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CONTROVERSIAL ISSUES AND NEW TRENDS IN ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY

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To Markus and Maria

ABSTRACT

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Controversial issues and new trends in elective laparoscopic cholecystectomy

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Aims: The incidence of bile duct injuries (BDI) and symptomatic residual bile duct stones in patients undergoing elective laparoscopic cholecystectomy (LC) without routine use of intraoperative cholangiography (IOC) were studied. The appropriateness and long-term results of elective LC in the treatment of gallstone disease in the elderly patients were analyzed. The rate of abdominal symptom persistence after elective LC along with its dependence from preoperative symptom severity in uncomplicated gallstone patients was clarified. In addition, the feasibility and applicability of single incision laparoscopic cholecystectomy (SILC) in small-volume community hospitals were assessed.

Patients and methods: Patient records of all 1,101 patients (mean age 53 years, range 15 - 89 years, 874 females and 227 males) who had elective LC for gallstone disease in Turku City Hospital for Surgery between 1992 - 2001 were retrospectively studied. Data concerning long-term outcomes were obtained with questionnaire sent to the available patients in 2004. Short- and long-term results of elderly patients (age ≥ 75 years, n = 80) were compared with the two younger age groups (< 65 years and 65 - 74 years, n = 80 in each). Recurrence rates of abdominal symptoms in patients who have had uncomplicated gallstone disease with severe (n = 380) and mild (n = 287) preoperative symptoms, were compared. The details and outcome of SILC in 51 consecutive patients were recorded and analyzed.

Results: The incidence of BDIs was 0.5% (n = 5) and symptomatic residual bile duct stones 0.9% (n = 10). The mean hospitalization time and the rate of complications increased with the age of the patients. Eighty percent of patients aged ≥ 75 years were satisfied or very satisfied with the long-term results of the procedure. Thirty-seven percent of patients continued to have abdominal symptoms postoperatively (41% of patients with mild preoperative symptoms and 33% with severe symptoms, p = 0.052). Eighty-two percent of SILCs succeeded without conversion to multi-port or open surgery. No major intra- or postoperative complications occurred in SILC patients, but 10% of patients had postoperative wound infection.

Conclusions: Both the incidence of BDIs and symptomatic postoperative bile duct stones remain low without the routine use of IOC. Also in elderly, elective LC seems safe and feasible operation with good long-term results. More than one third of the patients with uncomplicated gallstone disease experienced persistent symptoms after elective LC. Patients with mild preoperative symptoms may have more recurrences. SILC can be adopted without major complications in small-volume hospitals but the rate of wound infections seems to increase with the introduction of SILC.

Keywords: Bile duct injury; Elderly; Gallstone disease; Intraoperative cholangiography; Laparoscopic cholecystectomy; Pain; Single incision laparoscopic surgery

TIIVISTELMÄ

Sven Lill

Kiistanalaisia kysymyksiä ja uusia suuntauksia elektiivisessä sappirakon tähystysleikkauksessa

Turun Yliopisto, Lääketieteellinen tiedekunta, Kirurgian oppiaine, Vatsaelinkirurgian osasto, Turun yliopiston kliininen tohtoriohjelma, Turun yliopistollinen keskussairaala, Turku, Suomi

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Tavoitteet: Tutkimuksessa selvitettiin sappitievaurioiden ja oireisten sappitiehyeiden jäännöskivien esiintyvyyttä potilailla, joille elektiivinen laparoskooppinen kolekystektomia oli tehty ilman rutiininomaista leikkauksenaikaista kolangiografiaa. Tutkimuksessa analysoitiin myös elektiivisen laparoskooppisen kolekystektomian soveltuvuutta ja pitkäaikaistuloksia iäkkäiden potilaiden sappikivitaudin hoidossa. Sen lisäksi selvitettiin vatsan alueen oireiden uusiutumista komplisoitumatonta sappikivitautia sairastavilla potilailla elektiivisen laparoskooppisen kolekystektomian jälkeen. Lisäksi, tutkimuksessa arvioitiin yhden portin kautta tehtävän laparoskooppisen kolekystektomian käyttökelpoisuutta ja sovellettavuutta aluesairaaloissa.
Aineisto ja menetelmät: Tähän retrospektiiviseen tutkimukseen otettiin mukaan kaikki 1101 potilasta (keski-ikä 53 vuotta, vaihteluväli 15 - 89 vuotta, 874 naista ja 227 miestä), joiden sappikivitautia oli hoidettu elektiivisellä laparoskooppisella kolekystektomialla Turun kaupungin Kirurgisessa sairaalassa vuosina 1992 - 2001. Toimenpiteen pitkäaikaistuloksia selvitettiin vuonna 2004 lähetetyllä kyselyllä. Iäkkäämpien potilaiden (ikä $\geq$ 75 vuotta, n = 80) lyhyt- ja pitkäaikaistuloksia verrattiin kahteen nuorempaan ikäryhmään (ikä < 65 vuotta ja ikä 65 - 74 vuotta, n = 80 molemmissa ryhmissä). Komplisoitumatonta sappikivitautia sairastaneiden potilaiden vatsaoireiden uusiutumista sappileikkauksen jälkeen selvitettiin vertaamalla kahta potilasryhmää, joista toisessa ryhmässä leikkausta edeltäneet oireet olivat olleet voimakkaita (n = 380) ja toisessa lieviä (n = 278). Yhden portin kautta tehtävän laparoskooppisen kolekystektomian hoitotuloksia selvitettiin yksityiskohtaisesti 51:n peräkkäisen potilaan otoksella.
Tulokset: Sappitievaurioiden esiintyvyys tutkimusryhmässä oli 0.5% (n = 5) ja oireisten sappitiehyeiden jäännöskivien esiintyvyys oli 0.9% (n = 10). Iäkkäämmillä potilailla keskimääräinen sairaalassaoloaika oli pidempi sekä komplikaatioiden määrä suurempi. Kuitenkin 75 vuoden ikäisistä tai sitä vanhemmista potilaista 80% oli tyytyväisiä tai erittäin tyytyväisiä toimenpiteen pitkäaikaistulokseen. Komplisoitumatonta sappikivitautia sairastaneilla potilailla vatsaoireet jatkuivat sappileikkauksen jälkeen 37%:lla potilaista (leikkausta edeltävästi lieviä tai voimakkaita oireita kokeneiden potilasryhmien välillä ei ollut tilastollista eroa). Yhden portin tekniikalla aloitetuista leikkauksista 82% onnistuttiin toteuttamaan ilman lisäporttien laittamista tai konversiota avoleikkaukseksi. Yhden portin menetelmällä hoidetuilla potilailla ei esiintynyt vakavia leikkauksenaikaisia tai leikkauksen jälkeisiä komplikaatioita, mutta 10%:lla näistä potilaista todettiin leikkauksen jälkeinen haavainfektio.
Johtopäätökset: Sekä sappitievaurioiden että leikkauksen jälkeisten oireisten sappitiehyeiden jäännöskivien esiintyvyys pysyvät alhaisina ilman rutiininomaista leikkauksenaikaista kolangiografiaa. Iäkkäillä potilailla laparoskooppinen kolekystektomia vaikuttaa turvalliselta ja käyttökelpoiselta toimenpiteeltä, jolla saavutetaan myös hyvät pitkäaikaistulokset. Komplisoitumatonta sappikivitautia sairastavista yli kolmasosalla vatsaoireet eivät häviä elektiivisen sappileikkauksen jälkeen. Pysyviä oireita saattaa esiintyä enemmän potilailla, joilla

leikkausta edeltävät vatsaoireet ovat olleet enimmäkseen lieviä. Yhden portin kautta tehtävä laparoskooppinen kolekystektomia soveltuu käytettäväksi aluesairaaloissa, eikä menetelmän käyttöönottoon liity vaikeita komplikaatioita vaikkakin haavainfektioiden määrä tuntui yhden portin tekniikka käytettäessä kasvavan.

Avainsanat: Intraoperatiivinen kolangiografia; Iäkkäät; Kipu; Laparoskooppinen kolekystektomia; Sappikivitauti; Sappitievaurio; Yhden portin laparoskopia

TABLE OF CONTENTS

ABBREVIATIONS

ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASA	American Society of Anesthesiologists
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BDI	bile duct injury
BMI	body mass index
CBD	common bile duct
CT	computed tomography
ERCP	endoscopic retrograde cholangiopancreatography
ES	endoscopic sphincterotomy
ESWL	extra-corporeal shock wave lithotripsy
EUS	endoscopic ultrasonography
GBC	gallbladder cancer
GGT	gamma glutamyl transferase
IOC	intraoperative cholangiography
LC	laparoscopic cholecystectomy
LFT	liver function tests
MRCP	magnetic resonance cholangiopancreatography
MS	Mirizzi syndrome
NIRF-C	near-infrared fluorescence cholangiography
NOTES	natural orifice transluminal endoscopic surgery
OC	open cholecystectomy
PGB	porcelain gallbladder
PPV	positive predictive value
PSC	primary sclerosing cholangitis
PTBD	percutaneous transhepatic biliary drainage
RCT	randomized controlled trial
SILC	single incision laparoscopic cholecystectomy
SILS	single incision laparoscopic surgery
TEM	transanal endoscopic microsurgery
TSIH	trocar site incisional hernia
TV	transvaginal

US	ultrasonography
^{18}F-FDG PET/CT	^{18}F-fluorodeoxyglycose positron emission tomography/computed tomography

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numerals I-IV.

I Lill S, Rantala A, Pekkala E, Sarparanta H, Huhtinen H, Rautava P, Grönroos JM. Elective laparoscopic cholecystectomy without routine intraoperative cholangiography: a retrospective analysis of 1101 consecutive cases. Scand J Surg 2010; 99(4): 197-200

II Lill S, Rantala A, Vahlberg T, Grönroos JM. Elective laparoscopic cholecystectomy: the effect of age on conversions, complications and long-term results. Dig Surg 2011; 28(3): 205-9

III Lill S, Karvonen J, Hämäläinen M, Falenius V, Rantala A, Grönroos JM, Ovaska J. Adoption of single incision laparoscopic cholecystectomy in small-volume hospitals: initial experiences of 51 consecutive procedures. Scand J Surg 2011; 100(3): 164-8

IV Lill S, Rantala A, Karvonen J, Pölönen T, Grönroos JM. Elective laparoscopic cholecystectomy for symptomatic uncomplicated gallstone disease: do the symptoms disappear? Surg Endosc 2014; 28(6): 1816-20

1 INTRODUCTION

Laparoscopic cholecystectomy (LC) is the most common abdominal operation in western world; in Scandinavia the annual rate of LC varies between 60 and 140 per 100,000 inhabitants (Mjäland, Adamsen et al. 1998, Rosenmüller, Haapamäki et al. 2007). In Finland about 8,500 patients have LC annually, and 75% of the operated patients are of working age between 18 and 65 years (Paajanen and Mäkisalo 2012). Although the overall complication rate of LC is not high (3 - 5%), considering the large number of the operations, every measure, which helps to reduce the rate of complications or facilitates postoperative recovery, has a considerable socio-economic impact. Likewise, abandoning unnecessary technical steps of the procedure and, moreover, avoiding unnecessary operations help to reduce the health care costs.

Symptomatic gallstone disease is considered an indication for cholecystectomy. However, the diagnosis of symptomatic gallstones is dubious as connection between gallstones and abdominal symptoms remains largely obscure (Glambek, Arnesjø et al. 1989, Jørgensen 1989). Consequently, considerable proportion of patients experience persistence of abdominal symptoms postoperatively (Luman, Adams et al. 1996, Berger, Olde Hartman et al. 2003). So far, there are no tools for predicting the putative benefit of cholecystectomy for a particular gallstone patient. Therefore, the severity rather than nature of patient′s symptoms remains often one of the key factors in clinical decision making whether to proceed to cholecystectomy although no scientific evidence on this issue exists.

According to the web pages of Statistics Finland, the proportion of the elderly (aged > 75 years) of the Finnish population will grow two-fold during the next quarter century (Statistics Finland 2012). Since gallstone disease is the most common cause of acute abdomen in the elderly, the appropriate treatment modality of gallstones is of utmost importance in this patient population and remains perhaps the most common clinical problem in geriatric digestive surgery (Bingener, Richards et al. 2003, Weber 2003). Although at present LC is the treatment of choice for gallstone disease, its appropriateness and long-term results in elderly patients need further evaluation.

Before the laparoscopic era intraoperative cholangiography (IOC) was generally considered a fundamental step in cholecystectomy. However, with the advent of LC, the routine use of IOC decreased yet almost a quarter century later the role of routine IOC in LC is still controversial (Richardson, Bell et al. 1996, Sheffield, Riall et al. 2013). Proponents of routine IOC argue that it reduces the rate and severity of bile duct injuries (BDI), facilitates early recognition and repair of such an injury and enables to detect unsuspected common bile duct (CBD) stones (Vezakis, Davides et al. 2000, Ludwig, Bernhardt et al. 2002). On the other hand,

evidence is inconsistent regarding those arguments and moreover, IOC prolongs surgery, increases cost of the procedure and, in false positives, leads to unnecessary CBD explorations (Metcalfe, Ong et al. 2004). Opponents of routine IOC claim that safe LC can be performed without routine IOC (Akolekar, Nixon et al. 2009).

Due to its less invasiveness LC has replaced open cholecystectomy (OC) in the treatment of gallstone disease. In recent years, a search for even more minimally invasive approaches has led to innovative techniques of single incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES). While substantial drawbacks of NOTES technique, including transgression of sensitive mucosal barriers and walls of hollow viscera, technical challenges and scarcity of instrumentation, have limited its adoption so far, the SILS has met more favorable acceptance in surgical community (Tomikawa, Xu et al. 2010). Its feasibility and safety have been tested in a number of surgical procedures including cholecystectomy (Ahmed, Wang et al. 2011, Antoniou, Pointner et al. 2011). Compared to conventional LC, which is performed via three or four abdominal ports, the single incision laparoscopic cholecystectomy (SILC) is performed using only one transumbilical entry into the abdominal cavity. Diminishing the number of ports to only one seems attractive due to its potential to reduce wound related complications, to decrease postoperative pain and to improve cosmetic outcome.

The current research ascertains the rate of symptom persistence after elective LC performed for symptomatic uncomplicated gallstone disease and, in particular, clarifies whether the recurrence rate differs in accordance with the severity of preoperative symptoms. Nowadays when proportion of elderly patients in population grows, present research adds the knowledge of the overall results and potential problems of the elective LC specific to the aged patients. In addition, the results of the current research herein challenge the routine use of complex, time consuming and sometimes inaccurate exploring of bile ducts with contrast media (i.e. IOC) in elective LC. Further, the current research explores feasibility of SILC and its applicability in small-volume community hospitals.

2 REVIEW OF THE LITERATURE

2.1 GALLSTONE DISEASE

Gallstone disease is a significant health problem in western countries, affecting 5% to 22% of the adult population (Shaffer 2006). In United States 20 to 25 million people have gallstone disease, it causes about 1.8 million ambulatory care visits each year and is a leading cause for hospital admissions related to gastrointestinal problem. The estimated direct and indirect cost of gallstone disease in United States are about $6 billion annually (Shaheen, Hansen et al. 2006, Everhart and Ruhl 2009, Stinton and Shaffer 2012). Cholesterol or cholesterol predominant (mixed) stones are the most common type of gallstones, making up about 80% of gallstones in developed countries (Portincasa, Moschetta et al. 2006).

2.1.1 Bile formation and enterohepatic circulation of bile salts

Bile consists of water (90%) and solutes of which 70% constitute of bile salts, 23% of phospholipids, 4% of cholesterol and 3% of other compounds including bile pigments (mainly conjugated bilirubin), proteins and electrolytes (Marschall and Einarsson 2007, Lambou-Gianoukos and Heller 2008). It is secreted by hepatocytes, additional water and electrolytes are added to the bile by cholangiocytes as the bile passes the bile ducts. Bile is stored and concentrated in gallbladder and released into duodenum during the meals. The total daily bile secretion is about 600ml. Bile facilitates the digestion of lipids by emulsifying fat and forming micelles around fat droplets. This increases the surface area of the fat droplets, which acts to enhance the action of pancreatic lipase. Since bile facilitates the absorption of fats, it has also an important role in the absorption of the fat-soluble vitamins A, D, E and K. In addition to its digestive function, bile serves also as the route of excretion for bilirubin and of excess cholesterol from the body (Boyer 2013).

Bile salts are the primary driving force for bile secretion. They are synthesized in the hepatocytes from cholesterol molecules by hydroxylation and carboxylation. These bile acids, mostly cholic acid and chenodeoxycholic acid are also called primary bile acids. Further on the carboxyl group of the primary bile acids is conjugated with the amino acid glycine or taurine. At neutral pH, the bile acids, particularly conjugated bile acids are mostly ionized and referred as bile salts. Hepatocytes secrete bile acids and other components of bile such as phospholipids, cholesterol and bilirubin into bile canaliculi via an active process involving specific ATP-

binding-cassette transport proteins. The osmotic pressure generated as a result of the secretion of bile acids draws water into the canaliculi through the paracellular pathway. Bile acids pass in composition of bile through biliary tract into duodenum. Because of conjugation, they are poorly absorbed in small intestine allowing them to play an integral role in the intestinal absorption of dietary lipids. However, some 85% to 90% of secreted bile acids are finally reabsorbed by ATP-dependent intestinal bile acid transporter in enterocytes of the distal ileum. The remaining bile acids are deconjugated and dehydroxylated by ileocolonic bacteria yielding secondary bile acids deoxycholate and lithocholate, which are passively absorbed in the colon. Around 5% of secreted bile acids are excreted within faeces. The absorbed bile acids are transported to the liver, cleared from the portal blood flow by hepatocytes and secreted into bile again. This kind of enterohepatic circulation occurs 6 - 10 times daily irrespective of eating, with additional cycles occurring during meals (Lambou-Gianoukos and Heller 2008).

2.1.2 Formation of gallstones

Based on their composition, gallstones are categorized as cholesterol, black pigment and brown pigment stones. Cholesterol stones are most prevalent in Western populations while pigment stones are less frequent. Brown pigment stones are found mostly in Asian populations. Formation of cholesterol stones requires the presence of several factors as cholesterol supersaturation, accelerated nucleation and gallbladder hypomotility/bile stasis (Lambou-Gianoukos and Heller 2008). All these factors in turn are result of complex interaction of genetic and environmental factors. As cholesterol is made soluble through formation of mixed micelles with bile salts and phospholipids, supersaturation occurs if there is an imbalance in concentrations of these three substances in bile. The most common reason is a hypersecretion of cholesterol. Less common is hyposecretion of bile salts caused by reduction of bile salt production or excessive intestinal losses. Excess cholesterol precipitates from solution as microscopic crystals - the crystals are trapped in mucus, producing sludge. When the crystals grow, aggregate, and fuse macroscopic stones are formed (Beckingham 2001).

2.1.3 Risk factors of gallstone disease

Gallstone formation is multifactorial including the effects of multiple undetermined genes and environmental factors. Several risk factors have been identified as being associated with gallstones - some of these are immutable such as ethnicity, genetics, age and female gender whereas others (e.g. physical activity, diet, obesity and rapid weight loss) are modifiable.

Importance of genetic susceptibility in formation of gallstones has been demonstrated in familial studies where incidences of gallstones in first-degree relatives of gallstone patients were two to four-fold compared to stone-free controls (Gilat, Feldman et al. 1983, Sarin, Negi et al. 1995, Attili, De Santis et al. 2005). By Swedish twin-study the concordance rate for symptomatic gallstone disease in monozygotic pairs was 12% compared to 6% in dizygotic pairs. However, the low concordance rates indicate the importance of environmental factors in the pathogenesis of gallstone disease. Thus, heritability is estimated to account for 25%, shared environmental effects for 13% and unique environmental effects for 62% of the phenotypic variance (Katsika, Grjibovski et al. 2005).

2.1.4 Epidemiology of gallstone disease

The prevalence of gallstone disease varies in different ethnicities. The highest prevalence has been found in North American Indians being 64% in women and 30% in men. Particularly high is the prevalence of gallstone disease among Pima Indian women over the age 30 of whom 73% have gallstones. At the same time white Americans have a prevalence of 17% in women and 9% in men and African Americans 14% and 5%, respectively (Stinton, Myers et al. 2010). In Europe the highest rates are found in Norway where 22% of the population between the ages of 20 and 70 years have gallstones. In other European countries the overall prevalence of gallstone disease in the same age group varies between 9% (Denmark) and 20% (Germany) (Shaffer 2005). According to the autopsy study the prevalence of gallstone disease in Finland was 16% in women and 9% in men (Domellöf, Lowenfels et al. 1984). Gallstones are less frequent in Eastern-Asians and sub-Saharan black Africans with prevalence below 5% (Shaffer 2006).

2.1.5 Diagnosis of gallstones

2.1.5.1 Symptoms

There are no symptoms specific to gallstones. By the study of Glambek et al. (1989) the frequency of different abdominal symptoms (upper or lower abdominal pain, heartburn, fat intolerance) in general population lack statistically significant differences in individuals with or without gallstones. The sensitivity and positive predictive value (PPV) of these symptoms in diagnosing gallstones were 25% and 38% at most, respectively. Contrary to common conception, right upper abdominal pain with or without radiation seems to have no substantial association with the presence of gallstones when studied in random sample of population. Likewise, PPV remains low even when right upper abdominal pain is further specified with one

or several pain characteristics as severity, continuity and duration (Jørgensen 1989). However, the diagnostic accuracy of biliary colic, defined as "an episodic, severe steady right upper quadrant abdominal pain lasting more than half an hour", appears to be somewhat higher among referred patients, particularly with severe disease. Nevertheless, PPV of biliary colic does not exceed 50% in these patients and, moreover, 80% of suspected gallstone patients are referred with other abdominal symptoms than biliary colic (Berger, van der Velden et al. 2000).

2.1.5.2 Laboratory tests

Uncomplicated gallstone disease typically does not cause abnormal blood test results. In symptomatic gallstone patients elevated liver function tests (LFT) such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), particularly gamma glutamyl transferase (GGT), alkaline phosphatase (ALP) and bilirubin may indicate the obstruction of CBD by gallstones (Yang, Chen et al. 2008). In acute cholecystitis LFT may be abnormal also without obstruction of CBD due to the spread of inflammation to adjacent liver tissue (Peng, Sheikh et al. 2005).

2.1.5.3 Imaging

Abdominal ultrasonography (US) as non-invasive, inexpensive and simple procedure is the imaging modality of choice in suspected gallstone disease. Its sensitivity and specificity for the diagnosis of gallbladder stones are 84 - 95% and 99 - 100%, respectively (Ahmed and Diggory 2011). The diagnostic accuracy of abdominal US is somewhat lower in obese patients and in detecting biliary sludge or gallstones less than 3mm (Uppot, Sahani et al. 2006). In addition, the diagnostic accuracy of abdominal US is low (20 - 85%) in detecting CBD stones (Ripollés, Ramírez-Fuentes et al. 2009).

The reported sensitivity for gallstone detection at computed tomography (CT) is only 74 - 79% (Barakos, Ralls et al. 1987, Fagenholz, Fuentes et al. 2015). The identification of stones depends on the differing density of the gallstone relative to bile. Thus, calcified stones are the most readily identified. Similarly, gallstones with less density than bile like stones with high concentrations of cholesterol may be detected at CT. However, many stones are composed of a mixture of calcium, bile pigments, and cholesterol having similar density to bile and therefore not detectable at CT (Bennett 2015).

For diagnosing CBD stones by non-invasive means, magnetic resonance cholangiopancreatography (MRCP) with diagnostic accuracy of 97 - 98% is superior to abdominal US (Varghese, Liddell et al. 2000, Ke, Zheng et al. 2003, Topal, Van de Moortel et al. 2003). However, the sensitivity of MRCP seems to decrease in diagnosing CBD stones with

diameter less than 5mm. In addition, morbid obesity, claustrophobia, presence of intracranial metallic clips or implanted devices such as pacemaker might preclude MRCP (Kondo, Isayama et al. 2005).

Endoscopic retrograde cholangiopancreatography (ERCP) is generally considered to be the reference standard for diagnosis of CBD stones as its accuracy may reach 100% (Williams, Green et al. 2008). Additionally, ERCP can be used to provide definitive or temporary treatment of CBD stones. However, ERCP is an invasive procedure with related 5 - 10% morbidity and 0.1 - 0.4% mortality (Masci, Toti et al. 2001, Schreurs, Juttmann et al. 2002, Williams, Taylor et al. 2007, Wang, Li et al. 2009, Shiozawa, Kim et al. 2011). Therefore, it is not recommended for using solely as a diagnostic test but reserved as therapeutic tool for patients with confirmed or high index of suspicion for CBD stones (Williams, Green et al. 2008).

Recent technological advances have complemented diagnosis and treatment of CBD stones by peroral cholangioscopy (Ghersi, Fuccio et al. 2015). Several technical solutions are currently available including devices employed through the working channel of a therapeutic duodenoscope during ERCP (ultrathin videocholangioscope [CHF-B260; Olympus Medical System, Tokio, Japan]; single-operator cholangioscope [Spyglass™ DS System, Boston Scientific, Natic, MA, USA]) or ultraslim cholangioscopes for direct peroral videocholangioscopy (Xu and Kahaleh 2016). In addition to direct visualization of ductal clearance and examination for residual stones after stone extraction in ERCP, cholangioscopy enables intraductal fragmenting of difficult-to-remove stones by electrohydraulic lithotripsy or laser lithotripsy (Shah 2015, Ishida, Itoi et al. 2016).

Endoscopic US (EUS) is considered to have high sensitivity (94%), especially for small CBD stones but the accuracy is highly dependent on the skills of the operator, procedure has the risk of complications specific to endoscopy and it may not be feasible in patients with altered gastric or duodenal anatomy (Tse, Liu et al. 2008).

2.1.6 Natural history of gallstone disease

At the time of diagnosis approximately 60 - 70% of gallstone patients are asymptomatic. The results of follow-up studies in asymptomatic gallstone patients to observe the natural history of gallstones are inconsistent. Relatively low number of patients per study and short time of observation along with indistinctness of biliary symptoms explain the variability of these results. However, it has been found that during 20 - 25 years after the initial diagnosis 75 - 90% of the patients remain asymptomatic (Sakorafas, Milingos et al. 2007). For asymptomatic

patient the annual risk of developing biliary pain is 1 - 4% (Beckingham 2001). Whether the risk increases over time remains controversial. The aging seems to be associated with the development of symptoms or complications (Glenn 1981, Glenn 1981, Gracie and Ransohoff 1982, Lowenfels, Domellöf et al. 1982, McSherry, Ferstenberg et al. 1985, Hermann 1989, Wada and Imamura 1993). Of these patients who develop symptoms, 60 - 70% present with mild complaints, 20% have acute cholecystitis and 10% develop other complications as jaundice, cholangitis or biliary pancreatitis (Hermann 1989). For symptomatic gallstone patients the annual rates of developing complicated gallstone disease and recurrence of biliary symptoms are about 1% and 50%, respectively (Beckingham 2001). On the other hand, in symptomatic gallstone patients during the follow-up period (mean 9 years) symptoms disappeared in 58% and 52% of patients with mild and severe symptoms at enrollment, respectively (Festi, Reggiani et al. 2010).

2.1.7 Treatment of gallstone disease

2.1.7.1 Treatment of symptomatic and complicated gallstone disease

In case of symptomatic gallstone disease removing the gallbladder along with gallstones is warranted unless the patient′s poor health precludes the surgery. In majority of cases the laparoscopic procedure is feasible (Gurusamy and Davidson 2010).

Acute cholecystitis is caused by gallstones in 90% of cases while 1 - 3% of all individuals who have gallstones, develop acute cholecystitis (Halldestam, Enell et al. 2004). Traditionally, initial treatment has consisted of bowel rest, intravenous hydration, correction of electrolyte imbalances, and analgesia. Although the bacterial infection is not believed to play initial role in acute cholecystitis, secondary infection with more severe clinical course may complicate up to 50% of cases (Elwood 2008). Thus, in mild cholecystitis antimicrobial therapy is warranted for prophylaxis whereas in severe disease antibiotics are therapeutic (Gomi, Solomkin et al. 2013). In most patients symptoms subside with conservative treatment. However, up to 24% of patients may experience recurrence. Hence LC is indicated as definitive treatment in medically fit patients (Schmidt, Søndenaa et al. 2011). Apart from about 20% of cases where emergency operation is needed, the optimal timing of surgery in remaining patients with acute cholecystitis has been the matter of debate (Indar and Beckingham 2002, Lee, Carter et al. 2008, Siddiqui, MacDonald et al. 2008). Based on the assumption that surgery in inflamed tissue increases the risk of complications, many surgeons favour initial conservative treatment followed by delayed LC several weeks or months later when inflammation has subsided (Kum, Eypasch et al. 1996, Vetrhus, Søreide et al. 2003). There is, however, growing body of evidence that early LC during

the index admission is associated with less morbidity, shorter hospital stay and lower total costs without increase in conversion to open operation or mortality rates when compared to delayed procedure (Vetrhus, Søreide et al. 2003, Siddiqui, MacDonald et al. 2008, Duncan and Riall 2012, Gutt, Encke et al. 2013, Koti, Davidson et al. 2015). Yet the optimal timing for early LC remains somewhat unclear (Yamashita, Takada et al. 2013, Ansaloni, Pisano et al. 2016). According to available reports, patients seem to benefit from LC performed up to one week of symptom onset while surgery within the first 72 h appears to be the most optimal (Zhu, Zhang et al. 2012, Ambe, Weber et al. 2014, Cao, Eslick et al. 2016). In patients medically unfit for cholecystectomy percutaneous transhepatic cholecystostomy is indicated if conservative treatment appears unsuccessful (Elwood 2008).

About 10 - 15% of gallstone patients have CBD stones. The natural history of CBD stones is not well defined but related complications appear to be more severe than with gallbladder stones (Ko and Lee 2002). It is therefore recommended that if CBD stones are confirmed, extraction of stones should be performed if possible. The treatment chosen depends on patient and disease related variables as well as the local expertise but LC for removing the source of stones is recommended for all medically fit patients. Endoscopic sphincterotomy (ES) and removal of stones in conjunction with ERCP, whether before or after cholecystectomy, has a success rate of 70 - 90% (Joyce and Heiss 2008). Alternatively, CBD exploration and extraction of CBD stones can be performed during the LC or OC (Verbesey and Birkett 2008). Open operation for bile duct exploration and CBD stone removal can be employed with or without bilioenteric anastomosis in cases of “difficult” stones (large or numerous stones, stones proximal to biliary stricture). In addition, modalities like mechanical lithotripsy, extra-corporeal shock wave lithotripsy (ESWL), intra-corporeal electro-hydraulic and laser lithotripsy as well as percutaneous radiological treatments have been used in difficult cases. Occasionally, in cases of biliary cannulation difficulty during ERCP, double guidewire, precut and rendezvous (insertion of guidewire into bile ducts either percutaneously or under the EUS guidance) techniques may be applied to facilitate stone extraction (Calvo, Bujanda et al. 2001, Tsuchiya, Itoi et al. 2016). Sometimes, with irretrievable stones, biliary stent whether as temporary or definitive treatment can be used (Williams, Green et al. 2008).

Acute pancreatitis is caused by CBD stones or sludge in 35 - 60% of cases. Diameter of smallest gallbladder stone ≤ 5mm, diameter of cystic duct ≥ 5mm and number of gallbladder stones ≥ 20 were shown to be risk factors for acute biliary pancreatitis (Sugiyama and Atomi 2004). Biliary pancreatitis is mostly mild. Spontaneous passage of stones into duodenum occurs in about 80 % of patients and full recovery can be expected with supportive treatment only (van

Geenen, van der Peet et al. 2010). Subsequent non-invasive biliary imaging is recommended and, if CBD stones are still present, previously mentioned treatment modalities can be applied followed by LC in elective settings (Williams, Green et al. 2008). Alternatively, LC with IOC and, if CBD stones are present, ERCP/ES during the index admission can be performed for patients with mild gallstone pancreatitis (Aboulian, Chan et al. 2010). In case of ongoing biliary obstruction or particularly, with co-existing cholangitis, emergency (within 24 hours of admission) ERCP/ES is indicated (Kuo and Tarnasky 2013). However, there is no consensus on the role of early ERCP/ES in patients with predicted severe acute biliary pancreatitis without cholestasis but there is general agreement that in severe biliary pancreatitis LC is safe only after the patients have sufficiently recovered to tolerate the operation (Overby, Apelgren et al. 2010, van Geenen, van Santvoort et al. 2013).

The most common etiopathogenesis of acute cholangitis in western world is CBD obstruction by gallstones complicated further on by bacterial infection. Management of acute cholangitis includes broad-spectrum antibiotics and biliary decompression, preferably by ERCP/ES, supplemented by stone extraction or biliary stenting (Gomi, Solomkin et al. 2013). However, up to 70 - 85% of patients with acute cholangitis present with mild to moderate disease and respond satisfactorily to initial antimicrobial treatment (van Erpecum 2006). In these patients biliary decompression can be performed on an elective basis, however, biliary intervention within 24 hours of admission has shown to bring benefits in terms of shorter hospital stay and shorter time for control of infection (Jang, Park et al. 2013). Patients who fail to respond to antimicrobial treatment or who have signs of septic shock need urgent biliary decompression (Williams, Green et al. 2008). If ERCP is impossible or fails, percutaneous transhepatic biliary drainage (PTBD) can be considered (Williams, Green et al. 2008).

Mirizzi syndrome (MS) is a rare complication of gallstone disease, its incidence among patients undergoing biliary surgery varies from 0.2% to 3% (Lai and Lau 2006). In MS biliary obstruction due to extrinsic compression of the common hepatic duct by gallstones impacted in gallbladder neck or cystic duct occurs. In more severe cases bile duct wall necrosis and subsequent cholecystobiliary fistula develops (Antoniou, Antoniou et al. 2010). Accordingly, MS can be classified into two types respective to the presence (Type I) or absence (Type II) of a fistula (Lai and Lau 2006). For the clinician the classification of Csendes et al. (Table 1) appears more relevant (Csendes, Díaz et al. 1989).

Table 1. Classification of Mirizzi syndrome, according to Csendes et al.

Type	Characteristics
Type I	External compression of the common hepatic duct without a cholecystobiliary fistula
Type II	Presence of a cholecystobiliary fistula, defect involves < 1/3 of the bile duct circumference
Type III	Cholecystobiliary fistula involves up to 2/3 of the bile duct circumference
Type IV	Cholecystobiliary fistula involves the entire circumference of the bile duct

Patients with MS present with unspecific complaints, upper abdominal pain (61 - 100%) and jaundice (50 - 70%) being the most common symptoms. The treatment options consist of partial or complete cholecystectomy with or without CBD exploration. Endoscopic biliary decompression by CBD stent or nasobiliary drain placement before cholecystectomy may be indicated particularly in cases of suppurative cholangitis (Li, Li et al. 2013, Le Roux, Sabbagh et al. 2015). In MS type I an attempt to remove the impacted stone(s) endoscopically is recommended provided high-level ERCP service is available (Grönroos 2007, Pelaez-Luna, Levy et al. 2008). Choledochoplasty with a gallbladder flap or cystic duct stump and T-tube placement may be needed in type II and III whereas the treatment of type IV lesion usually requires hepaticojejunostomy (Al-Akeely, Alam et al. 2005, Erben, Benavente-Chenhalls et al. 2011, Cui, Liu et al. 2012, Xu, Hong et al. 2013). Procedures are demanding due to the distorted biliary anatomy and dense inflammatory adhesions in Calot′s triangle, therefore open operation is preferable. Attempts of LC in MS patients have resulted with conversion in 41 - 89% of cases (Antoniou, Antoniou et al. 2010, Erben, Benavente-Chenhalls et al. 2011, Cui, Liu et al. 2012, Xu, Hong et al. 2013). However, LC can be applicable to selected patients with type I and even with type II lesions (Kok, Goh et al. 1998, Rohatgi and Singh 2006, Li, Li et al. 2013).

Gallstone ileus and its variant of gastroduodenal obstruction, also known as Bouveret′s syndrome, are rare complications of gallstone disease constituting less than 0.1% of the total number of mechanical bowel obstructions (Halabi, Kang et al. 2014). Mean age of the patients is > 70 years; over 2/3 of them have multiple co-morbidities and ASA score ≥ 3 (Mallipeddi, Pappas et al. 2013). Surgical treatment is inevitable but consensus is lacking in respect to necessity and optimal timing to address the associated biliary-enteric fistula. A one-stage procedure with enterolithotomy and cholecystectomy is theoretically the ideal treatment. The advantage of this technique is prevention of further complications from a persistent fistula, such as cholangitis and recurrence of gallstone ileus (Rodríguez-Sanjuán, Casado et al. 1997, Fitzgerald, Fitzgerald et al. 2009). However, few patients can tolerate such an invasive procedure. Therefore most surgeons prefer simple enterolithotomy, which is associated with

lower morbidity and mortality compared to the one-stage procedure (Mallipeddi, Pappas et al. 2013). In presence of sufficient expertise, laparoscopic stone extraction could be feasible (Sesti, Okoro et al. 2013). Delayed cholecystectomy as a second procedure seems to be justified only in medically fit patients with persistent biliary symptoms (Halabi, Kang et al. 2013).

2.1.7.2 Treatment of asymptomatic gallstones

As cumulative risk to have severe symptoms or complications of gallstone disease is relatively low it is generally agreed that asymptomatic gallstone patients need no treatment. (Halldestam, Kullman et al. 2008)

In solid organ transplant recipients an increased prevalence of gallstones are found. In addition, there seems to be an increased risk of infectious morbidity from biliary complications due to immunosuppression and increased morbidity and mortality associated with emergency cholecystectomy post-transplantation (Kao, Kuhr et al. 2003, Richardson, Surowiec et al. 2003). Management of asymptomatic gallstones in this patient population remains controversial (Jackson, Treleaven et al. 2005, Takeyama, Sinanan et al. 2006, Taghavi, Ambur et al. 2015). Results of the recent study in 1,687 heart transplant recipients with asymptomatic gallstone disease warrant prophylactic cholecystectomy in these patients (Kilic, Sheer et al. 2013). Likewise, according to the Finnish study, complications of gallstone disease in kidney transplantation patients may be severe. Therefore cholecystectomy in cases of gallstones is considered as prerequisite for acceptance to the transplantation waiting list in Finnish Transplantation Unit (Sarkio, Salmela et al. 2007).

By altering the gallbladder motility and enterohepatic circulation of bile salts various abdominal operations may affect either the natural course of gallstone disease or promote silent gallstones to become symptomatic. Therefore in gallstone patients prophylactic cholecystectomy should be considered in conjunction with gastrectomy particularly if extended (D2) lymphadenectomy is concurrently performed. Likewise, accompanying prophylactic cholecystectomy may be indicated in small bowel resections resulting in short bowel syndrome with a need for prolonged total parenteral nutrition. In addition, concurrent prophylactic cholecystectomy is indicated if splenectomy is undertaken in patients with chronic haemolytic anaemia who have simultaneous gallstones. Besides, prophylactic cholecystectomy is also recommended during intestinal resections for neuroendocrine tumors if subsequent treatment with somatostatin is likely (Cabarrou, Portier et al. 2013). On the other hand, the role of prophylactic cholecystectomy for asymptomatic gallstones during bariatric operations remains controversial (Warschkow, Tarantino et al. 2013, Amstutz, Michel et al. 2015).

Gallstones are present in 75 - 90% of patients with gallbladder cancer (GBC) and the incidence of this malignancy correlates with the prevalence of cholelithiasis among different geographic areas and ethnicities (Hundal and Shaffer 2014). Development of cancer in the setting of gallstones probably occurs through chronic irritation and inflammation leading to preneoplastic lesions such as hyperplasia, metaplasia, dysplasia and finally carcinoma (Shaffer 2008, Jain, Mohapatra et al. 2014). Gallstones in patients with GBC tend to be larger in size and number while stones are asymptomatic in about 20% of these patients (Csendes, Becerra et al. 2000, Cariati, Piromalli et al. 2014). Although gallstone disease is considered an important risk factor for GBC no scientific evidence exists to favor prophylactic LC in asymptomatic gallstone patients (Tewari 2006, Hundal and Shaffer 2014). However, the exception may be patients with large gallstones since the relative risk to have GBC increases from 2.4 for stones 2.0 - 2.9 cm in diameter to 10.1 for the stones > 3 cm (Tewari 2006). In addition, prophylactic LC in asymptomatic gallstone patients may be indicated in high-risk populations such as Chilean Mapuche Indian females, East Indian females and Pima Indian females (Shrikhande, Barreto et al. 2010, Hundal and Shaffer 2014).

2.1.8 Porcelain gallbladder

The term "porcelain gallbladder" (PGB) refers to the presence of calcifications in gallbladder wall. The extent of calcification can range from small focal plaques within the mucosal layer up to diffuse full-thickness involvement causing characteristic bluish discoloration and brittle consistency of the gallbladder (Stephen and Berger 2001). The etiology and pathogenesis of gallbladder wall calcifications are poorly understood. While chronic inflammation and ischemia seem to be involved, the association with gallstones remains unclear since up to 40% of patients with PGB do not have gallstones (Khan, Livingston et al. 2011). Although the true prevalence is not known, the PGB seems to be relatively rare as in cholecystectomy specimens the prevalence has been 0.1% to 0.2% (Cunningham and Alexander 2007, Khan, Livingston et al. 2011). The clinical importance of PGB lies in apprehension of coincidental presence of or the future development of GBC in calcified gallbladder. The incidence of GBC in PGB was reported to be 12% to 61% in the studies from the 1950s and 1960s (Liang, Cheung et al. 2008). However, in more recent studies the incidence has been lower approximating 6%, while in patients without gallbladder calcifications malignancy was found in about 1% of cholecystectomy specimens (Schnelldorfer 2013). In addition, the risk for GBC seems to depend on the pattern of calcification since GBC has been found mostly in association with focal mucosal calcium deposits (Stephen and Berger 2001, Schnelldorfer 2013).

Although the risk for GBC in calcified gallbladder appears to be lower than previously thought, the current practice is to recommend prophylactic cholecystectomy to medically fit patients (Brown and Geller 2011).

2.1.9 Gallbladder polyps

Polypoid lesions of the gallbladder are detected in about 6% of patients undergoing abdominal US. In approximately half of them the US is undertaken for upper abdominal symptoms while in the rest of the patients polyps are incidental findings (Cairns, Neal et al. 2012). Only about 5% of gallbladder polyps are found to be neoplastic including 1% of malignancies. Thus the majority (95%) of the polypoid lesions detected in gallbladder are non-neoplastic (adenomyomatosis, inflammatory polyps, cholesterol polyps) or gallstones accreted to mucosa mimicking polyps (Gallahan and Conway 2010). However, the sensitivity and PPV of abdominal US for gallbladder polyps are only 50% and 11%, respectively and moreover, it is unlikely that abdominal US can reliably differentiate neoplastic and non-neoplastic lesions (French, Allen et al. 2013). At the same time the accuracies of novel imaging modalities as high-resolution US, endoscopic US, multi-detector CT and ^{18}F-fluorodeoxyglycose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to distinguish the nature of the gallbladder polyps with the diameter over 10mm are around 85% (Jang, Kim et al. 2009, Lee, Yun et al. 2012). Nevertheless, by most experts polyps < 6mm are unlikely to be neoplastic while the polyp′s size over 10mm, sessile polyps, patients age over 50 years and concurrent gallstones are the risk factors for malignancy (Gallahan and Conway 2010, Corwin, Siewert et al. 2011, Bhatt, Gillis et al. 2016). In addition, another risk factor for malignancy is primary sclerosing cholangitis (PSC) (Eaton, Thackeray et al. 2012). Accordingly, the proposed treatment options for gallbladder polyps follow the size of the polyp, the presence of risk factors for malignancy and abdominal symptoms. Thus, in PSC patients cholecystectomy is recommended irrespectively of polyp′s size unless the patient has poor liver function in which case US surveillance every 3 - 6 months should be performed (Razumilava, Gores et al. 2011, Schramm and Lohse 2012). Similarly, cholecystectomy is recommended in symptomatic patients (without other source of symptoms) regardless of the size of the polyp. Cholecystectomy is also recommended in patients with polyp larger than 6mm and concurrent risk factors for malignancy other than PSC. On the other hand, in asymptomatic patients with 6 - 10mm polyp and without risk factors for malignancy US surveillance every 6 - 12 months is advisable and cholecystectomy is indicated if subsequent grow in size of the polyp is detected. Yet, the recommendations concerning the duration of follow-up are controversial (Babu,

Dennison et al. 2015). According to majority of experts, asymptomatic patients with small (≤ 6mm) polyps need neither treatment nor surveillance (Gallahan and Conway 2010, Corwin, Siewert et al. 2011, Cairns, Neal et al. 2012).

2.2 LAPAROSCOPIC CHOLECYSTECTOMY

Due to its clear advantages over conventional i.e. open cholecystectomy, LC has become the standard treatment for symptomatic gallstone disease since its introduction in 1985 (Macintyre and Wilson 1993). Nowadays over 90% of all cholecystectomies are performed laparoscopically; in Scandinavia the annual rate of cholecystectomies has varied between 60 and 140 per 100,000 inhabitants after the introduction of LC (Mjäland, Adamsen et al. 1998, Rosenmüller, Haapamäki et al. 2007). In Finland about 8,500 patients have LC annually and around 75% of these patients are of working-age (18 - 65 years) (Paajanen and Mäkisalo 2012).

2.2.1 History

The first open cholecystectomy was performed in 1882 by German surgeon Carl Langebuch (McAneny 2008). Over a century later, in 1985 another German surgeon Erich Mühe performed the first LC with an endoscope constructed by himself and called “Galloscope”. However, Mühe's presentation of his experience with LC at the Congress of German Surgical Society in 1986 was met with scepticism and ridicule (Reynolds 2001). LC gained credibility few years later after French surgeons Dubois and Perissat, being inspired by Philippe Mouret from Lyon who had performed his first LC in 1987 independently from Mühe, presented new technique to international surgical community (Blum and Adams 2011). Since by the late 1980s the attitude of general surgeons towards laparoscopy had changed more favourable rapid acceptance of a new surgical method followed (Litynski 1999). In addition, technological progress, particularly development of a video computer chip that allowed the magnification and projection of images onto television screens, contributed to the widespread introduction of laparoscopic technique. As a result, by the year 1992 more than a half of all cholecystectomies done in United States were performed laparoscopically (Spaner and Warnock 1997). The success of LC became the stimulus for expanding the role of laparoscopic surgery which in the following years changed the field of surgery perhaps more drastically and more rapidly than earlier had done the introduction of anesthesia or antibiotics (Spaner and Warnock 1997, Himal 2002).

2.2.2 Technique of laparoscopic cholecystectomy

The patient is operated in the supine or lithotomy position with head-up tilt once the pneumoperitoneum is established. Surgeon stands at the left side of the patient with the assistant either by his left side or between the legs of the patient. Pneumoperitoneum with CO2 is created either by closed technique with Veress needle or after insertion of the trocar under visual control. While intra-abdominal pressure of 12 to 16mm/Hg is commonly used, it has been shown that decreasing intra-abdominal pressure under 12mm/Hg reduces postoperative pain and analgesic consumption without increasing operation time (Gurusamy, Samraj et al. 2009). Laparoscope is placed adjacent to the umbilicus, 10 mm trocar is inserted next to xiphosternum and two additional 5mm trocars are placed, one at the right mid-clavicular line lateral to gallbladder and another at the right anterior axillary line. Surgeon uses the ports in epigastrium and in mid-clavicular line while remaining trocar is used by assistant for fundus grasper (Cuschieri 1999). With the alternative, so-called French technique, patient is in the lithotomy position, surgeon operates between the legs and assistant stands at the left side of the patient (Dubois 1995). Accordingly, except for laparoscope, different location of trocars is used: 5mm trocar for assistant is placed next to xiphosternum while surgeon operates through 10mm trocar inserted in left hypochondrium and 5mm trocar placed at right anterior axillary line (Figure 1).

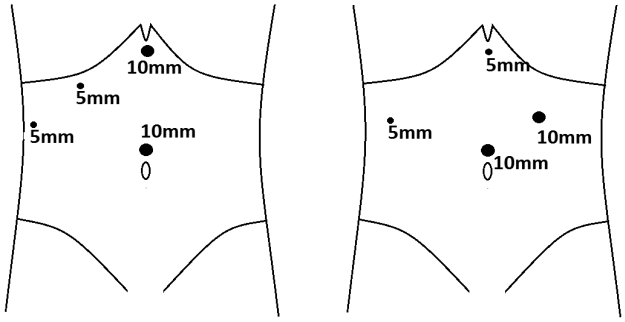

Figure 1. Common trocar configurations in LC

Gallbladder fundus is grasped and retracted cephalad to expose infundibulum and hepatoduodenal ligament, retraction of infundibulum with another grasper facilitates access to Calot's triangle (Figure 2). As operation proceeds the direction of retraction of infundibulum must be continuously adjusted for optimal exposure and safe dissection in Calot's triangle (Litwin and Cahan 2008). Before clipping and dividing cystic duct and artery, some surgeons recommend to ensure that there is no any other ductal structure attached to gallbladder by

detaching the lower part of gallbladder from liver bed (Strasberg and Brunt 2010). After the cystic duct and artery are divided, separation of gallbladder from liver bed and extraction from abdominal cavity follows. In case of friable or perforated gallbladder, extraction inside the retrieval bag to avoid bile leakage or stone spillage is recommended. Before evacuation of pneumoperitoneum the stumps of the cystic duct and artery, the liver bed and adjacent organs are inspected and irrigation of operative field with saline is performed when needed. Fascia closure of the large port wounds with absorbable sutures is advisable to prevent herniation (Cuschieri 1999).

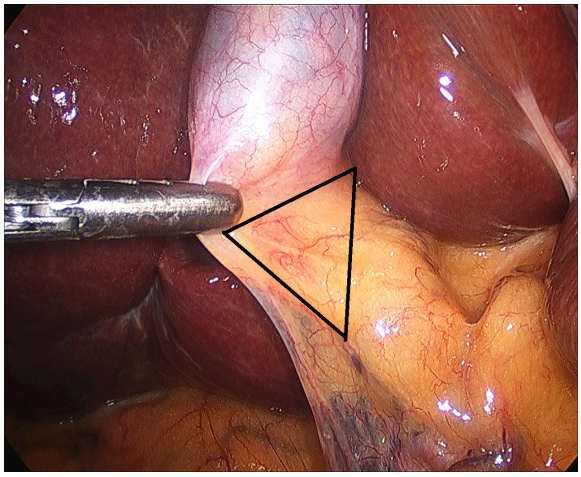

Figure 2. Calot's triangle

Alternative to conventional technique, where dissection is started from Calot's triangle, is a retrograde or fundus-first LC. The operation begins with dissection near the fundus of the gallbladder and dissection in Calot's triangle is performed after the gallbladder has been separated from the liver bed (Raj, Castillo et al. 2001). Although some authors recommend its routine use, retrograde LC seems primarily advantageous in difficult cases with inflammation and/or fibrosis where conventional technique fails to provide adequate exposure or to allow safe dissection (Tuveri, Calò et al. 2008, Kelly 2009). Advocates of retrograde LC suggest that in difficult cases it may decrease the rate of BDIs and avoid conversion to open surgery (Raj, Castillo et al. 2001, Mahmud, Masaud et al. 2002, Rosenberg and Leinskold 2004).

The need for antibiotic prophylaxis for patients undergoing elective LC remains unclear. The majority of existing randomized clinical trials suggest that antibiotic prophylaxis in elective LC may not be needed (Al-Ghnaniem, Benjamin et al. 2003, Catarci, Mancini et al. 2004). However, these studies have been underpowered and for methodological flaws with high-risk for bias. Recent RCT from Japan with over 1000 elective LC patients randomized to antibiotic prophylaxis and no prophylaxis groups revealed significant reduction in infectious complications in prophylaxis group (Matsui, Satoi et al. 2014). It seems that, until there is no trustworthy scientific evidence available, the need for antibiotic prophylaxis should be assessed individually for each patient (Sanabria, Dominguez et al. 2010).

Most surgeons are using monopolar electrocautery for dissection in LC. However, according to some studies, with ultrasonic dissection less gallbladder perforations, shorter operative time and even less postoperative pain with shorter hospital stay and sick leave can be achieved (Sasi 2010, Xiong, Altaf et al. 2012). The reason for reduced postoperative pain by ultrasonic dissection remains unclear, as existing data regarding its impact on tissues is controversial (ten Broek, Wilbers et al. 2011, Homayounfar, Meis et al. 2012).

Increasing number of elective LCs are performed as a day-case surgery, the proportion being between 50 - 80% (Victorzon, Tolonen et al. 2007, Clarke, Wheatley et al. 2011). American Society of Anesthesiologists (ASA) score < 3, age 18 - 70 years, home within acceptable range from the hospital and assistance by a healthy adult at home until the next morning are considered prerequisites for scheduling to day-case surgery (Tenconi, Boni et al. 2008). Elective LC as a day-case surgery appears safe; in randomised controlled studies no statistically significant difference in serious adverse events, pain, time to return to daily activities, time to return to work, number of hospital readmissions and failed discharge were detected when compared to overnight stay LC (Vaughan, Gurusamy et al. 2013). Discharge fails in 7 - 47% of patients whereas over half of them for other than medical reasons (patients prefer to stay at the hospital or for social reasons), which may reflect the need for better preoperative counselling (Victorzon, Tolonen et al. 2007, Vaughan, Gurusamy et al. 2013). Readmission rates are in range of 2 - 7% (Vaughan, Gurusamy et al. 2013). The estimated saving in overall costs with day-case LC may reach 30 - 40% when compared with standard inpatient procedure (Victorzon, Tolonen et al. 2007, Tenconi, Boni et al. 2008).

2.2.3 Intraoperative cholangiography

The purposes of IOC (Figure 3) are to detect asymptomatic CBD stones and to delineate biliary anatomy in order to prevent or diagnose bile duct injuries (BDI) (Ford, Soop et al. 2012). In IOC cystic duct is incised and cannulated, contrast dye is injected into bile ducts while patient is in 30˚ Trendelenburg position and X-ray images are captured by mobile (C-arm) digital fluoroscopic device (MacFadyen 2006, Dip, Asbun et al. 2014). Sometimes cystic duct cannulation fails, therefore alternative method of IOC by Kumar (1992) is proposed where by application of specialized instrument the contrast dye is injected into the distal infundibulum instead of cystic duct. Regardless of the technique, in experienced hands IOC takes about 10 to 20 minutes to perform and the success rate is reported to be 82 - 95% with very low (< 0.1%) associated morbidity (Videhult, Sandblom et al. 2009, Buddingh, Bosma et al. 2013). The radiation received during IOC with contemporary equipment is only around 0.18 mSv and

represents for patient a less than 0.001% lifetime added risk of developing cancer (Buddingh, Nieuwenhuijs et al. 2011).

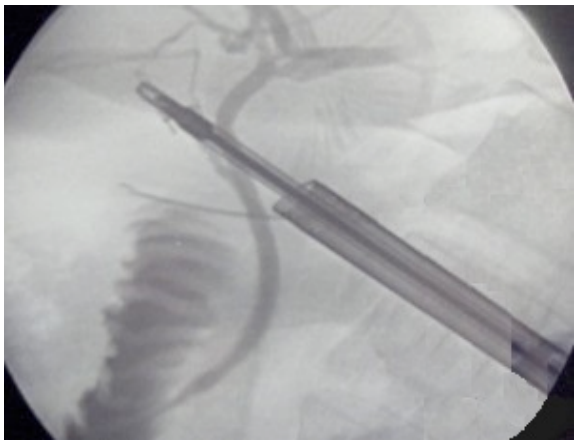

Figure 3. IOC

However, due to disadvantages of IOC (invasiveness, technical complexity, need for expertise to interpret cholangiograms, chronic exposure of personnel to radiation) in recent years new modalities for assessment of biliary anatomy during LC have been developed. Among these are near-infrared fluorescence cholangiography (NIRF-C), dye cholangiography, light cholangiography, passive infrared cholangiography and hyperspectral cholangiography (Buddingh, Nieuwenhuijs et al. 2011). According to preliminary reports, NIRF-C seems the most promising as being not invasive, radiation-free, simple-to-perform and cheaper than conventional IOC (Ishizawa, Bandai et al. 2010, Dip, Asbun et al. 2014, Zroback, Chow et al. 2016).

2.2.4 Complications of laparoscopic cholecystectomy

The rate of LC associated complications ranges from 2% to 7% and mortality is 0.3 - 0.5% (Giger, Michel et al. 2006, Murphy, Ng et al. 2010, Ausania, Holmes et al. 2012). The most common complications are bleeding, pulmonary and urinary complications and surgical site infections (Shea, Healey et al. 1996, Murphy, Ng et al. 2010). The risk factors for complications are patient related factors (as advanced age, male gender, presence of comorbidities and increased bodyweight), acute cholecystitis, emergency operation, prolonged procedure, and conversion to open operation (Giger, Michel et al. 2006). The risk of complications decreases with the increase of surgeon's experience while surgeons who have performed between 11 and 100 LCs seem to have the highest incidence of complications (Giger, Michel et al. 2006, Hobbs, Mai et al. 2006). However, according to Murphy et al. based on the analysis of > 1,000,000 LCs, neither surgeon nor hospital operative volume is associated with an increased risk of complications (Murphy, Ng et al. 2010).

2.2.4.1 Bile duct injuries

There are several classifications of BDIs according to level, extent, type and accompanying vascular injury (Ausania, Holmes et al. 2012). BDIs can be also categorized into severe/major

injuries (including extended strictures, transectional injuries, injuries with structural defect and injuries above the hepatic confluence) requiring reconstructive surgery and less severe/minor injuries as small tangential injuries, bile leakages from cystic duct and aberrant ducts in liver bed (Table 2) (Neuhaus, Schmidt et al. 2000, Törnqvist, Strömberg et al. 2012).

Table 2. Classification of bile duct injuries according to Neuhaus et al.

Type	**Type of injury**	**Specification**
A	Peripheral minor leak	A1 - cystic duct leak A2 - aberrant bile duct leak
B	Occlusion of CBD without sharp injury	B1 - incomplete B2 - complete
C	Tangential injury / dissection of the CBD	C1 - small dissection (< 5 mm) C2 - extended dissection (> 5 mm)
D	Complete transection of the CBD	D1 - without structural defect D2 - with structural defect
E	(Late) stenosis of the CBD	E1 - short CBD stenosis (< 5 mm) E2 - extended CBD stenosis (> 5 mm) E3 - stenosis of the confluence E4 - stenosis of right hepatic duct or segmental bile duct

CBD, common bile duct

The rate of BDIs, which in OC era had been 0.1 - 0.3%, increased after the adoption of LC up to 0.8 - 1.5% (Shea, Healey et al. 1996, Karvonen, Salminen et al. 2011, Törnqvist, Strömberg et al. 2012). Although slight reduction due to learning curve thereafter occurred, the incidence of major BDIs in contemporary series has remained approximately one per 200 procedures (Ausania, Holmes et al. 2012). Concurrently increase of the incidence of BDis in OC up to 1.2% has been observed. However, this may be due to the fact that in laparoscopic era OC is reserved for more complex cases (Karvonen, Salminen et al. 2011).

While minor injuries are more common (60 - 90% of all BDIs), the major injuries have more devastating consequences, including 3 times higher hazard of death within the first year after the injury (Flum, Cheadle et al. 2003). Even in highly specialized centres the postoperative morbidity as high as 43% and mortality of 2% in patients undergoing biliary reconstruction after BDI have been reported (Sicklick, Camp et al. 2005). Major determinants of patients outcomes after BDI are early recognition of an injury and surgeons experience performing biliary reconstruction (Flum, Cheadle et al. 2003). Even in the event of successful repair, up to 21% of patients may have long-term complications (Karvonen, Gullichsen et al. 2007).

The most common mechanism of BDI is misinterpretation of the CBD or hepatic duct, as the cystic duct, resulting in clipping and division (Way, Stewart et al. 2003). Factors contributing to BDI include inflammation, scarring of Calot's triangle, poor vizualisation of the field and excessive bleeding (Karvonen, Gullichsen et al. 2007, Ausania, Holmes et al. 2012). Unlike other complications of LC, the BDIs seem to be unrelated to surgeons' experience (Francoeur, Wiseman et al. 2003). This is in accordance with the outcomes of the study by Way et al. (2003) where the causes of BDIs were analyzed according to the principles of the cognitive science of visual perception, judgment and human error. This study revealed that the primary cause of error in 97% of cases was a visual perceptual illusion. Faults in technical skill were present in only 3% of injuries while knowledge and judgment errors were contributory but not primary. The same authors also conclude that with current technology, including IOC, the rate of BDIs around 0.1% may be nearing the upper limits of human performance for such a complex task as LC (Way, Stewart et al. 2003).

2.2.4.2 Trocar site incisional hernias

The incidence of LC related trocar site incisional hernias (TSIH) has been shown to be 0.2 - 4% with majority of hernias located in umbilical incision (Helgstrand, Rosenberg et al. 2011, Erdas, Dazzi et al. 2012, Comajuncosas, Hermoso et al. 2014). According to Uslu et al. (2007) leaving the fascia defects unsutured leads to TSIH in 5% of LC patients. In recent study by Comajuncosas et al. (2014) the incidence of TSIH after LC was as high as 26% while all TSIHs occurred in umbilical wound. Authors believe that owing to sufficiently long follow-up time (3 years) their results are closer to true incidence of TSIH. However, in this study open technique of abdominal entry and Hasson 12mm trocar next to the umbilicus were exclusively used. In addition, specimen was extracted through umbilical incision in all patients and most importantly, postoperative umbilical wound infection rate was high (18%). Therefore these results may not be extrapolated to all LCs. Besides, the TSIH rate with newer bladeless trocars, which split rather than cut tissue fibers upon entry is reported to be 0.6 - 1.6% even without a closure of the

fascia defect (Chiong, Hegarty et al. 2010, Pilone, Di Micco et al. 2014). Nevertheless, TSIH may be underdiagnosed since follow-up time in most studies is short and nearly half of patients with TSIH are asymptomatic (Erdas, Dazzi et al. 2012). Hence, repair of midline trocar sites ≥ 10 mm particularly in the umbilicus region is recommended by most authors regardless of trocar design or patient and procedure variables. (Uslu, Erkek et al. 2007, Helgstrand, Rosenberg et al. 2011, Erdas, Dazzi et al. 2012, Swank, Mulder et al. 2012, Comajuncosas, Hermoso et al. 2014).

2.2.5 Persistence of abdominal pain after cholecystectomy

Complicated gallstone disease is considered an indication for cholecystectomy unless the patient is unfit for surgery. Similarly, cholecystectomy is recommended for patients with symptomatic gallstones particularly in case of abdominal pain. However, there is no consensus what kind of pain is typical for gallstones. Although episodic moderate or intense steady pain, lasting more than 15 - 30 minutes, located in the right upper abdomen and/or epigastrium, and sometimes radiating to the back is often considered as typical biliary pain, its diagnostic accuracy does not exceed 50%. Thus the diagnosis of symptomatic gallstones remains often uncertain. As a consequence, about one-third of patients with uncomplicated symptomatic gallstone disease continue to have abdominal pain after cholecystectomy (Berger, Olde Hartman et al. 2003, Halldestam, Kullman et al. 2008, Schmidt, Dumot et al. 2012, Lamberts, Lugtenberg et al. 2013). Moreover, up to 14% of patients may experience de novo upper abdominal pain after the cholecystectomy (Lamberts, Lugtenberg et al. 2013). Halldestam et al. (2008) have compared the outcome after elective LC in terms of abdominal pain persistence between gallstone patients with “typical biliary” pain and patients with atypical and/or multiple pain locations. Abdominal pain persisted in 29% of patients in both groups. However, in spite of pain persistence, significantly larger proportion of patients with typical preoperative pain experienced improvement of their symptoms than patients with atypical pain (21 vs. 6%, respectively). Similarly, fewer patients with typical pain considered their symptoms as unchanged or worse after the operation (9 vs. 23%) (Halldestam, Kullman et al. 2008). On the contrary, clear difference (8 vs. 28%) in symptom persistence rate between patients with biliary colic and patients with less specific upper abdominal pain was found by Berger et al. (2003). Schmidt et al. (2012) detected a trend towards the greater rate of postoperative symptom relief among symptomatic gallstone patients with less frequent pain attacks (≥ 1 pain attack per week vs. ≤ 3 pain attacks per month vs. ≤ 2 pain attacks per 3 months). Verthus et al. (2002) randomized symptomatic gallstone patients to operation and observation. Although 51% of

observation group eventually underwent cholecystectomy during 5-year follow-up period, the unoperated patients demonstrated similar improvement in abdominal symptoms and quality of life scores with operated patients (Vetrhus, Søreide et al. 2004). In addition, of operated patients 7% had major and 4% minor postoperative complications whereas in observation group complications of gallstone disease occurred in only 4% of patients (Vetrhus, Søreide et al. 2002).

2.3 NOVEL TECHNIQUES OF CHOLECYSTECTOMY

In recent years, a search for less invasive alternatives to conventional multiport laparoscopy has led to innovative techniques of single incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES) (Soper 2011). In SILS single incision at the umbilicus with either multiple transfascial ports or one purpose-built port is used for abdominal entry. NOTES uses vaginal, gastric, colonic, or vesical routes to access abdominal cavity (Pollard, Fung et al. 2012). As cholecystectomy is the most commonly performed laparoscopic surgical procedure, much of the development of SILS and NOTES techniques has been directed toward it. Regarding robotic cholecystectomy, meta-analysis consisting of five RCTs revealed no significant advantages over conventional LC (Gurusamy, Samraj et al. 2012). In addition, robotic cholecystectomy has significantly longer operative time and higher cost (Maeso, Reza et al. 2010).

2.3.1 Single incision laparoscopic cholecystectomy

The related expectation of single incision laparoscopic cholecystectomy (SILC) has been that diminishing the number of abdominal incisions may reduce the wound related complications, decrease postoperative pain and improve cosmetic outcome (Curcillo, Podolsky et al. 2011). In theory, the SILC technique should be easy to adopt by experienced laparoscopic surgeons since umbilical access affords a view of the peritoneal cavity identical to multiport LC (Figure 4) and it is performed with either conventional laparoscopic instruments or instruments very similar to

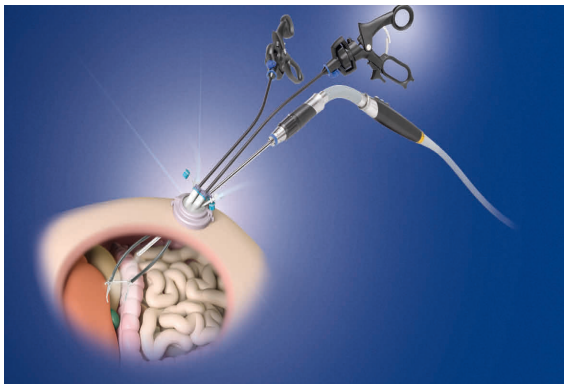

Figure 4. SILC

them (Pollard, Fung et al. 2012). However, it appears that even with the expertise in laparoscopic surgery the acceptable level of competence may be achieved after 20 and well-developed skills only after 40 SILC procedures (Hernandez, Ross et al. 2010, Qiu, Sun et al. 2011, Pan, Liang et al. 2013). The main drawbacks of SILS are collision and loss of triangulation of instruments, compromised field of view due to obstruction by instruments entering the common port, and inadequate retraction and exposure (Shussman, Schlager et al. 2011). In review of 103 early case series with total of 3,989 SILCs, the mean operative time was 79 (range 19 - 276) minutes and length of stay 1.5 (0 - 10) days. There was no mortality, complications occurred in 4% of patients while the wound related problems were most frequent. The incidence of BDI was 0.5% including 3 (0.1%) major BDIs. Many of the studies have excluded patients with elevated BMI, significant co-morbidities, acute pathology and previous abdominal surgery (Pollard, Fung et al. 2012, Lirici, Tierno et al. 2016). Recent meta-analysis by Trastulli et al. (2013) including 13 randomized clinical trials comparing SILC with conventional LC, concluded that SILC has longer operating time, greater intraoperative blood loss but better cosmetic outcome. There were no differences in rate of conversion to open, length of hospital stay, postoperative pain, adverse events, wound infections or TSIH. However, the results regarding TSIH must be interpreted with caution, as follow-up time of SILC patients in analyzed studies was short (a median of 9 months) (Trastulli, Cirocchi et al. 2013). According to prospective randomized, multicenter, single-blind trial published after cited meta-analysis, the rate of TSIH after one year follow-up was 1% and 8% ($p = 0.03$) in LC and SILC, respectively (Marks, Phillips et al. 2013). The instrumental cost analyses have revealed significantly higher expenditures in association with SILC, particularly if SILS-specific ports as well as instruments (with curved or articulating shaft) are used (Henriksen, Al-Tayar et al. 2012, Leung, Yetasook et al. 2012).

2.3.2 Natural orifice transluminal endoscopic surgery

Unlike SILS the NOTES implementation into clinical practice has been limited due to concerns regarding the safety of transluminal access and a lack of appropriately designed instrumentation (Moris, Bramis et al. 2012). Among NOTES procedures cholecystectomy is by far the most common operation while in the majority of cases the procedure is hybrid (involving transabdominal assistance, usually through umbilicus) and by transvaginal (TV) access (Arezzo, Zornig et al. 2013). Several different sets, combinations and arrangements of instruments have been described including TV inserted one or two flexible endoscopes or rigid laparoscope or instruments designed primarily for transanal endoscopic microsurgery (TEM) combined with

transumbilically placed grasper. Transgastric route has been used in less than 3% of reported cases (Moris, Bramis et al. 2012, Arezzo, Zornig et al. 2013). In reported series of TV cholecystectomies the mean operative time has been 49 - 107 minutes and hospital stay 2.2 (0 - 11) days. The rates of additional transabdominal trocar usage and conversion to laparoscopy were 5 - 6% and 0.7 - 3%, respectively. Overall complication rates were 1 - 17% without reported mortality. Similarly, minor (biliary leaks) but no major BDIs in published series have occurred (Pollard, Fung et al. 2012, Arezzo, Zornig et al. 2013, Wood, Panait et al. 2014). According to small prospective cohort studies, TV access seems not to affect female sexual function 1, 3 and 12 months postoperatively (Linke, Luz et al. 2013, Wood, Solomon et al. 2014). When compared to conventional laparoscopic procedure, TV cholecystectomy has comparable intra- and postoperative complication rates, tends to last longer with an average of 17 - 25 minutes, and seems to cause less postoperative pain (Wood, Dabu-Bondoc et al. 2014, Borchert, Federlein et al. 2014, Bulian, Knuth et al. 2015, Sodergren, Markar et al. 2015). Further studies in well-controlled settings along with development of multitasking platforms to perform pure NOTES are needed to reveal potential advantages of NOTES cholecystectomy over the current gold standard of LC (Soper 2011, Fuchs, Meining et al. 2013).

2.4 LAPAROSCOPIC CHOLECYSTECTOMY IN ELDERLY PATIENTS

Definitions of old age are not consistent from the standpoints of biology, demography, employment and retirement, and sociology. For statistical and public administrative purposes as well as in biomedical research the old age is frequently defined as 65 years or older (Orimo 2006).

The prevalence of gallstone disease increases with age in almost all populations and in both sexes (Sakorafas, Milingos et al. 2007). It is estimated that up to 28 - 32% of men and 42 - 53% of women aged >75 years have either gallstones or had previously undergone cholecystectomy (Borch, Jönsson et al. 1998, Arthur, Edwards et al. 2003). About 30% of elderly patients with gallstones develop symptoms and the disease is usually more severe with a greater percentage (43 - 55%) of complicated cases than in younger patients (Arthur, Edwards et al. 2003, Urbach and Stukel 2005, Bergman, Sourial et al. 2011). Biliary disease is the most common indication for intra-abdominal surgery in the elderly (Sanson and O'Keefe 1996). As in younger patients, LC is considered a treatment of choice for gallstone disease also in elderly patients (Bingener, Richards et al. 2003). However, in addition to decreased functional reserve also the rate of severe comorbidities in geriatric patients is high and may reach 100% in octogenarians

(Leandros, Alexakis et al. 2007, Lupinacci, Nadal et al. 2013). Similarly, 28 - 57% of octogenarians have had previous abdominal surgery (Brunt, Quasebarth et al. 2001, Leandros, Alexakis et al. 2007). Therefore, there is a tendency for increased use of nonoperative management with increasing age. Bergman et al. (2011) have found that within one year after initial visit for symptomatic or complicated gallstone disease the cumulative incidences of surgery were 87%, 63% and 22% among patients of 65 - 74 years, 75 - 84 years and ≥ 85 years, respectively. Yet, over 70 % of octogenarians with symptomatic gallstones initially treated nonoperatively remain symptomatic or later develop complicated disease (Arthur, Edwards et al. 2003, Bergman, Sourial et al. 2011). By the Kauvar et al. (2005) laparoscopic cholecystectomy is more often undertaken for acute cholecystitis in patients > 65 years than in younger patients (31% vs. 16%, $p < 0.05$). Procedure lasts longer (108 ± 55 min. vs. 83 ± 34 min, $p < 0.05$) and is more often converted to open procedure (15% vs. 1%, $p < 0.05$). Additionally, patients > 65 years have more complications than younger patients (15% vs. 2.8%, $p < 0.05$) (Kauvar, Brown et al. 2005). Bingener et al. (2003) have found that patients aged 65 - 69 years did not show worse outcomes than their younger counterparts, whereas in patients ≥ 80 years conversion rates 10 - 16%, morbidity rates 17 - 38% and mortality rates 2 - 3% after LC have been reported (Brunt, Quasebarth et al. 2001, Bingener, Richards et al. 2003, Kuy, Sosa et al. 2011). Throughout all studies the LC associated length of stay is longer among older age groups. At the same time, a recent study (Rao, Polanco et al. 2013) assessed the safety of elective outpatient LC in the elderly. The mean age of patients was 73 (± 6) years and ASA classification 2.5 (± 0.6). The mean operative time was 58 min. while reoperation rate was 0.8%, morbidity 3% and mortality 0.2%. The authors conclude that ambulatory LC in patients older than 65 years of age is safe and older age alone should not be considered a strong indicator for hospital admission.

3 AIMS OF THE PRESENT STUDY

The aims of the present study were:

1) To analyze the number and severity of BDIs in elective LCs performed without routine IOC. In addition, to find out the proportion of those patients who present symptoms and signs related to CBD stones after these operations.
2) To analyze the appropriateness of elective LC in the treatment of gallstone disease in the elderly patients by determining the effect of age on the treatment results. Also, to clarify the long-term results of this procedure in the elderly when compared to younger patients.
3) To assess the feasibility and applicability of SILC in small-volume community hospitals.
4) To find out the rate of abdominal symptom persistence after elective LC performed for symptomatic uncomplicated gallstone disease and, in particular, to clarify whether correlation exists between the severity of preoperative symptoms and the rate of postoperative symptom persistence.

4 MATERIALS AND METHODS

The data for studies I, II and IV was retrospectively collected from patient records of 1,101 patients (mean age 53 years, range 15 - 89 years, 874 females and 227 males) who had elective LC for symptomatic gallstone disease in Turku City Hospital for Surgery during ten years (1992 - 2001). In all cases, the diagnosis of gallbladder stones had been made by US. Out of the total of 1,101 cholecystectomies 1,022 (93%) were completed laparoscopically while 79 (7%) had to be converted to an open procedure. In all laparoscopic operations the basic technical steps were similar: pneumoperitoneum was created with Veress needle, procedures were performed with four ports, Calot's triangle was carefully dissected using diathermy hook and Maryland dissector to identify the cystic duct and artery. Metallic clips were used to close the stumps of cystic duct and artery. Gallbladder was extracted from the abdominal cavity through the epigastric incision. In converted procedures abdominal cavity was entered through the right subcostal incision and gallbladder was dissected in fundus-first manner. All the operations were performed or supervised by one of six experienced gastrointestinal or general surgeons working in the Turku City Hospital for Surgery during 1992 - 2001.

Data for studies II and IV regarding long-term outcomes of the operation was obtained by the specially designed questionnaire (Table 3) sent to 1,053 available patients a median of 6 years (range 3 to 12 years) after the operation. The questionnaire had been designed to ascertain the severity of the prevailing preoperative symptom and the recurrence of symptoms postoperatively along with the early and late complications of the procedure. Additionally, the patients were asked to assess their overall satisfaction with the results of the operation. The questionnaire was returned by 833 (79%) patients, 49 of returned questionnaires were incomplete.

Table 3. Questionnaire sent to the patients

Before the operation		
Did you experience symptoms like:		
episodic vague abdominal complaints	yes	no
attacks of intense upper abdominal pain	yes	no
which of the aforementioned symptoms was the prevailing symptom	vague	intense
Have you been in emergency department or hospitalized for your abdominal symptoms?	yes	no

After the operation		
Within one month after the operation, did you have complications as:		
wound infection (please specify, in which wound)	yes	no
fever	yes	no
prolonged wound pain (please specify in which wound)	yes	no
other complications (please, specify)	yes	no
Later after the operation, did you have:		
the same abdominal symptoms you experienced before the operation	yes	no
diagnosed biliary stones in bile ducts	yes	no
diagnosed stricture of bile ducts	yes	no
diagnosed incisional hernia after cholecystectomy (please specify in which scar)	yes	no
pain in scar after cholecystectomy (please specify in which scar)	yes	no
heartburn as a new symptom (absent before the operation)	yes	no
Have you had procedures like:		
endoscopic retrograde cholangiopancreatography (ERCP) (where, when?)	yes	no
magnetic resonance cholangiopancreatography (MRCP) (where, when?)	yes	no
abdominal operation because of bile disorders (where, when?)	yes	no
hernioplasty for incisional hernia (where, when?)	yes	no
How satisfied are you with the outcome of the operation?		
very satisfied		
satisfied		
no effect		
worse		
do not know		

The current research was approved by the Institutional Review Boards of Turku City Hospital for Surgery and Turku University Hospital.

4.1 STUDY I

The number and findings of IOCs as well as the amount and severity of BDIs, classified according to Neuhaus et al. (2000), were determined among all 1,101 operated patients (Table 1). IOC was done by cystic duct cannulation technique in patients with preoperatively abnormal LFT and/or in those whose CBD was considered to be dilated either in preoperative abdominal US or during the operation. Prior to operation 40 (4%) patients underwent ERCP for a suspicion of CBD stones. In 11 of those patients CBD stones were diagnosed and removed endoscopically.

Out of the 1,101 operated patients 33 (3%) underwent IOC. One IOC failed due to unsuccessful cannulation of cystic duct. Of 32 successful IOCs 20 were performed

laparoscopically and 12 after conversion to an open procedure. There were no complications related to IOC. CBD stones were revealed in seven (22%) patients, by laparoscopic IOC in four and by open IOC in three patients. Stone extraction laparoscopically with Dormia basket was performed in one patient. The remaining three patients with CBD stones in laparoscopic IOC had ERCP and endoscopic stone extraction postoperatively. Among three patients with bile duct stones found in open IOC, stones were extracted with Dormia basket in two and via choledochotomy in one patient. The patient with failed IOC developed jaundice within few days after operation. ERCP revealed CBD stones which were successfully removed endoscopically. Two (6%) out of the 32 IOCs were false positive leading to unnecessary CBD explorations (after conversion to open procedure in one case and via laparoscopic choledochoscopy in another case). Additionally, two (6%) IOCs were false negative as patients with normal IOC had later on ERCP for jaundice. One of them had CBD stones, which were extracted endoscopically. The other patient had stones in intrahepatic ducts. In this case clearance of stones was not achieved at ERCP. In addition, suspicion of malignancy arose, and therefore a liver resection eventually was performed. Thereafter the recovery of the patient was uneventful and no malignancy was found in histological examination.

The cases with postoperative symptoms and signs characteristic to biliary pathology and leading to ERCP and/or MRCP in follow-up were detected from patient records and the radiological database of the Hospital District of Southwest Finland. The findings of ERCP and MRCP were recorded.

4.2 STUDY II

The study population comprised all patients aged ≥ 75 years (n = 80, 67 females and 13 males) at the time of the operation. For controls, 80 patients aged 65 - 74 years and 80 patients < 65 years were used, both groups with female to male ratio identical to study group. As our study began with the first LCs in our institution and the team of surgeons remained constant during the study period, the patients could be matched for the learning curve of the surgeons by picking up corresponding controls whose operations were close in time to the operations of the patients in the study group. There were higher prevalence of comorbidities and complicated disease (defined as history of cholecystitis, jaundice, cholangitis or biliary pancreatitis) in patients belonging to the older age groups while by other characteristics there were no differences between the groups (Table 4).

Operative and hospitalization times, conversions to open surgery, intraoperative and postoperative complications, reoperations, re-hospitalizations and mortalities were analyzed. Long-term results were obtained from the above-mentioned questionnaire which was returned by 84, 80 and 56% of patients in the groups aged < 65, 65 - 74 and ≥ 75 years, respectively.

Table 4. Comparability of the three age groups of patients (n = 80 in each group) scheduled to undergo LC.

	< 65 years	**65 - 74 years**	**≥ 75 years**	**Overall *p*-value**
Females/males (%)	67 (84)/13 (16)	67 (84)/13 (16)	67 (84)/13 (16)	
Mean BMI ± SD	25.9 ± 3.4	26.3 ± 4.5	25.6 ± 4.5	0.810
Operated earlier, n (%)	43 (54)	50 (63)	37 (47)	0.139
Upper abdomen	0	3	2	
Lower abdomen	43	47	35	
Comorbidity, n (%)	25 (31)	50 (63)	62 (78)	< 0.001
Main preoperative symptom, n (%)				0.018
Biliary colic	33 (41)	27 (34)	21 (26)	
Unspecific	39 (49)	37 (46)	34 (43)	
Complicated disease	8 (10)	13 (20)	25 (31)	

LC = laparoscopic cholecystectomy

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4.3 STUDY III

From January to July 2010, a total of 51 patients [41 females and 10 males, the mean age 44 (21 - 75) years, BMI 26 (18 - 35)] underwent elective SILC in small-volume Salo (n = 29) and Loimaa (n = 22) community hospitals. The main preoperative symptom was biliary colic in 30 (59%) patients and unspecific upper abdominal pain in 13 (25%) patients. Eight (16%) patients had had some complication of gallstone disease including jaundice, acute cholecystitis, cholangitis and biliary pancreatitis. Eight (16%) patients had preoperative MRCP and/or ERCP while bile duct stones were found in four (8%) of them

Figure 5. TriPort™

and removed at ERCP. Seventeen (33%) patients had undergone previous abdominal surgery. Fourteen (27%) patients had cardiovascular, respiratory, endocrine, renal or other co-morbidity with potential to affect the course of the operation or the recovery after the procedure.

The operations were performed by two separate surgical teams, of which both included two experienced laparoscopic surgeons. In all 51 procedures, purpose-built multichannel port devices were used. Thirty-four (67%) operations were done through TriPort™ (Olympus, Bray, Ireland) (Figure 5) and 17 (33%) through GelPOINT™ (Applied Medical, Rancho Santa Margarita, California) devices (Figure 6).

Peritoneal cavity was entered under visual control through 2 cm incisions in umbilical skin and fascia. Multichannel port device was fixed in place, followed by insufflation of the abdominal cavity up to the pressure of 8-12 mmHg. The patients were placed in reverse Trendelenburg position with slight tilt to the left. The surgeon stood between the legs and the first assistant on the left side of the patient. Most of the operations were performed with standard 5-mm 30-degree rigid laparoscopes, in some procedures 5-mm or 10-mm laparoscope with deflectable-tip (EndoEYE; Olympus, Tokyo, Japan) was applied.

Figure 6. GelPOINT™

In all operations with TriPort™, also instruments with curved shaft [grasping forceps, dissection forceps and monopolar hook (Olympus Medical Systems Europe, Hamburg, Germany)] were used (Figure 3). Before dividing, the cystic duct and artery were closed with 5-mm clip applicator. In the early phase of the current series, one or two additional 5-mm abdominal trocars for graspers were placed if sufficient view of the triangle of Calot was not achieved with single port technique. Later on, transabdominal suture retraction was applied to facilitate safe access to Calot's triangle. Sutures were inserted at the upper midline near the falciform, passed through the Hartmann`s pouch in a figure-of-eight fashion, and brought out at the right lower quadrant. After extraction of the gallbladder, fascial incision was sutured with polydioxanone (PDS®;

Ethicon GmbH, Norderstedt, Germany), and skin closed with either interrupted polyglactin (Vicryl Rapide®; Ethicon GmbH, Norderstedt, Germany) or continuous intradermal poliglecaprone (Monocryl®; Ethicon Ltd, Edinburgh, UK) sutures.

Routine antibiotic prophylaxis was not used. Thirteen (25%) patients received antibiotic (cefuroxime 1.5g) during the operation for protraction of the procedure or for profuse spillage of contents of gallbladder into abdominal cavity.

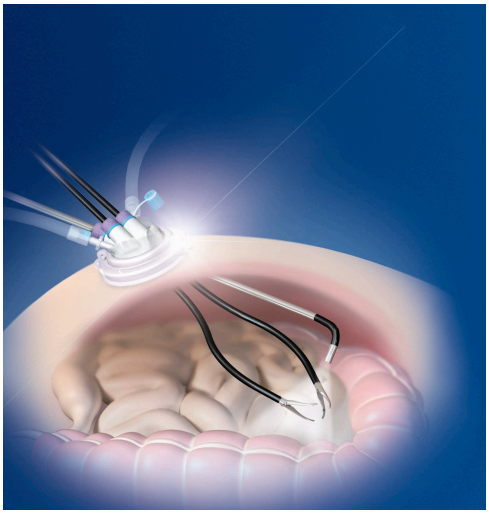

Figure 7. Curved instruments

Operative and hospitalization times, conversions to multiport or open surgery, intraoperative complications and mortality were prospectively recorded. To detect postoperative early and late complications, rehospitalizations, reoperations and duration of sick leave the operated patients were seen in outpatient clinic or interviewed by phone. The results concerning complications, rehospitalizations and reoperations were verified and reinforced from a digital database covering the entire Hospital District of Southwest Finland.

4.4 STUDY IV

The principal data for the study IV was obtained from the questionnaire described above. The data regarding patients demographics, co-morbidities, previous abdominal operations, details of operation, hospitalization times, complications, reoperations, rehospitalizations and mortalities were obtained from patient records and digital database covering the whole Hospital District of Southwest Finland. Of the patients who returned the completed questionnaire, 667 [554 (83.1%) females and 113 (16.9%) males] were eligible (uncomplicated cases) for the analysis (Figure 4). The patients were divided into two groups according to the prevailing preoperative symptom: group 1 (n = 380) with severe symptoms (defined as attacks of intense upper abdominal pain), and group 2 (n = 287) with mild symptoms (defined as episodic vague abdominal complaints). Except for the age, which was less in the group 1 the characteristics of the two groups were comparable (Table 5). Likewise, there were no statistically significant

differences in perioperative data and postoperative complications between the two groups (Table 6).

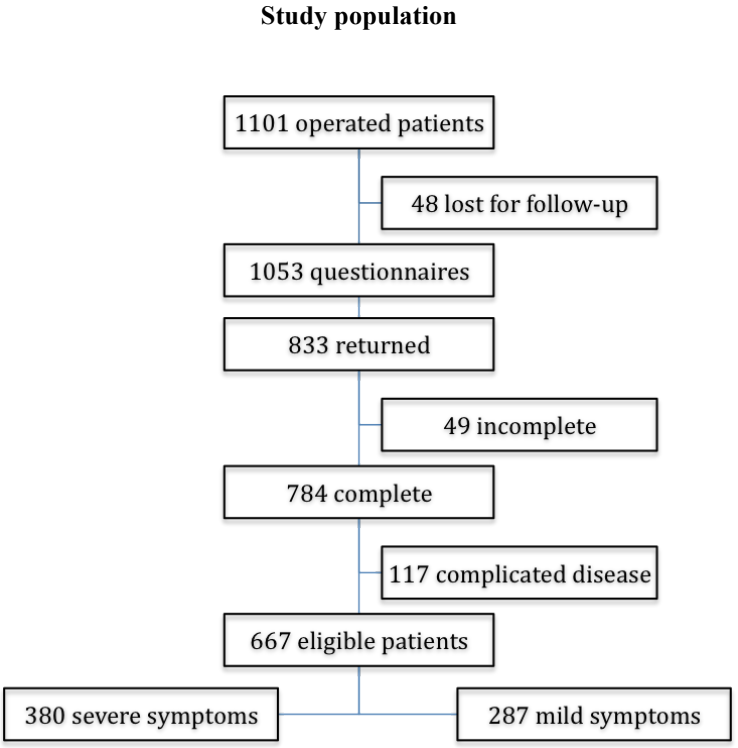

Figure 8. Patient selection for analysis
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Table 5. Characteristics of the two patient groups with the different preoperative symptoms

	Severe n = 380	**Mild n = 287**	***p***
Age, years[1], median (range)	57 (21 - 94)	63 (25 - 94)	< 0.0001
Females, n (%)	312 (82.1)	242 (84.3)	0.4674
BMI, median (range)	27.1 (13.7 - 41.9)	26.7 (18.1 - 47.3)	0.4505
Comorbidity, n (%)	141 (37.1)	120 (41.8)	0.2299
Operated earlier, n (%)	199 (52.4)	163 (56.8)	0.2722

[1] Age of the patients when returning the questionnaire

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Table 6. Perioperative characteristics and postoperative complications in the two patient groups with different preoperative symptoms

	Severe n = 380	**Mild n = 287**	***p***
Operative time, minutes, median (range)	65 (20 - 255)	60 (25 - 270)	0.1866
Conversions, n (%)	28 (7.4)	19 (6.6)	0.7614
Hospitalization, days, median (range)	2 (1 - 29)	2 (1 - 25)	0.3342
Complications[1], n (%)	26 (6.8)	15 (5.2)	0.4199
Reoperations, n (%)	2 (0.5)	2 (0.7)	1
Readmissions, n (%)	7 (1.8)	3 (1.0)	0.5276
ERCP, n (%)	3 (1.2)	2 (0.7)	1
BDI, n (%)	3 (1.2)	0	0.2635
Prolonged wound pain, n (%)	46 (12.1)	40 (13.9)	0.4865
Incisional hernia, n (%)	2 (0.5)	3 (1.0)	0.6564

[1] Complications other than BDI and incisional hernia

ERCP = Endoscopic retrograde cholangiopancreatography postoperatively; BDI = Bile duct injury

4.5 STATISTICS

Differences measured in the study II were overall differences comprising all three age groups. A Kruskal-Wallis test was used to compare the differences in continuous variables between the age groups (< 65, 65 - 74, ≥ 75 years). Categorical variables were analyzed with a χ^2 or Fisher's exact test. In study IV continuous variables were characterized with medians and range of values. Differences between patient groups were tested with non-parametric tests due to skewed distributions of variables. Categorical variables were cross-tabulated and differences in distributions were tested with χ^2 or Fisher's exact test when applicable. *P*-values < 0.05 were considered statistically significant.

5 RESULTS

5.1 BILE DUCT INJURIES AND SYMPTOMATIC RESIDUAL COMMON BILE DUCT STONES WITH SELECTIVE USE OF INTRAOPERATIVE CHOLANGIOGRAPHY (STUDY I)

5.1.1 Bile duct injuries

BDIs were detected in five (0.5%) patients: CBD injuries in two (0.2%), minor bile leakages in two (0.2%) and late stricture of CBD in one (0.1%) patient. Of CBD injures one was complete transection (type D1) and the other was small tangential injury (type C1). Both were diagnosed during the initial procedure and operations were converted to laparotomy. The continuity of transected CBD was restored by primary end-to-end anastomosis and secured by T-tube. The tangential injury was sutured and T-tube left in CBD. There was no need for re-interventions and no long-term complications occurred in these patients. Two minor bile leakages (one type A1 and the other type A2) were diagnosed in the early postoperative period by ERCP. One of these patients was treated with endoscopic sphincterotomy and biliary stenting while the other one with endoscopic sphincterotomy only. In both cases, intra-abdominal bile collections were drained percutaneously. Both patients had uneventful recovery. There was one late stricture of CBD (type E1) found in ERCP seven months postoperatively. This patient underwent successful hepaticojejunostomy after repeated treatment attempts via endoscopic and percutaneous approaches. No further late complications occurred in this case.

5.1.2 Symptomatic residual common bile duct stones

During a mean follow-up of 72 months (range 36 - 144) 22 (2%) out of 1,101 patients were found to present symptoms and signs characteristic to biliary pathology leading to MRCP and/or ERCP. Of them ERCP was performed in 16 and MRCP in three patients. Three patients underwent both MRCP and ERCP. CBD stones were found in ten (0.9%) cases including two patients with false negative IOCs. All patients underwent successful stone removal at ERCP except for the patient with stones in intrahepatic radicals leading to liver resection (see 4.1 Study I, Patients and Methods section).

5.2 ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY IN ELDERLY PATIENTS (STUDY II)

The data regarding operative and hospitalization times, conversions, intraoperative and postoperative complications, reoperations, rehospitalizations and mortalities in the three age groups are presented in Table 7. Although the mean duration of operations (61, 65, 72 min) and conversion rate to open surgery (6%, 11%, 16%) seemed to increase with age, the differences were not statistically significant. In hospitalization times (2.1 days, 3.3 days, 4.4 days) and in complication rates (0%, 11%, 13%) significant increase was found in older age groups. There were neither severe complications, such as bile duct injuries, nor mortality in any of the age groups. Only small minority of the patients in the two oldest age groups had to be rehospitalized afterwards. Two (3%) patients underwent reoperations, both in the age group ≥ 75 years.

Table 7. Operative and hospitalization times, conversions to open surgery, intra- and postoperative complications, reoperations, rehospitalizations and mortality in the three age groups of patients (n = 80 in each group) who underwent laparoscopic cholecystectomy

	< 65 years	**65 - 74 years**	**≥ 75 years**	Overall *p*-value
Mean operative time ± SD, min	61 ± 23	65 ± 23	72 ± 35	0.139
Mean hospitalization ± SD, days	2.1 ± 1.4	3.3 ± 2.4	4.4 ± 3.4	< 0.001
Conversions, n (%), due to	5 (6)	9 (11)	13 (16)	0.135
Anatomy	4	4	11	
Bleeding	0	3	1	
Bile duct stone	1	0	0	
Malignancy	0	1	0	
Insufflation failure	0	1	0	
Biliary fistula	0	0	1	
Complications, n (%)	0 (0)	9 (11)	10 (13)	< 0.006
Infections	0	7	6	
Bleeding	0	1	4	
Pulmonary embolism	0	1	0	
Bile duct injury	0	0	0	
Reoperation, n (%)	0	0	2 (3)	0.331
Rehospitalization, n (%)	0	3 (4)	3 (4)	0.252
Mortality	0	0	0	

Postoperatively MRCP and/or ERCP for symptoms and signs characteristic to biliary pathology were performed to 3%, 6% and 13% of patients in the age groups < 65 years, 65 - 74 years and ≥ 75 years, respectively. In the same age groups CBD stones were found in 0%, 5% and 6% of patients (Table 8).

Table 8. Number of cases with CBD stones found in postoperative MRCP and/or ERCP in three age groups of patients

	< 65 years	**65 - 74 years**	**≥ 75 years**
MRCP, n (%)	1 (1)	1 (1)	3 (4)
ERCP, n (%)	0	3 (4)	5 (6)
MRCP + ERCP, n (%)	1 (1)	1 (1)	2 (3)
CBD stones, n (%)	**0**	**4 (5)**	**5 (6)**

Regarding long-term results, 28%, 32% and 28% of the patients in the age groups < 65 years, 65 - 74 years and ≥ 75 years, experienced recurrence of preoperative symptoms, respectively. However, 97% of the patients in the youngest group as well as 83% and 80% of the patients in the two groups of older patients were very satisfied or satisfied with the long-term results of the procedure (Table 9). Nevertheless, the satisfaction of the patients decreased with increased age.

Table 9. Long-term results of laparoscopic cholecystectomy in the three age groups of patients

	< 65 years	**65 - 74 years**	**≥ 75 years**	
Very satisfied, n (%)	50 (75)	36 (56)	25 (56)	Overall *p*-value 0.037
Satisfied, n (%)	15 (22)	17 (27)	11 (24)	
No effect, n (%)	1 (1)	9 (14)	7 (16)	
Worse, n (%)	1 (1)	2 (3)	2 (4)	
67 out of 80 patients aged < 65 years, 64/80 patients aged 65 - 74 years and 45/80 patients aged ≥ 75 years returned the questionnaire.				

5.3 INITIAL EXPERIENCES OF SINGLE-INCISION LAPAROSCOPIC CHOLECYSTECTOMY IN SMALL-VOLUME HOSPITALS (STUDY III)

Of the total of 51 procedures, 42 (82%) were completed without conversion to multiport or open procedure. Of these 17 (33%) were performed with single port device only while in 25 (49%) transabdominal retraction suture was additionally applied. Seven (14%) operations were converted to multiport and two (4%) operations to open procedure (Table 10). The mean operative time was 74 (31 - 155) minutes.

Table 10. Use of retraction sutures and conversions to multiport and to open surgery in patients with an attempt of single incision laparoscopic cholecystectomy

Total number of operations	**51**
Single port device only	17 (33%)
Retraction suture	25 (49%)
One additional trocar	4 (8%)
Two additional trocars	1 (2%)
Retraction suture and additional trocar	2 (4%)
Conversion to open surgery	2 (4%)

The mean hospital stay for all patients was 0.6 (0 - 3) days. Out of the 42 patients operated without conversion to multiport or open procedure, 21 (50%) were discharged within 8 hours, 18 (43%) within 24 hours and three (7%) within 48 hours. The mean duration of sick leave among all patients was 14 (4 - 22) days.

One minor intraoperative complication (superficial liver laceration) was encountered but there were neither major intraoperative complications nor mortality in our series. Postoperatively after an average of 4 (1 - 7) months, 48 (94%) patients could be reached for follow-up. Of them 25 (52%) were very satisfied, 21 (44%) satisfied and two (4%) dissatisfied with the outcome of the procedure. Eight (16%) out of the 51 patients had complications (Table 11). Additionally seven (14%) patients reported of having prolonged wound irritation and pain without signs of infection. After day-case surgery, one patient had severe upper abdominal pain on the first postoperative day. Evaluation in emergency department revealed no complications and this patient was discharged after additional prescription of analgesics.

Table 11. Complications of the operated patients (n = 51)

Complication	**n (%)**
Wound infection	5 (10)
Hematoma in abdominal wall	1 (2)
Severe prolonged wound pain	1 (2)
Subphrenic abscess	1 (2)

5.4 PERSISTENCE OF PREOPERATIVE SYMPTOMS AFTER ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY (STUDY IV)

The overall rate of symptom persistence in the whole study population was 37%. Among patients with predominantly mild symptoms preoperatively, 42% had recurrences and, in the group with severe preoperative symptoms, 34% of patients reported persistence of symptoms ($p = 0.052$) (Table 12).

The proportion of patients who were very satisfied or satisfied with the result of the operation, exceeded 90% in both groups (Table 13). Although the rate of very satisfied and satisfied patients was also high, exceeding 85% among the patients with persistent symptoms, the overall satisfaction with the outcome of the procedure was lower in this patient group when compared to patients without recurrent symptoms ($p < 0.0001$) (Table 14).

Table 12. Recurrence of symptoms in the two patient groups with different preoperative symptoms, n (%)

Recurrence	**Severe (n = 380)**	**Mild (n = 287)**	***p***
Yes	129 (34)	119 (42)	0.0522
No	251 (66)	168 (58)	

Table 13. Satisfaction with the outcome of the operation according to the preoperative symptoms, n (%)

	Severe (n = 380)	**Mild (n = 287)**	***p***
Very satisfied or satisfied	350 (92)	260 (91)	0.2699
No effect or worse	21 (6)	23 (8)	0.2699
Do not know	9 (2)	4 (1)	

Table 14. Satisfaction with the outcome of the operation according to the postoperative symptom recurrence, n (%)

	No recurrence (n = 419)	**Recurrence (n = 248)**	***p***
Very satisfied	343 (82)	123 (50)	< 0.0001
Satisfied	56 (13)	88 (35)	
No effect	15 (4)	22 (9)	
Worse	0	7 (3)	
Do not know	5 (1)	8 (3)	

6 DISCUSSION

6.1 INTRAOPERATIVE CHOLANGIOGRAPHY

Necessity of IOC during cholecystectomy has been the subject of debate since its introduction by Mirizzi in the 1930s. The purposes of IOC are to detect asymptomatic CBD stones and to delineate biliary anatomy in order to prevent or diagnose BDIs (Ford, Soop et al. 2012). IOC may also protect against medical malpractice claims. Therefore, many consider IOC as a mandatory part of the LC. However, the data concerning utility of IOC remains controversial and the policy of routine IOC is not universally accepted.

As regards of CBD stones, in contemporary series IOC has been highly reliable having 88 – 97% sensitivity and 96 - 99% specificity with unsuspected CBD stones detected in 3 - 11% of patients undergoing LC with routine IOC (Collins, Maguire et al. 2004, Videhult, Sandblom et al. 2009). Management options for detected stones include laparoscopic transcystic stone extraction, laparoscopic or open CBD exploration and intraoperative or postoperative ERCP procedure (Overby, Apelgren et al. 2010). Considering low incidence of unsuspected CBD stones, few surgeons are able to develop or maintain skills necessary for laparoscopic CBD exploration. With conversion to open CBD exploration, advantages of minimally invasive approach are lost. Intraoperative ERCP procedure creates an organizational challenge, and is not available in all institutions (Ammori and Al-Dabbagh 2012). Moreover, as shown by Collins and al. (2004) up to one third of patients with detected CBD stones clear their ducts spontaneously after the operation thus making instrumentation of CBD unnecessary (Collins, Maguire et al. 2004). In addition, the alternative strategies with selective IOC or omitting IOC altogether and performing pre- or postoperative MRCP and therapeutic ERCP in patients with suspicion of CBD stones have proved to yield very low incidence of severe complications caused by missed CBD stones (Hamad, Nada et al. 2011, Ammori and Al-Dabbagh 2012). Although the cost-effectiveness analyses seem to favour single-stage approaches containing routine IOC and laparoscopic CBD exploration, these results cannot be extrapolated worldwide due to dissimilarities in healthcare reimbursement policies (Brown, Rogers et al. 2011, Epelboym, Winner et al. 2013).

Twenty-two patients (2%) of our study population underwent postoperatively MRCP and/or ERCP for symptoms and signs characteristic to biliary pathology. Residual CBD stones were found in ten (0.9%) patients. Two of these patients had false negative IOC. Additionally, two patients manifested their symptoms 27 and 33 months postoperatively thus having probably CBD stones that have arisen de novo after operation. Consequently, we can assume that, at most,

only six patients (0.5%) could have been spared from symptomatic residual stones by routine IOC.

Studies regarding the effectiveness of IOC in preventing BDIs, tend to favour routine use of IOC (Ludwig, Bernhardt et al. 2002, Flum, Dellinger et al. 2003, Alvarez, de Santibañes et al. 2014). However, whether the association between IOC and a lower BDI rate found in cohort studies and case series is causal or confounded by another variable is unknown (Sheffield, Riall et al. 2013). Other limitations of these studies are variability in the definition of BDI and the lack of quality control over reporting standards (Ford, Soop et al. 2012). Likewise, given the low incidence of BDIs, existing randomized control trials (RCT) may be underpowered (Sheffield, Han et al. 2012). Moreover, a RCT to demonstrate a difference in BDIs seems unrealistic, as sample size of > 15000 to give 90% power would be needed (Ford, Soop et al. 2012).

In our study there was one transection of CBD and routine use of IOC could probably have prevented this injury. However, in this case instead of transection there would have been incisional injury of CBD since cannulation for IOC would have been made through CBD. As regards other two CBD injuries in our study (one tangential injury and one late stricture), it is generally accepted that IOC does not prevent this kind of injuries. Similarly, IOC does not prevent cystic dump leakages and usually does not reveal small-volume leaks from aberrant bile ducts. Thus, in our patient population the routine use of IOC may not have reduced the overall incidence of BDIs.

6.2 ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY IN ELDERLY PATIENTS

We determined the effect of age on outcomes of elective LC. Our results encourage to employ elective LC also in the treatment of elderly gallstone patients. However, considering the heterogeneity of health status in older adults, the patients' physiologic reserves rather than chronological age determines the outcome of surgical procedures. Thus, studies like ours, where outcomes are analyzed according to patient's age, provide insufficient data to predict the outcome of surgical procedure for individual elderly patient. Meanwhile, the concept of frailty has been recognized as a unique domain of health status that can be a marker of decreased reserves and resultant vulnerability in older patients. Frailty is defined as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss (5kg in past year), self-reported exhaustion, decreased grip strength (weakness), slow walking speed, and low physical activity (Fried, Tangen et al. 2001, Robinson, Walston et al. 2015). In elderly

surgical patients frailty seems to predict postoperative complications, increased length of stay, and discharge to an assisted or skilled nursing facility (Makary, Segev et al. 2010).

Unlike other reports, in our study the mean operative time and conversion rates as well as rehospitalisation and reoperation rates did not differ between younger and older patients (Qasaimeh and Banihani 2012). This may be explained by the fact that we analyzed elective procedures only whereas in most other studies acute cases were included as well (Leandros, Alexakis et al. 2007). However, in a recent population-based study by McKay et al. (2013) emergency gallbladder surgery in the elderly was not associated with higher mortality or complication rate compared with the elective setting. Nevertheless, similarly to other studies also in our research the rate of complications and the mean hospitalization time increased in older age groups. Obviously, decreased physiologic reserves in older patients with or without concurrent comorbidities predispose to complications (Alcock and Chilvers 2012, McKay, Katz et al. 2013). On the other hand, there were neither major complications nor mortality in our series, which enables us to conclude that elective LC is safe and applicable in the treatment of gallstone disease also in elderly patients.

Traditionally, "elderly" has been defined as a chronological age of 65 years or older, even though the rationale for such a definition is unknown. With advances in medicine and public health, improved living standards, greater educational attainment, and decreased fertility the life expectancy as well as healthy life expectancy have increased rapidly in most regions of the world (Salomon, Wang et al. 2012). Thus, to simply categorize all persons over 65 years as elderly seems no longer appropriate. Based on comprehensive analysis of Japanese data from a survey on public attitudes, surveys on elderly requiring nursing care, longitudinal studies of functional independence in the elderly and clinical and pathological data, the researches have proposed to change the definition of elderly to those over 75 years of age (Orimo 2006). Indeed, as Japanese have the world's highest life expectancy, their data cannot be extrapolated to other developed countries, let alone worldwide. However, redefining the concept of elderly in the face of aging society while the proportion of healthy aged persons increases, seems inevitable for most industrialized countries.

For obvious reasons the data concerning long-term results of any treatment modality in elderly patients is difficult to obtain. Accordingly, we found no earlier studies on the long-term results of LC in the elderly. Of our study population after a median of seven years only 64/80 patients aged 65 - 74 years and 45/80 patients aged ≥ 75 years were available for follow-up. Additionally, regarding the putative decline of cognitive abilities in elderly and in order to get higher response rate, the long-term results in our study were assessed by simplified 4-grade

scale (very satisfied, satisfied, no effect, worse). In spite of these limitations, the knowledge about the long-term results of elective LC in elderly patients obtained by current study seems plausible. The decrease in satisfaction with long-term results of the procedure among older patients corresponds well with the higher rate of postoperative complications and particularly with biliary symptoms along with higher rate of detected residual bile duct stones postoperatively. To some extent, the greater dissatisfaction of older patients may be because of misinterpretation of questionnaire so that the estimation of outcome concerns the overall health status more than the outcome of the operation.

6.3 SINGLE INCISION LAPAROSCOPIC CHOLECYSTECTOMY

Study to assess feasibility and applicability of SILC in small-volume hospitals was undertaken after emergence of two new concepts in minimally invasive surgery. Of these the NOTES is more radical and intriguing due to the idea of entering abdominal cavity through natural orifices instead of transabdominal route. However, unaccustomed access routes, problems with visualization and unconventional dissection techniques in NOTES necessitate radically different instrumentation, which has been unavailable so far. Therefore, the implementation of NOTES to clinical practice has remained limited. On the other hand the concept of SILS has met more favourable acceptance in surgical community. Applicability of conventional laparoscopic instruments and development of purpose-built multichannel ports helped the introduction and adoption of SILS. Reduction of the number of ports to only one raises expectations about diminished wound related complications, decreased postoperative pain and improved cosmetic outcome after SILS. In addition, SILS is also seen as “stepping stone to NOTES” (Froghi, Sodergren et al. 2010, Ahmed and Paraskeva 2011).

Contrary to expectations the results of our study demonstrate increased rate of wound related problems after SILC. Five (10%) patients had wound infection, one patient (2%) had severe prolonged wound pain and additional seven (14%) patients had prolonged wound irritation accompanied with some pain. It can be speculated that having wound in navel, i.e. in deep and narrow skin fold, may predispose to wound complications. Another predisposing factor for wound complications could be the multichannel port device itself, which after fixation in wound may cause a hypoperfusion of adjacent tissues by stretching and squeezing of wound edges. In addition, in our series routine antibiotic prophylaxis was not used, even in patients at high risk of post-operative infections (age > 60 years, a recent history of acute cholecystitis, cholangitis, jaundice and obesity). In the studies with routine use of antibiotic prophylaxis the postoperative wound infection rates in SILC patients have been around 2% (Cao, Cai et al. 2011,

Phillips, Marks et al. 2012, Chang, Wang et al. 2015). As four out of five our patients with wound infection were high-risk patients, antibiotic prophylaxis may have prevented wound infection in these patients.

The most serious complication in our study was subphrenic abscess. In a patient with history of biliary pancreatitis diffuse omental adhesions to thick-walled gallbladder were found in operation. During the dissection gallbladder perforation and spillage of bile and numerous gallstones into abdominal cavity occurred. Since operation was converted to multiport procedure in early phase of the operation, this complication cannot be attributed solely to SILC.

The most alarming disadvantage, encountered by us with SILC, was the inability to achieve a clear view of the triangle of Calot. Since reduced number of graspers in SILC precludes sufficient retraction of the infundibulum, the anatomy of the triangle of Calot is difficult to identify, thus predisposing to bile duct and other injuries (Allemann, Demartines et al. 2014). Although, we succeeded to perform 17 operations without applying additional measures to improve retraction and no complications followed, in the later phase of our study transabdominal retraction sutures were routinely used to improve the feasibility and safety of the procedure (MacDonald, Alkari et al. 2010). However, placing transabdominal suture is time consuming, predisposes to visceral injuries and by perforating gallbladder causes spillage of bile with some deterioration of visibility in the operating field. In addition, one patient in our series had painful hematoma in abdominal wall in site of suture insertion.

Another complication, which may be regarded as specific to SILC, was related to instruments with curved shaft. Advantages of these instruments are diminished collision and improved angulation but due to the curved shaft these instruments behave differently when movements habitually used with straight instruments are applied. For instance, rotation around longitudinal axis leads to swinging of the tip of the curved instrument with wide amplitude. Likewise, passing curved instrument through the port is accompanied with large-scale movements of the tip of the instrument. We believe that unfamiliarity of the surgeon with these instruments contributed to the superficial liver laceration encountered in our study.

6.4 SYMPTOM PERSISTENCE AFTER ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY IN PATIENTS WITH SYMPTOMATIC UNCOMPLICATED GALLSTONE DISEASE

Symptomatic gallstone disease is considered an indication for cholecystectomy. However, considerable proportion of patients experience persistence of abdominal symptoms postoperatively. Predicting the putative benefit of cholecystectomy for a particular gallstone patient is challenging because connection between gallstones and abdominal symptoms remains

obscure and the decision whether to proceed to cholecystectomy seems to rely more often on the severity than on the nature of patients' symptoms. Therefore, we decided to ascertain whether the rate of symptom persistence after elective LC in symptomatic gallstone patients varies according to the severity of preoperative symptoms. We found overall symptom persistence rate of 37%. Patients with mainly mild preoperative symptoms seem to have more recurrences than those with severe symptoms (42% vs. 34%); yet, the difference lacks statistical significance.

The main limitations of our study are retrospective design and potential recall bias, as the questionnaire was completed up to 12 years postoperatively. In addition, a long follow-up time forced us to simplify questions concerning symptoms. On the other hand, the follow-up time of our study was long enough to reveal the final outcome of LC. Additionally, we believe that a simplified questionnaire contributed to the high response rate (79%).

In our study the vast majority of patients with persistent symptoms (> 85%) were satisfied or very satisfied with the outcome of the procedure. In previous reports it has been found that the nature of persistent symptom is important in determining postoperative satisfaction. By Weinert et al. (2000) among patients with a persistence of abdominal pain, 42% were dissatisfied compared with 7% among those with recurrence of symptoms other than pain. In addition, although symptoms persist, they seem to be significantly less frequent, severe and distressing (Weinert, Arnett et al. 2000, Finan, Leeth et al. 2006).

Surprisingly, 3% of patients without recurrent symptoms evaluated the outcome of the operation as `no effect`. These patients could have misinterpreted the questionnaire so that their evaluation concerns the overall health status rather than the outcome of the operation. This assumption is supported by the fact that the average age of these patients was older (76 years vs. 59 years) when compared with the rest of the patients without recurrent symptoms.

Studies attempting to reveal predicting factors of symptom persistence after cholecystectomy have produced results with limited clinical usefulness. For example, knowing that preoperative dyspeptic symptoms, bad taste and flatulence are associated with three to seven times higher risk of postoperative biliary and dyspeptic symptoms barely influences the decision to proceed to cholecystectomy (Mertens, De Vries et al. 2009, Mertens, Roukema et al. 2010, Thistle, Longstreth et al. 2011, Wanjura and Sandblom 2016). Nevertheless, it is of utmost importance to adjust patients' expectations of the outcome of the procedure by explaining the abstruse relationship between gallstones and abdominal symptoms. As long as the association of abdominal symptoms and gallstones stays unclear, the rate of patients with persistent symptoms after cholecystectomy does not decrease.

7 CONCLUSIONS

The data of the present study lead to the following conclusions:

1. In elective LCs with selective IOC the incidence of BDIs remains low and, later, only few patients have symptomatic CBD stones.
2. Elective LC is a safe and feasible operation with good long-term results in elderly patients.
3. SILC might be adopted without major complications in small-volume hospitals. The rate of wound infections seems to increase with the adoption of SILC.
4. More than one-third of patients with symptomatic uncomplicated gallstone disease experience persistent symptoms after elective LC. The rate of symptom persistence tends to be higher in patients with mild preoperative symptoms.

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