3 and 5 years was 7.6% and 10.8%, respectively. CBD stone recurrence was observed in 9 (5.2%) patients. On-demand cholecystectomy was performed in 6 (3.3%) patients. 30-day mortality was 3.9% and 30–day morbidity 9.4%. Overall cumulative mortality rate at 3 and 5 years after ES was 31.4% and 49.7%, respectively. Long-term biliary related mortality was 1.7%. No significant difference in long term complications or biliary mortality was observed between patients< 75 or ≥75 years of age.

Conclusion: Prophylactic cholecystectomy after ES has been shown to reduce mortality even in high-risk patients. In our series late biliary related mortality and morbidity were relatively low, because a considerable number of patients died from non-biliary related causes.However, most biliary-related events seem to occur evenly during the follow-up after ES. A prompt risk assesment and consideration of surgical treatment during index admission may prevent late biliary −related complications.

1. Introduction

Modern alternatives for CBD stone removal in patients with gallbladder stones include laparoscopic CBD exploration and stone removal at the time of surgery, or pre-, intra or postoperative ERCP together with LC [1]. Even in high-risk patients laparoscopic CBD clearance can be achieved efficiently, without an increase in complications and with fewer procedures per patient. However, some patients are thought to be high-risk candidates for surgery or refuse cholecystectomy. Therefore a wait-and-see policy, e.g. leaving the gallbladder in situ after endoscopic sphincterotomy (ES) for bile duct stones, is increasingly used in poor surgical candidates [2].

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Patients with expectant management after endoscopic clearance of CBD, however, are prone to adverse complications such as biliary pain, acute cholecystitis, cholangitis and pancreatitis. Randomized studies have shown that cholecystectomy after ES reduces biliary events from 21-47% to 2–7% when compared to wait-and-see policy [3–6]. Nearly half of the patients managed with wait-and see policy have to undergo a subsequent cholecystectomy or an additional ERCP due to frequent episodes of biliary pain, cholecystitis or recurrent bile duct stones. Moreover, conversion rate to open surgery may be higher in those patients needing emergency cholecystectomy after expectant management [5] Despite the fact that retrospective studies have been shown controversial results with high incidence of late biliary complications, in the elderly and high-risk surgical patients the expectant management has been seen as a safe option [7–11].

Elective cholecystectomy after a finding of choledocholithiasis is supported by many, and has been common strategy in our institution. From existing studies, the decision to perform cholecystectomy after endoscopic sphincterotomy in high-risk elderly patients appears to be somewhat subjective. We therefore set out to determine the fate and long-term outcome of patients having cholecystectomy deferral after endoscopic removal of common bile duct stones.

1.1. Patients and methods

From January 1999 to December 2014 181 patients with gallbladder stones and known CBD stones underwent ES and stone extraction without subsequent cholecystectomy in our institution which is the only hospital offering advanced endoscopic services for 276 000 inhabitants in the Central Finland Health Care District. The diagnosis of CBD stones was done by MRCP or ERCP. All 181 patients underwent endoscopic sphincterotomy and clearance of CBD with balloon or Dormia basket and mechanical lithotripsy, when appropriate. In case of unsuccessful CBD stone clearance during the first ERCP a subsequent ERCP was scheduled, often after placement of a biliary stent. Wait-and-see policy was selected if the patient refused the forthcoming cholecystectomy or was evaluated to be a high-risk patient for surgery. This decision was made by the consultant internist and operating surgeon and was based on physical and mental performance status, age and significant comorbidities. Patients with biliary tract or pancreatic malignancies were excluded.

The main measures of outcome were biliary complications, mortality, CBD stone recurrence and subsequent surgical interventions in the long-term, with 30-day mortality and morbidity as secondary outcome measures. The study was approved by hospital administration. Data were collected retrospectively from hospital records. The interval between the first ERCP and recurrent biliary symptoms, additional ERCPs, hospital readmission, complications, surgical interventions and causes of death were recorded. Biliary pain episodes not needing hospital readmission were not documented. Comorbid illnesses were calculated using Charlson Comorbidity Index and ASA score. Retained CBD stones and long-term complications were defined when biliary event occurred after 30 days from primary ERCP + ES.

Ethics approval was not sought as retrospective data were collected from hospital records and National Registry of Death. This study was reviewed according to guidelines from the Strengthening the Reporting of Observational Studies in Epidemiology [12].

1.2. Statistical analysis

The data are presented as means with standard deviations (SD), medians with interquartile range.

(IQR) or counts with percentages. Pearson's $\chi 2$ or Fisher's exact tests were used to compare frequencies, and Student's *t* and Mann-Whitney *U* tests were used for continuous variables.

The Kaplan-Meier method was used to calculate the cumulative long-term mortality and complication rate, and the differences between groups were compared with the log-rank test. Survival times were calculated from the date of ES until the time of death, long-term complication or the end of follow-up. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS statistical software.

2. Results

A total of 181 patients with a mean age of 79.6 ± 9.2 years underwent ERCP + ES for the treatment of CBD stones. Baseline characteristics are shown in Table 1. All patients had also gallbladder stones or sludge verified by ultrasound (US). Charlson Comorbidity Index (CCI) in patients <75 years was significantly lower [mean 3.9 (SD 2.8)] than in patients ≥75 years [mean 5.8 (SD 2.6)], p < 0.001. At the index admission all patients had biliary pain, 93 (51.4%) had jaundice or elevated liver enzymes, 34 (18.8%) biliary pancreatitis, 29 (16.0%) acute cholecystitis and 25 (13.8%) acute cholangitis. Diagnosis of CBD stones was performed with MRCP in 97 patients (53.6%), CT in 16 (8.8%) and US in 10 patients (5.5%). The remaining CBD stone detection was made during ERCP procedure. Endoscopic clearance was successful in 168 (92.8%) patients at first attempt and 13 (7.2%) patients had ≥2 ERCP procedures during 30–day time.

Table 1
Baseline demographic characteristics, n = 181.

Age, mean (SD) years	79.6 (9.2)
Gender male, n (%)	91 (50.3)
ASA I, n (%)	1 (0.6)
ASA II,n (%)	21 (11.6)
ASA III,n (%)	103 (56.9)
ASA IV,n (%)	56 (30.9)
Charlson Comorbidity Index, mean (SD)	5.4 (2.8)
Comorbidity, n (%)[a]	168 (92.8)
Cardiovascular	121 (66.9)
Neurologic	68 (37.6)
Hypertension	64 (35.4)
Pulmonary	34 (18.8)
Diabetes	30 (16.6)
Renal	10 (5.5)
Liver	6 (3.3)
Other	59 (32.6)

[a] Figures in the columns are not additive because some patients had more than one symptom.

Table 2
30-day mortality and morbidity after endoscopic sphincterotomy, n = 181.

30-d mortality, n (%)	7 (3.87)
Cholangitis and sepsis	4 (2.21)
Myocardial infarction	2 (1.10)
Post ERCP bleeding	1 (0.55)
30-d morbidity, n (%)	17 (9.4)
Residual CBD stones, n (%)	10 (5.5)
Pancreatitis, n (%)	3 (1.66)
Post ERCP bleeding, n (%)	3 (1.66)
Retroperitoneal perforation, n (%)	1 (0.55)
Clavien-Dindo complications, n (%)	24 (13.3)
Gr I	1 (0.55)
Gr II	3 (1.66)
Gr IIIa	12 (6.6)
Gr IIIb	1 (0.55)
Gr IVa	0 (0)
Gr IVb	0 (0)
Gr V	7 (3.87)

Table 3
Long-term biliary complications.

	All (n = 174)[a]	Young group <75 years (n = 40)	Elderly group ≥75years (n = 134)
Long-term complication, n (%)	24 (13.8)	8 (20.0)	16 (11.94)
Acute cholecystitis, n (%)	10 (5.75)	4 (10.0)	6 (4.48)
Recurrent CBD stones, n (%)	9 (5.17)	1 (2.5)	8 (5.97)
"sine materia" cholangitis, n (%)[b]	2 (1.15)	1 (2.5)	1 (0.74)
Acute biliary pancreatitis, n (%)	2 (1.15)	2 (5.0)	0 (0)
Gallstone ileus, n (%)	1 (0.57)	0 (0)	1 (0.74)
Biliary related mortality, n (%)	3 (1.72)	0 (0)	3 (2.24)

[a] Without 30-day mortality (n = 7).
[b] Cholangitis without evidence of stones or sludge.

2.1. Short-term complications

Thirty-day morbidity and mortality after ERCP and ES are shown in Table 2. Four patients died due to conditions related to severe complications of gallstone disease and two patients due to heart failure. One ES-related death from sphincterotomy site bleeding occurred in the immediate follow-up time. Seven (3.9%) patients developed complications after endoscopic sphincterotomy (haemorrhage, pancreatitis or retroperitoneal perforation), but were all managed conservatively. Residual CBD stones were treated with repeat ERCP. The reasons for deferral of cholecystectomy were poor surgical candidate for surgery in 158 (87.3%) and patient refusal in 23 (12.7%) patients. Intensive Care Unit treatment during index admission was needed in 6 (3.3%) patients (see Table 3).

2.2. Long-term mortality and biliary complications

The median follow-up time was 3.9 (IQR 1.6–6.6) years. During the follow-up 112 (61.9%) of the 181 patients died. Overall cumulative mortality rate at 3 and 5 years after ES was 31.4% and 49.7%, respectively (Fig. 1). Mortality after 30 days was observed for following reasons; heart disease in 60, cerebrovascular disease in 20, non-biliary malignancy in 10,non-biliary sepsis in 4, pulmonary in 4, trauma in 2, liver cirrhosis from alcohol etiology in 2, acute cholecystitis in 2 and acute cholangitis in 1 patient. Thus, long-term biliary related mortality was observed in 3 patients (1.7%). These patients had severe comorbidity with ASA grade 4 and after preoperative risk evaluation the treatment strategy was conservative with antibiotics only.

Late biliary complications were observed in 24 (13.8%) of the 174 patients. The late cumulative biliary related morbidity at 3 and 5 years was 7.6% and 10.8%, respectively (Fig. 2). No significant differences were observed in total long term complications between patients <75 or ≥75 years of age, p = 0.458. During follow-up 17 (9.8%) interventions were performed with no related mortality. On demand cholecystectomy for recurrent biliary pain or cholecystitis was performed in 7 (4.0%) patients; LC in 3, LC with conversion to open procedure in 2 and open cholecystectomy in 2 patients. Intraoperative cholangiography revealed recurrent CBD stones in one patient. No major intra-or postoperative complications occurred in cholecystectomized patients. Percutaneous cholecystostomy was required in one patient with significant comorbidity. Conservative treatment with antibiotics for acute cholecystitis was chosen in 6 patients. Nine patients (5.2%) underwent additional ERCP and CBD clearance for recurrent bile duct stones. Patients with additional ERCPs were all managed without

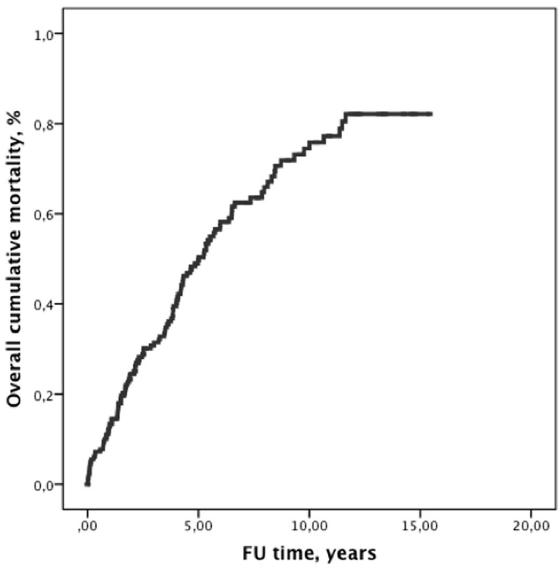

Fig. 1. Overall cumulative mortality.

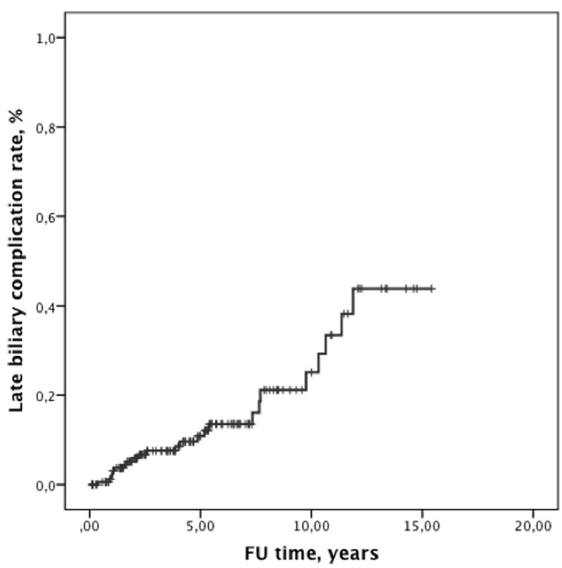

Fig. 2. Late biliary complications.

further cholecystectomy. One fragile patient (77 years)with gallstone ileus was operated 1 year after ES by enterolithotomy.

3. Discussion

Our results show that late biliary complication rate is relatively low in patients having undergone endoscopic clearance of CBD stones, and managed expectantly with regard to gallbladder stones. Our findings are in agreement with retrospective studies describing a similar low incidence (7.4–11%) of biliary events in elderly patients who do not have routine cholecystectomy after endoscopic bile duct stone clearance [10,11,13]. In our study, however, episodes of biliary pain were not assessed in contrast to a randomized study demonstrating episodes of biliary pain in 31% of expectantly managed patients [5]. Moreover, a significant number of our patients died for non-biliary related causes during the follow-up which may explain the low rate of long-term biliary related mortality and morbidity. Relatively high overall mortality was related to high amount of underlying comorbidity in the patients over 75 years of age ($p < 0.001$).

The incidence of acute cholecystitis in the wait-and −see arm of randomized trials has been from 5.6 to 12%, and further on-demand cholecystectomy has been done in 13.5%–36% patients [4–6]. In our study the occurrence of acute cholecystitis and our on demand cholecystectomy rate were low. However, the conversion rate to open surgery was 29%, the reason being severe adhesions and chronic inflammation in the triangle of Calot. In randomized trials the conversion rate has varied from 50% to 55% in patients treated initially with wait-and −see policy in contrast to 20% in those undergoing immediate LC after ES. These conversions were related to complicated gallstone disease itself leading to inflammation of the hepatoduodenal triangle [5,6].

Retained CBD stones after first ERCP were detected in 10 (5.5%) patients. Suc et al. found 16% incidence of retained CBD stones in their randomized trial [14]. The long-term recurrence of CBD stones after ES is reported to be 10–18% [5,6]. In our study the incidence of long-term recurrent biliary stones (5.0%) is well acceptable. In RCTs [10,11] most biliary related events seemed to occur shortly after the ERCP and endoscopic sphincterotomy, in contrast to our study where biliary-related events occurred evenly in the course of time after endoscopic sphincterotomy. Short-term ERCP complications occur in 5–11% of patients undergoing ERCP and endoscopic removal of CBD stones including pancreatitis, duodenal perforation, sepsis and bleeding [1]. Immediate mortality after ES in randomized trials has been between 0 and 6% [4,5,14]. In our study 30–day post-ERCP mortality was 3.9%, mainly due to underlying cardiac illness or severe cholangitis, and ERCP contributed to only one death. Our 30-day post-ERCP morbidity (9.9%) was in line with RCTs demonstrating post-ERCP morbidity rates of 5.6%–10% [5,6].

The incidence of recurrent biliary pancreatitis has been between 0 and 10% in RCTs of wait-and-see policy [5,6,14], and was 1.1% in our study. Cholangitis has been reported to be a significant long-term complication after ES. However, it is not necessarily linked to the formation of recurrent CBD stones but can occur as a sine materia cholangitis [13,15]. Previous studies have not shown any convincing evidence of increased risk of biliary carcinogenesis after ES [16]. Also, we did not observe any biliary malignancies during our median 3.9-year follow up time.

Some important limitations of this study must be acknowledged. A major challenge with this study is its retrospective nature. In addition, many patients died for non-biliary related causes resulting in lower than expected rate of late biliary complications. Minor biliary pain episodes not necessitating hospital readmission were not registered as long-term biliary complication, because some patients may have been treated in health care centers without contact to hospital. Also the selection of patients for expectant management (wait-and −see) may be somewhat subjective. Due to the evolvement of laparoscopic techniques even high-risk patients cn be efficiently treated with laparoscopic CBD clearance without majorly increase in complications and with fewer procedures per patient [1,17,18].

4. Conclusion

Biliary-related events occur evenly after endoscopic sphincterotomy. Prophylactic cholecystectomy after ES has been shown to reduce mortality even in high-risk patients [2]. With this in mind, wait-and-see policy after ES can not be routinely recommended as a standard treatment for CBD stones. For this reason, a more prompt surgical approach with two-stage endoscopic CBD clearance followed by LC or one stage LC + laparoscopic CBD clearance should be implemented after careful risk assessment.

Ethical approval

No ethical approval was needed because the study was retrospective in nature.

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None.

Author contribution

Anne Mattila: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Johanna Mrena: Participated substantially in the drafting and editing of the manuscript.

Ilmo Kellokumpu: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Conflicts of interest

None.

Trail registry number

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Concomitant gallbladder and common bile duct stones can be operated by laparoscopic one-stage procedure. The aims of this study were to assess the outcomes of day-care laparoscopic cholecystectomy comparing ultrasonic versus diathermy dissection methods, and to examine the success and the costs of different treatment options of concomitant gallbladder and common bile duct stones in the short-and long-term.

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