Department of Gastrointestinal Surgery, Abdominal Centre
Helsinki University Hospital
Doctoral Programme in Clinical Research
Faculty of Medicine
University of Helsinki, Finland

Gallbladder surgery – novel insights into treatment of benign and malignant diseases, complications, and treatment outcomes

Hanna Koppatz

DOCTORAL DISSERTATION

To be presented for public discussion with the permission of the Faculty of Medicine of the University of Helsinki, in Auditorium 2, Biomedicum, University Meilahti Campus, on the 18th of June, 2021 at 12 o'clock.

Helsinki 2021

Supervisors
Adjunct professor Ville Sallinen M.D., Ph.D.
Department of Liver and Transplantation Surgery
Department of Gastrointestinal Surgery
Helsinki University Hospital
Helsinki, Finland

Adjunct professor Tom Scheinin M.D., Ph.D.
Department of Gastrointestinal Surgery
Helsinki University Hospital
Helsinki, Finland

Reviewers
Adjunct professor Jukka Karvonen M.D., Ph.D.
Department of Gastrointestinal Surgery
Turku University Hospital
Turku, Finland

Adjunct professor Joonas Kauppila M.D., Ph.D.
Department of Surgery
Oulu University Hospital
Oulu, Finland

Opponent
Professor Kjetil Søreide, M.D., Ph.D.
Department of Gastrointestinal Surgery
Stavanger University Hospital,
Stavanger, Norway
Department of Clinical Medicine
University of Bergen,
Bergen, Norway

ISBN 978-951-51-7207-5 (paperback)
ISBN 978-951-51-7208-2 (PDF)

Picaset Oy
Helsinki 2021

To Niklas, Ida and Emilia

CONTENTS

ABSTRACT

Background: Laparoscopic cholecystectomy (LCC) is one of the most common surgical procedures in Finland and other countries. This procedure may be associated with an increased risk of biliary complications compared to the open procedure. A three-dimensional (3D) view in laparoscopy could reduce complications and shorten the operation time of LCC compared to conventional 2D laparoscopy, but there is no previous data on this. Since bile duct injury is the most feared complication of LCC, the impact on the patient's quality-of-life (QOL) after LCC complicated by biliary injury has been extensively studied. However, little is known about the QOL of patients with biliary injury compared to patients who have undergone uncomplicated cholecystectomy. On the other hand, it has been challenging to assess the success of the reconstructive operations for biliary injury without a uniform classification, which has only recently been proposed.

The high number of cholecystectomies also results in a high burden in the pathology units since all gallbladder specimens are routinely sent for histopathological evaluation. A malignant tumor is rarely found in the gallbladder, and therefore a selective histopathologic examination could be considered. At present, it is not clear whether the selective histopathologic examination would be safe without compromising the patient's safety, as gallbladder cancer (GBC) has poor prognosis. No population-based studies are available on changes and GBC treatment outcomes in the Finnish population in recent decades.

Material and methods: This thesis consist of four studies. It included 2600 patients operated on or treated for gallbladder findings in the Helsinki University Hospital specific catchment area during 2000–2017.

The first study was a randomized controlled trial. In this study we explored whether the LCC is faster and safer with a 3D rather than a 2D laparoscope in the surgery of patients eligible for day surgery. The primary outcome was operation time. *The second study* was a retrospective cohort study including patients with a major bile duct injury. QOL was measured with three questionnaires (Gastrointestinal quality-of-life, SF-36, and a non-validated questionnaire) and compared with patients with an uncomplicated cholecystectomy. The outcomes of reconstruction of major bile duct injury were evaluated with the newly proposed standards of Cho and Strasberg. *The third study* examined the need for routine histopathologic examination of gallbladder removed for benign indication in a retrospective setting. *The fourth study* continued by clarifying the incidence, management, and prognosis of diagnosed GBC in a retrospective population-based study.

Results: In *Study I*, 105 and 104 patients were randomly allocated to be operated with a 3D or a 2D laparoscope, respectively. The 3D-system did not reduce the LCC operation time (3D vs 2D; 49.0 vs 48.0 min, p=0.703). The operation time was not shorter if performed by residents (3D vs. 2D; 62.0 vs. 60.0 min, p=0.596) or attendings (42.5 vs. 42.0 min, p=0.406). The 3D technique did not affect intraoperative or postoperative complications, and no biliary tract complications occurred. *Study II* included 52 patients with a major bile duct injury and 53 patients who had had an uncomplicated cholecystectomy as controls. All patients were operated on during 2000–2016. We found no difference in the long-term (median follow-up 90 months) QOL between patients with bile duct injury and the controls. Three patients (5.8 %) died due to the injury. The 'primary patency' rate was 71% and the 'actuarial primary patency' at 1 and 5 years was 58% and 53%, respectively. The patency was achieved in 83% if the primary reconstructive operation was performed by a hepatobiliary surgeon. *Study III* showed that GBC is rarely (n=10/2034; 0.5%) found in gallbladders removed for primarily benign reasons. Specimen with GBC in the histopathologic examination were always macroscopically abnormal (wall thickening, tumor, or local hardening). No malignancy was found from macroscopically normal gallbladders. In *Study IV,* we had 294 patients with GBC and revealed a low and slightly declining GBC incidence in Southern Finland, 1.32/100,000 inhabitants during the study period 2006-2017. The number of patients proceeding to curative-intent surgery was 19%, and the estimated overall 5-year survival was 12%. Neoadjuvant therapy was not used, but 21 (40%) patients received adjuvant therapy. If curative-intent surgery was performed, the estimated 5-year survival reached 57%, otherwise it was 1.3%.

Conclusions: Cholecystectomy is a common and safe procedure when the correct surgical technique and the possibility of anatomical variations are considered. The use of 3D laparoscopy system does not improve the safety or efficacy compared to 2D laparoscopy. If a severe bile duct injury occurs, biliary reconstruction is recommended to be performed by a hepatobiliary surgeon. Regardless of the success of the biliary reconstruction or the stage of achieved patency, the long-term QOL of patients with achieved and maintained patency is comparable to that of control patients.

A gallbladder that is macroscopically normal and removed for benign reason, may not need histopathologic examination. A substantial amount of health care resources can be saved in adopting a selective histopathologic examination after cholecystectomy for benign reason. GBC is a rare malignancy with poor prognosis. Increasing the proportion of patients undergoing curative-intent resection, as well as initiating neoadjuvant therapy and increasing adjuvant therapy could possibly increase the survival of patients with GBC.

TIIVISTELMÄ

Tausta: Laparoskooppinen sappirakonpoisto on yksi yleisimmistä kirurgisista toimenpiteistä niin Suomessa kuin muissa maissa. Tähän voi liittyä avotoimenpidettä useammin sappitiekomplikaatio. Kolmiulotteinen (3D) näkymä laparoskopiassa voisi vähentää komplikaatioita ja lyhentää sappirakonpoiston leikkausaikaa verrattuna tavanomaiseen 2D-laparoskopiaan, mutta näyttöä tästä ei vielä ole. Sappitievaurio on mahdollisesti pelätyin sappirakonpoiston komplikaatio, ja sen vaikutusta potilaan elämänlaatuun on tutkittu laajasti. Komplikaation kohdanneiden ja komplisoitumattoman sappirakonpoiston läpikäyneiden potilaiden elämänlaadun eroista tiedetään kuitenkin vähän. Toisaalta on ollut haastavaa arvioida sappitievaurion korjauksen onnistumista ilman yhtenäistä luokitusta, jota ehdotettiin vasta äskettäin.
Sappirakonpoistojen suuri määrä johtaa patologian yksiköiden suureen kuormaan, kun poistetut sappirakot on tavattu lähettää rutiininomaisesti histopatologiseen tutkimukseen. Pahanlaatuinen muutos on löydöksenä harvinainen, ja siksi voitaisiin harkita valikoivaa patologista tutkimusta. Tällä hetkellä ei ole selvää, olisiko tämä toimintatapa turvallinen eikä vaarantaisi potilaan turvallisuutta, sillä sappirakon syövällä on huono ennuste. Sappirakon syövän ilmaantuvuuden ja hoitotulosten muutoksista Suomen väestössä ei kuitenkaan ole vielä saatavilla väestöpohjaisia tutkimuksia viime vuosikymmeninä.

Materiaali ja menetelmät: Tämä väitöskirja koostuu neljästä osatyöstä. Potilaita oli kaiken kaikkiaan noin 2600, joita oli hoidettu sappirakon löydöksien vuoksi Helsingin ja Uudenmaan sairaanhoitopiirin erityisvastuualueen (HYKS-erva) sairaaloissa vuosina 2000-2017.
Ensimmäinen osatyö oli satunnaistettu kontrolloitu tutkimus. Tässä tutkimuksessa selvitimme, olisiko 3D-laparoskooppinen sappirakonpoisto nopeampi ja turvallisempi kuin 2D-laparoskoopilla tehty toimenpide päiväkirurgisilla potilailla. Päävastemuuttuja oli leikkausaika. Toinen tutkimus oli retrospektiivinen kohorttitutkimus, johon osallistuneilla potilailla oli todettu vakava sappitievaurio. Elämänlaatua mitattiin kyselylomakkein ja verrattiin potilaisiin, joilla sappirakonpoiston yhteydessä ei tullut komplikaatiota. Vakavan sappitievaurion korjauksen onnistumista arvioitiin Chon ja Strasbergin äskettäin ehdottamien standardien mukaisesti. Kolmannessa osatyössä selvitimme sappirakon rutiininomaisen histopatologisen tutkimuksen tarvetta, kun sappirakko oli poistettu hyvänlaatuisen syyn vuoksi. Neljäs osatyö jatkoi selvittämällä sappirakon syövän ilmaantuvuutta, hoitoa ja ennustetta retrospektiivisessä populaatiopohjaisessa tutkimuksessa.

Tulokset: Osatyössä I, 105 ja 104 potilasta randomoitiin 3D- ja 2D-laparoskooppisiin sappirakonpoistoihin. 3D-järjestelmä ei nopeuttanut sappirakonpoiston leikkausaikaa (3D vs. 2D; 49,0 vs. 48,0 min, p = 0,703) eikä se myöskään lyhentynyt erikoistuvilla (3D vs. 2D; 62,0 vs. 60,0 min, p = 0,596) tai erikoislääkäreillä (42,5 vs. 42,0 min, p = 0,406). 3D-tekniikka ei vaikuttanut myöskään leikkauksenaikaisiin tai leikkauksen jälkeisiin komplikaatioihin, eikä sappitiekomplikaatioita esiintynyt. Osatyöhön II otettiin 52 potilasta, joilla oli todettu vakava sappitievaurio. 53 potilasta ilman vauriota toimi verrokkeina näille potilaille. Kaikki potilaat oli leikattu vuosina 2000–2016. Sappitievauriopotilaiden ja verrokkien välillä ei havaittu eroa pitkäaikaisessa (mediaaniseuranta-aika 90 kuukautta) elämänlaadussa. Kolme potilasta (5,8 %) kuoli sappitievaurion vuoksi. ”Primary patency”, sappiteiden aukipysyvyyden aste, oli 71 %. Yhden ja viiden vuoden kohdalla ”Actuarial primary patency rate” oli 58 % ja 53 %. Avoimuus saavutettiin 83 %:lla, jos ensisijaisen korjausleikkauksen suoritti maksakirurgi. Osatyö III osoitti, että sappirakon syöpää esiintyy harvoin (n = 10/2034; 0,5 %) sappirakoissa, jotka poistetaan hyvänlaatuisista syistä. Sappirakko, josta syöpä löytyi, oli aina makroskooppisesti poikkeavaa (seinämän paksuuntuminen, kasvain tai paikallinen kovettuminen). Makroskooppisesti normaaleista sappirakoista ei löytynyt pahanlaatuisuutta. Osatyössä IV löysimme 294 syöpäpotilasta ja paljastimme matalan ja hieman laskevan sappirakon syövän ilmaantuvuuden Etelä-Suomessa, 1,32/100 000 asukasta tutkimusjaksolla 2006–2017. Kuratiivistavoitteiseen leikkaukseen päätyneiden potilaiden osuus oli 19 %, ja arvioitu 5 vuoden kokonaiselossaoloaika 12 %. Neoadjuvanttihoitoa ei käytetty, mutta 21 (40 %) potilasta sai adjuvanttihoitoa. Kuratiivistavoitteisen leikkauksen jälkeen viiden vuoden eloonjääminen oli 57 %, mutta muuten se oli 1,3 %.

Johtopäätökset: Sappirakonpoisto on tavallinen ja turvallinen toimenpide, kun huomioidaan oikea kirurginen tekniikka ja anatomisten vaihtelujen mahdollisuus. 3D-tekniikan käyttö ei kuitenkaan paranna sappirakonpoiston turvallisuutta tai tehokkuutta 2D-laparoskopiaan verrattuna. Vakavan sappitievaurion ilmaantuessa, maksakirurgin tulisi suorittaa korjaustoimenpide. Riippumatta kuitenkaan korjaustoimenpiteen onnistumisesta tai korjauksen jälkeisen sappiteiden auki pysyvyyden asteesta, potilaiden pitkäaikainen elämänlaatu on samanlainen kuin kontrollipotilailla.
Makroskooppisesti normaali ja hyvänlaatuisista syistä poistettu sappirakko ei tarvinne histopatologista tutkimusta. Ottamalla käyttöön selektiivinen histopatologinen tutkimus hyvänlaatuisista syistä poistetuissa sappirakkonäytteissä, voitaisiin säästää huomattava määrä terveydenhuollon resursseja. Sappirakon syöpä on harvinainen, mutta sen ennuste on huono. Ei pelkästään lisäämällä kuratiivistavoitteisten

leikkausten määrää, vaan myös neoadjuvanttihoidon käytöllä ja lisäämällä adjuvanttihoitoa saavien potilaiden määrää, voitaisiin todennäköisesti parantaa sappirakon syöpäpotilaiden ennustetta.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Koppatz H, Harju J, Sirén J, Mentula P, Scheinin T, Sallinen V. Three-dimensional versus two-dimensional high-definition laparoscopy in cholecystectomy: a prospective randomized controlled study. Surgical endoscopy 2019. Epub 2019 Feb 1.

II Koppatz H, Sallinen V, Mäkisalo H, Nordin A. Outcomes and quality of life after major bile duct injury in long-term follow-up. Surgical Endoscopy 2020. Epub 2020 Jun 22.

III Koppatz H, Nordin A, Scheinin T, Sallinen V. The risk of incidental gallbladder cancer is negligible in macroscopically normal cholecystectomy specimens. HPB 2018; 20(5): 456-461. Epub 2017 Dec 13.

IV Koppatz H*, Takala S*, Peltola K, But A, Mäkisalo H, Nordin A, Sallinen V. Gallbladder cancer epidemiology, treatment and survival in Southern Finland – population-based study. (Submitted)

*These authors contributed equally to the study and share equally first authorship

ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
ADM	Adenomyomatosis
AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiologists
ASCO	American Society of Clinical Oncology
BDI	Bile duct injury
BMI	Body mass index
CBD	Common bile duct
CCI	Charlson comorbidity index
CD	Cystic duct
CDi	Clavien-Dindo classification
CHD	Common hepatic duct
CI	Confidence interval
CRT	Chemoradiotherapy
CT	Computed tomography
CVS	Critical view of safety
ERC	Endoscopic retrograde cholangiography
FCR	Finnish Cancer Register
FICAN	Finland Regional Cancer Center
GBC	Gallbladder cancer
GCPS	Gallbladder Cancer Predictive Risk Score
GIQLI	Gastrointestinal quality-of-life index
HB	Hepatobiliary
HD	High-definition
HJ	Hepaticojejunostomy
HPE	Histopathologic examination
HUH	Helsinki University Hospital
iGBC	Incidental gallbladder cancer
IRR	Incidence rate ratio
LCC	Laparoscopic cholecystectomy
MIS	Mini-invasive surgery
MRI	Magnetic resonance imaging
NCCN	The National Comprehensive Cancer Network
NACRT	Neoadjuvant chemoradiotherapy
NACT	Neoadjuvant chemotherapy
OS	Overall survival
PSC	Primary sclerosing cholangitis
QOL	Quality-of-life
SF-36	Short Form Health Survey
TNM	Tumor-Node-Metastasis classification
XGD	Xanthogranulomatous cholecystitis
US	Ultrasound

1 INTRODUCTION

Gallstone disease is common in the Western population, with a 9-21 % prevalence (1). Annually, 9000, 76000, and 370000 cholecystectomies, the most common treatment for gallbladder disease, are performed in Finland, the United Kingdom, and the United States, respectively, making it one of the most common abdominal surgical procedure (2-4).

Upper right abdomen pain is an unspecific symptom caused by various reasons. Postprandial right upper abdominal pain with or without elevation of liver transaminases hints at symptomatic stones in the gallbladder or bile ducts (5). Acute jaundice with pain is more likely to be a benign disease than malignancy (5-7). In other words, with different combinations of different symptoms, benign or malignant disease can be suspected. Radiological investigations, such as ultrasound, have an essential role in diagnosing the stone disease and the cause of pain in the right upper quadrant of the abdomen.

Laparoscopic cholecystectomy (LCC) was developed four decades ago and after harsh criticism against mini-invasive surgery (MIS) in the mid-1980s, it was accepted as a gold standard when treating symptomatic gallstone disease (8). It does not carry high risks, and provides a short recovery time for the patient. Later, the safety, efficacy, and patient friendliness has been proven in many other procedures as well (9). Today, 3D laparoscopic instruments are increasingly available and have been rapidly introduced in operating rooms, but possible benefits of these are still somewhat unclear. Thus, more detailed knowledge of the benefits of 3D laparoscopy in specific procedures could help direct the proper use of resources.

Compared to the open technique, LCC is thought to have a somewhat higher risk of unintentional bile duct injury (BDI). However, after introducing the first LCC, the standardized technique and use of the critical view of safety (CVS) have decreased the risk of BDI (10). Complications may have a significant impact on the patient's quality-of-life (QOL). Any complication after medical treatment or surgery affects the patient's QOL, but the severity of the complication has only a small effect on the level of QOL impairment (11, 12). Notable is that even after a major complication, the QOL is likely to return in the long-term follow-up (11).

The indication for LCC is predominantly benign, symptomatic gallstone disease. The wall of the gallbladder specimen in these circumstances is mainly macroscopically normal, but the possibility of a routine histopathologic examination (HPE) of the specimen has still not been abandoned. The reason for this routine action is the possibility of finding incidental gallbladder cancer (iGBC) (13, 14), though this has a low (0.5 %) incidence in Western countries in patients operated on for primarily benign gallbladder disease. iGBC is often found at an early stage, which improves the otherwise poor prognosis (15). Therefore, routine HPE has been justified in many centers (13, 16). Nevertheless, the incidence of gallbladder cancer (GBC) being low, more selective HPE could save millions of Euro's (17, 18).

This work investigated cholecystectomy from the perspective of diagnosis and treatment of complications and malignant findings. In the literature review, the surgically essential anatomy and pathologically meaningful structures are also described before diving further into the topics above.

Treatment of gallstone related diseases such as symptomatic cholelithiasis, cholecystitis, pancreatitis, bile duct stones, and GBC creates a significant economic burden (19). This burden has escalated, (e.g., an increasing number of patients with gallstone disease and operations) partly due to advances in surgical techniques (1, 20-22). Owing to the high incidence of gallbladder operations, there is much to gain with even minor changes and optimizations. Finding the patients who would benefit from cholecystectomy, using the right surgical techniques and equipment, and centralizing the treatment in the event of complications or GBC can improve resource utilization, patient satisfaction, and increase the likelihood of survival in severe gallbladder surgery and gallbladder-related disease.

2 REVIEW OF THE LITERATURE

2.1 GALLBLADDER

The gallbladder is a pear-shaped organ on the liver's inferior surface, located in the gallbladder fossa beside segments IVB and V of the liver (Figure 1). In the early weeks of gestation, the precursor of the extrahepatic biliary tree develops from the foregut. The gallbladder forms then from the precursor of the bile duct by dilating (23). The primary function of the gallbladder is to store bile. Bile is continuously produced in the liver and either stored in the gallbladder or drained into the small bowel. The bile salts of the bile are absorbed in the intestine back into the bloodstream and return to the liver in the enterohepatic circulation (24).

2.1.1 Anatomy of the extrahepatic ducts and gallbladder

The extrahepatic ducts arising from the foregut constantly maintain the contact with the intrahepatic ducts developing from the hepatic diverticulum. Via this relationship, a patent lumen between the intra- and extrahepatic biliary tree is achieved. Thus, the right and left hepatic duct, descending from the liver, appear at the liver hilum to combine into the common hepatic duct (CHD). After passing the joining cystic duct (CD), they form the common bile duct (CBD), or choledochus. Then the bile drains into the duodenum through the ampulla of Vater (sphincter of Oddi). Bile forms in the liver cells, from where it is secreted into the bile ducts. The gallbladder stores the bile if it is not secreted into the bowel. Further, some of the bile ducts may drain straight into the gallbladder through its bed. These ducts are called the ducts of Luschka (24, 25).

The gallbladder has four regions: fundus, corpus, infundibulum and neck. Additionally, the Hartmann pouch is a small bulge of the infundibulum and does not exist in all gallbladders. The gallbladder is 6–10 cm long and 3–4 cm wide. Lying in close proximity to the liver, the gallbladder is in contact with the liver bed via only loose connective tissue (adventitia) with no serosa. However, the serosa and the peritoneum coats the surface of the gallbladder that is not in contact with the liver. There, the peritoneum continues to cover the liver and the abdominal cavity. The arterial blood supply arises from the common hepatic artery, which divides into the right hepatic artery and further divides to the cystic artery. Venous blood, however, goes through small veins to the portal vein (24).

Multiple variations of the vascular system and biliary tract anatomy exist (26). Indeed, an accessory bile duct, single or complex, is found in 16% of patients, an aberrant right hepatic artery in 18% and in 14% a doubled cystic artery is present (27). A review including over 9000 radiologic or surgical cases revealed that almost 20% of cystic arteries were not found in the hepatobiliary triangle (detailed in section 2.3.2) (28). The most common biliary abnormalities found from a small cohort were short CD, left-sided insertion or insertion of the CD into the right hepatic duct, duct of Luschka or accessory hepatic duct (29).

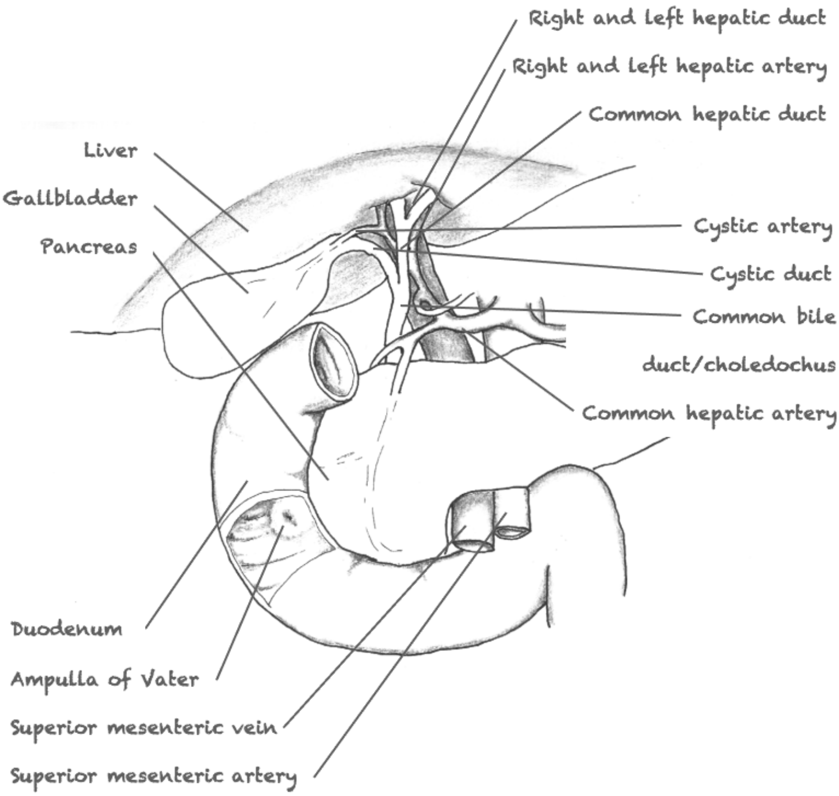


Figure 1. Schematic cross-sectional view of gallbladder and its relation to surrounding organs.

2.1.2 Gallbladder histology

The normal thickness of an uninflamed gallbladder wall is 1–3 mm. It consists of three layers; mucosa, muscle layer, and serosa/adventitia (Figure 2). The highly folded mucosa is lined with a single columnar cell layer, which then forms mucosal crypts between those folds (25). Glandular structures of the epithelium vary between different parts of the gallbladder; the neck encompasses mucous glands, but antral-type metaplastic glands are found from other parts (30). Under the epithelium lies the lamina propria with loose connective tissue structures, lymphatic channels, blood vessels, and nerves (25).

The smooth muscle is organized into an irregular layer of muscle fiber bundles. They travel in different directions, sometimes even reaching the lamina propria. Epithelia, in turn, may herniate into the muscle layer or further beneath, as Rokitansky-Aschoff sinuses, which are presented later. Under this smooth muscle layer is the perimuscular loose connective tissue called adventitia on the liver side. This layer is the only structure that separates the gallbladder from the liver tissue. On the opposite wall, the muscle is covered by serosa (25, 31).

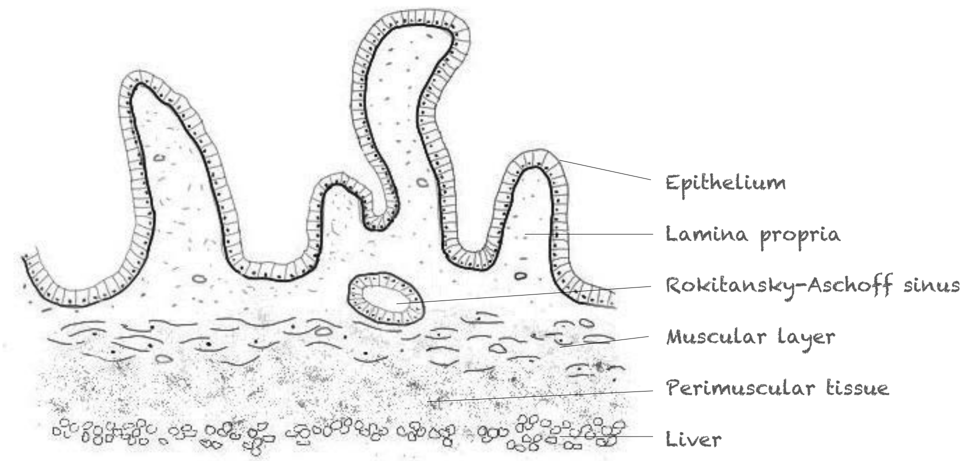


Figure 2. Gallbladder wall on the liver side

2.2 BENIGN GALLBLADDER FINDINGS

The most frequent abnormal radiological finding of the gallbladder are gallstones. However, there are also many other clinically relevant findings suspected or diagnosed radiologically. Gallbladder wall thickening is not only seen in GBC, but also in many benign circumstances. GBC is described in section 2.4.

2.2.1 Cholesterolosis and adenomyomatosis

Cholesterolosis, a frequent finding of the gallbladder, is a focal or general yellowish deposition on the gallbladder wall consisting of triglycerides and cholesterol esters (32). Cholesterolosis can be seen macroscopically after cholecystectomy, as well as radiologically as a polypoid lesion. It is an incidental finding with no association to clinical outcomes such as high serum cholesterol, pancreatitis, or GBC (33).

Adenomyomatosis (ADM) is a benign finding of the gallbladder wall occasionally difficult to distinguish from malignant lesions (32, 34). Histologically, it appears as hyperplasia of the mucosa and muscularis propria, which can be segmental, fundal, or rarely a diffuse type (34, 35). In distinguishing ADM from GBC, it is crucial to see the Rokitansky–Aschoff sinuses (tubular excavations through the muscle layer) in otherwise focal or generalized wall thickening (32). Asymptomatic ADM, when diagnosed with certainty, does not need to be operated on. On the other hand, ADM may also be symptomatic or appear as acalculous cholecystitis, indicating cholecystectomy (34).

2.2.2 Cholecystolithiasis

Cholecystolithiasis is a common phenomenon where the clinical presentation of the gallstone disease varies from asymptomatic to different complications caused by these stones. Gallstone disease is profoundly associated with dietary factors and is related to disturbances in enterohepatic circulation (36). Obesity with increased hepatic cholesterol secretion increases the risk of gallstones and is more common in women than men. In the Western world, stones are mostly composed of cholesterol and slightly mixed with calcium, whereas bile pigment stones predominate in East Asia (32, 37).

Symptomatic gallstone disease is classically manifested by postprandial abdominal colic at the right upper quadrant, especially triggered by fatty or heavy meals. Nausea and vomiting may be involved. In complicated gallstone disease, the stones can cause biliary obstruction, cholangitis or pancreatitis by emerging into the CBD. In Mirizzi's syndrome, a gallstone impacts the cystic duct causing compression to adjacent structures and finally leads to a fistula of the CHD or CBD. Stones are also associated with cholecystitis and further gallbladder abscess and perforation (32). In Swedish and Danish population-based studies, gallstones were associated with cholangiocarcinomas, but the risk decreased a few years after cholecystectomy (38, 39). One could speculate whether this is related to the formation of stones due to disturbed bile flow, which is still caused by obstruction in the bile duct caused by carcinoma. Further, large stones are associated with GBC (40, 41).

The first-choice treatment for symptomatic cholecystolithiasis is laparoscopic cholecystectomy. If a patient is not suitable or does not consent for surgery, they can be offered either oral dissolution therapy or extracorporeal shock wave lithotripsy (ESWL) (7). Oral litholysis is possible with ursodeoxycholic acid for patients with small diameter cholesterol stones (42). Due to the long duration of treatment, only moderate dissolution of the stones and possible complications, these non-surgical treatments are not widely used (7).

2.2.3 Cholecystitis

In inflammation of the gallbladder, the clinical presentation is seen as a thickening of the gallbladder wall in the radiological imaging. Histologically the presentation between chronic and acute cholecystitis differ.

2.2.3.1 Acute cholecystitis

In acute cholecystitis, the patient may have, unlike in bile colic, constant pain in the right upper abdominal quadrant, and elevated serum C-reactive protein and leukocyte levels. Fever, nausea and vomiting may also occur. The diagnosis is confirmed with abdominal ultrasonography (US) showing pericholecystic edema and gallbladder wall thickening.

Acute cholecystitis is often caused by an obstruction of the gallbladder neck or the cystic duct. Then the intraluminal pressure gradually increases and results in an inflammation of the gallbladder wall (37, 43-45). However, since acalculous cholecystitis also occurs in about 4 % of acute cholecystitis, factors other than stones are involved as well. Indeed, acute acalculous cholecystitis is most common in patients in intensive care units (46). If the inflammation proceeds further, the wall turns gangrenous and may perforate. This may appear especially in elderly or diabetic patients and in acalculous cholecystitis. Emphysematous cholecystitis, caused by gas-forming bacteria such as *Escherichia coli, Clostridium perfringens* or *welchii*, is also a severe disease (47). This is diagnosed with a computed tomography (CT) scan, which reveals air in the gallbladder wall. Clinically, these patients are critically ill. They may need vasoactive medication and other supportive treatment. After surgical treatment, morbidity and even mortality is high, up to 25 % (48, 49).

2.2.3.2 Chronic cholecystitis

Chronic cholecystitis is highly (95%) associated with cholelithiasis. In this condition, intraluminal stones cause recurrent mucosal irritation and microtrauma to the gallbladder wall (37, 45). Histologically, atrophic or ulcerated mucosa, smooth muscle hypertrophy, lymphoid infiltration and Rokitansky–Aschoff sinuses, due to continuous intraluminal pressure, may be seen (50). A chronically inflamed gallbladder may be rudimentarily atrophied and covered with adhesions, hence raising the risks of the surgical procedure.

Xanthogranulomatous cholecystitis (XGC) is a rare variant of chronic cholecystitis. It is highly associated with cholelithiasis and obstruction of the gallbladder. Though benign, the XGC strongly mimics GBC in a preoperative CT scan (51-53). It appears in approximately 1.5–5% of all gallbladder specimens (51, 54). XGC is diagnosed by specific histopathologic findings with giant foamy macrophages and proliferative fibrosis (54).

2.2.4 Mucosal polyps

Gallbladder polyps are normally asymptomatic mucosal extensions detected incidentally by ultrasound or CT (55). They may appear as single (62 %) or multiples and vary in size. Polyps are usually either pseudo-polyps or cholelithiasis; true polyps are rare (56, 57). Larger polyps with a size over ten millimeters are associated with gallbladder malignancy, particularly common in elderly patient (58, 59). Current practices suggest that asymptomatic polyps larger than ten millimeters should be removed by cholecystectomy (59), but an even higher (12 mm) cut-off point has been proposed for young and asymptomatic patients (60). Polyps between five and ten millimeters should be surveilled, but polyps smaller than five millimeter do not need any follow-up (59). Patients with primary sclerosing cholangitis (PSC) are an exception, since their lifetime risk of GBC is elevated around 2 %. Therefore, annual surveillance of the gallbladder to reveal any findings is recommended (61).

2.3 GALLBLADDER SURGERY

Symptomatic gallstone disease is the most common indication for gallbladder surgery.

2.3.1 Open cholecystectomy

The laparoscopic technique, discussed in the next section, established its place in the early 1990s. Before that, open cholecystectomy was the standard procedure to manage gallbladder diseases. In this procedure, the surgeon performs a Kocher (subcostal) or an upper middle-line incision with the patient under general anesthesia. The gallbladder is exposed from under the liver and removed from the liver bed (62).

Today, the direct open approach is somewhat rare and primarily used if laparoscopy is contraindicated (for instance for patients with multiple comorbidities or critically ill patients) or difficult to perform (63, 64). Additionally, the direct open approach may be used in open procedures primarily for other indications but when the gallbladder requires removal. On the other hand, following explorative laparoscopy in preoperatively known cases with gallbladder malignancy, an open cholecystectomy is used to perform curative intent resection (65). Mortality after open cholecystectomy is low (0.17–0.85%) and it is highly associated with the patients' age, the urgency level of gallbladder surgery, and the disease (66, 67).

If a safe laparoscopic approach does not seem possible, the conversion to open must be considered (68). In two statewide surveys from the UK and USA, the conversion rate was expectedly higher in emergency cases (9.4–17.5%) than in elective surgery (4.6–9.1%). Still, when considering morbidity and mortality, the LCC is safe in emergency cases as well (63, 69). The laparoscopic procedure is more likely converted to open when the patient is male, older, or if the gallstone disease is complicated and mainly due to difficult circumstances (69, 70). In elective operations, adhesions are a common indication for conversion (71). Other bail-out procedures managing difficult LCCs are described in the next section.

2.3.2 Laparoscopic cholecystectomy

Introducing the first LCC was an essential step in the rise of MIS (72). The laparoscopic technique for gallbladder surgery was introduced for the first time by the German surgeon Erich Mühe in 1985 using a single port technique (8, 73). However, the French physician Phillip Mouret in 1987, brought a video-laparoscope into the procedure, thus developing the modern LCC technique (74). The advantages of the laparoscopic approach were quickly approved, and laparoscopy displaced the open technique.

At present, LCC is the method of choice for gallbladder surgery for cholecystolithiasis and its complications when the equipment and knowledge of MIS procedures in the operating unit are adequate (7). Symptomatic cholecystolithiasis is the main indication for LCC. Other indications are acute cholecystitis, gallbladder polyps, or otherwise complicated stone disease (e.g., pancreatitis, ductal stones). For patients without any symptoms, LCC may be recommended when stones are large, or the follow-up for the lesion (e.g., polyp) of the gallbladder wall cannot be adequately controlled by imaging studies (7).

In LCC, a few anatomical landmarks, such as Rouviere's sulcus and the base of liver segment four, should be used to find the safest plane for surgery (75, 76). The presentation of Rouviere's sulcus (incisura hepatis dextra, Gans incisura) varies. However, it is visible in 90% of patients as a scar, slit, or deep sulcus showing the plane of the CBD (77). All surgical approaches should stay above these imaginary lines connecting the base of liver segment four and Rouviere's sulcus (75, 78). Regardless of laparoscopic instrumentation used, it is mandatory to identify the “CVS” (10, 79). The CVS is a view where the triangle of Calot (cystohepatic triangle) is prepared. Moreover, the liver bed and only two structures (cystic duct and artery) ascending to the gallbladder are visible (Figure 3). Gaining the CVS minimizes the risk of bile duct or arterial complications but does not remove the possibility of them completely (10).

On the other hand, in difficult circumstances if the CVS is not achievable, the fundus-first technique and subtotal cholecystectomy can be used as bail-out procedures in addition to open conversion (80). In the fundus-first technique, the preparation starts from the fundus and proceeds with retrograde dissection. This proceeds until the safe preparation line disappears. Some studies have showed a connection with the fundus-first technique and major venous and bile duct injuries (81). Keeping this in mind, the dissection plane is held close to the gallbladder. Combining the fundus-first technique with subtotal cholecystectomy might offer a safe approach for cholecystectomy without need of conversion. Depending on the surgeon’s experience, an appropriate technique to avoid BDI is chosen.

It is also possible to try to avoid a BDI by using intraoperative imaging. This includes cholangiography, intraoperative US, and fluorescence cholangiography. In cholangiography, a small tube is inserted into the bile duct to obtain a radiographic view of the biliary tree filled with contrast agent (Figure 4). A Swedish study found a BDI risk reduction when cholangiography was used in patients with a history of an acute cholecystitis or a concurrent cholecystitis (82). In fluorescence cholangiography, the contrast agent (fluorescing indocyanine green) is infused into a vein to illuminate the biliary system. An intraoperative US can visualize other structures as well. None of these are shown to be superior, nor do the current recommendations elevate one above another. However, some centers use these as a current routine during the LCC (76, 78, 83).

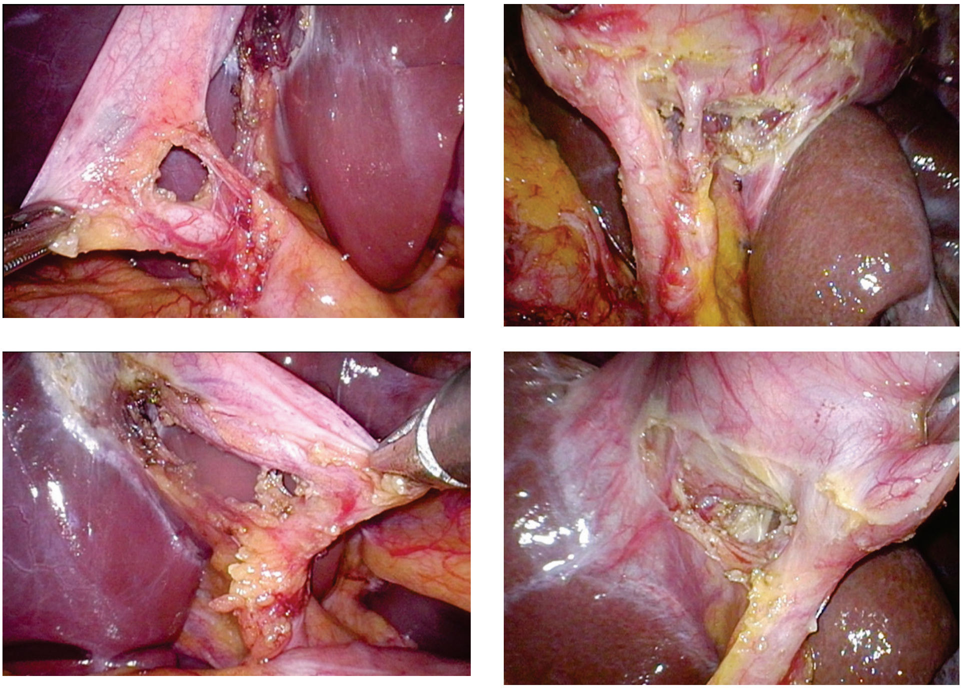


Figure 3. Critical view of safety in laparoscopy.

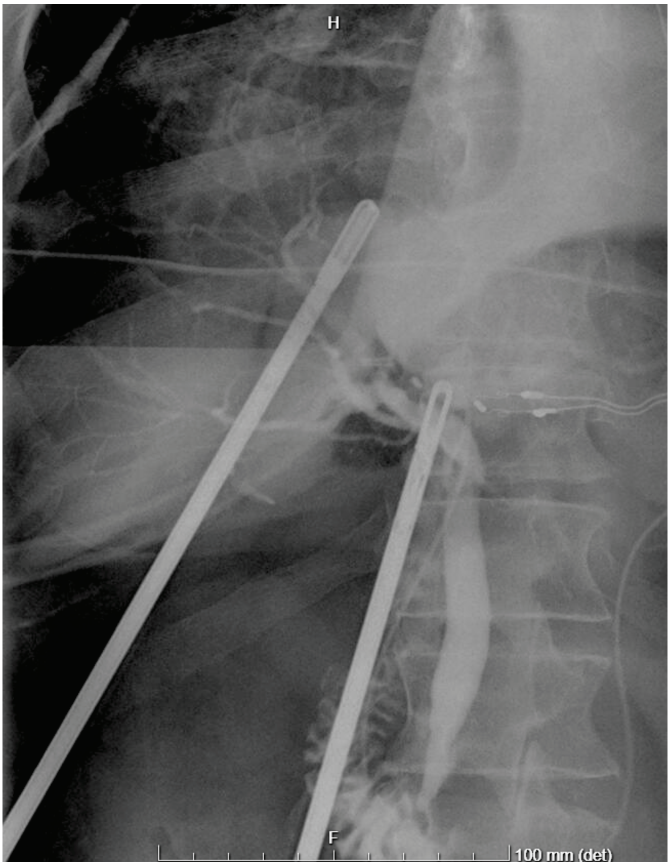


Figure 4. Cholangiography during LCC. The instrument on the left is holding the gallbladder fundus, while other holds the duct where the contrast agent was inserted in. No complication appeared, the contrast agent also flows upwards and shows the biliary tree.

2.3.2.1 Laparoscopic instrumentation

After the first LCC, the four-port laparoscopy became a standard for cholecystectomy (83). Beyond this standard, other LCC techniques have been developed and studied to improve results in cosmesis and painlessness. These techniques include the robotic, the natural orifice transluminal cholecystectomies, and the use of only 1–3 ports (84-86). However, the long learning curve has reduced the popularity of these techniques. Further, as the number of ports decreases, the possibility of traction and counter-traction, necessary for optimal surgery, is reduced and achieving a safe view may be challenging (83). On the other hand, the surgeons experienced workload during the operation, operation length, and thus costs of surgery may increase (87).

In the initial laparoscopic technique, four laparoscopy ports were used (8). First, a supraumbilical incision is made. Second, a pneumoperitoneum is performed after inserting a trocar openly or in direct visual control using an optical trocar. A Verres needle may also be used for insufflation. The other trocars are then inserted in direct visual control into subxiphoid, right subcostal midclavicular, and anterior axillary line positions (88-90). The operating surgeon stands either on the patient's left side or between the patient's legs, while the assistant is on the patient's left side. A video monitor is on the patient's right side facing toward the surgeon.

The benefits of LCC are unquestionable. Despite this fact, the operation in the 3D field with the two-dimensional (2D) view is challenging. The phenomenon called stereopsis, or stereo vision, is possible for humans having two eyes facing forward. The differences between two forward-looking retinas that deliver slightly different images to the brain are processed to develop an experience of stereoscopic view. The English physicist Charles Wheatstone first described this in 1838, when he first introduced the simple stereoscope (91). This stereoscopic vision is, however, lost with a 2D videoscope. Therefore, it demands that the surgeon understands the 3D space from a 2D screen, hence increasing the risk of misperception and complications.

The 3D laparoscopic system was introduced to improve results, reduce errors and shorten the learning curve of MIS (92). With the 2D view, the surgeon uses cues such as relative sizes of structures, shadows, and interposition to build a 3D picture (93). However, the 3D optic is a dual-channel scope connected to two cameras, which deliver two different views to display on a monitor. This blurred picture on the screen can be seen as a 3D-picture when viewed through polarized 3D glasses (94). Previous 3D glasses were heavy, causing headaches, dizziness, and nausea to the operating surgeon (95). Subsequently, 3D equipment, including 3D glasses, scopes, and monitors, have evolved, and the surgery experience is now pleasant (96, 97).

The 3D technique has been shown to improve the movement accuracy, speed, and learning curve in several non-clinical studies (98-102). The 3D equipment is even preferable to use in training since skills acquired with 3D-simulation are also transferable to the 2D environment (97, 99). However, 10% of people lack adequate stereoacuity (103). In the absence of this stereoscopic view, or when significantly reduced, the individual will not be able to take advantage of 3D technology (104).

In 1998, Hanna et al. studied how the use of a 3D-camera would impact LCC. Findings from this prospective research were not encouraging as they reported on the technical flaws of the 3D monitor and the increased visual strain caused by this technology (95). Given the advances in technology, it is understandable that similar problems do not occur in current 3D laparoscopy compared to a few decades ago. Since then, a few studies have demonstrated the benefits of 3D technology in laparoscopy (105, 106). However, the benefits of 3D technology are mainly limited to operations requiring exact depth vision, such as laparoscopic suturing (107-110). Therefore, a panel of European surgeons only made a cautious recommendation on the use of 3D technology in surgery (108). All available studies considering 2D versus 3D laparoscopy in cholecystectomy are detailed in Table 1.

Author	Country/ Publication year	Number of surgeons	Number of Patients, N		Operation time, min		Reporting measured errors, N (%)		Conclusions
			2D	3D	2D	3D	2D	3D	
Hanna et al. (95)	United Kingdom/1998	4 specialists	30	30	53 min	52 min	6 (20%)	6 (20%)	No advantage of 3D over 2D laparoscopy system was detected
Bilgen et al. (111)	Turkey/2013	4 specialists	11	11	30 min	21 min	NR	NR	3D laparoscopy system reduces operative time in LCC
Sahu et al. (112)	India/2014	NR	29	8	54 min	40 min	NR	NR	3D laparoscopy may reduce operative times in different procedures and increase the surgeon's comfort
Curró et al. (113)	Italy/2015	1 specialist	20	20	40 min	38 min	2 (10%)	1 (5%)	3D laparoscopy has no influence on operation time for a specialist but might be beneficial for a novice surgeon
		1 novice	20	20	60 min	48 min	5 (25%)	2 (10%)	
Zeng et al. (114)	China/2016 *	NR	43	46	65 min	51 min	NR	NR	3D laparoscopy can shorten the operation time and reduce conversion rate in LCC for complicated gallstone disease
Schwab et al. (115)	United Kingdom/2020	NR, specialists	50	49	23 min	20 min	45 (61%)	47 (66%)	No difference in performance by specialist surgeons. In complex cases, 3D reduced the Calot's triangle dissection time.

Table 1. Three-dimensional laparoscopy in cholecystectomy *Article in Chinese. Abbreviations: 2D – two-dimensional; 3D – three-dimensional; NR – not reported

2.3.2.2 Complications of laparoscopic cholecystectomy

LCC is safe, but as with all surgical procedures, includes potential risks. The laparoscopic procedure itself is associated with possible complications such as bowel or vascular injury caused by trocar insertion. However, in LCC in particular, biliary, liver hilar, or vascular complications cause the primary concern. These complications can have a remarkable impact on not only expenses of the healthcare system but also on patients mental and physical wellbeing. Depending on the degree of biliary complication, the patient may need repeated healthcare contacts and procedures to be able to maintain the biliary continuity. The impact of BDI to patients' QOL may be significant, which can be seen in short- and long-term follow-up (12, 116, 117).

The incidence of biliary complications is 0.39–1.1% (118-121), including a major BDI in 0.16–0.43% of cases (119, 120, 122). A vascular component is present in 5.1% of patients treated for BDI (123). The reason for complications in LCC is mainly surgeon's misperception, but several other reasons (inflammation and adhesions, Mirizzi's syndrome, hemorrhage) also exist. The use of scissors or clips on the wrong structures and the use of thermal instruments in direct proximity to vascular or main biliary structures are the primary mechanisms of BDI (10, 81, 124, 125).

Various classifications have been produced to depict the severity of the bile tract injuries. Some of them describe only injuries considering bile ducts (Bismuth, Strasberg, Amsterdam), while some take into account blood vessels (Steward-Way) and the functionality of the biliary tract (Hannover, ATOM-classification) (79, 126-129). The Bismuth classification was an initial way to illustrate complications but included only defects of the main bile duct (127). After that, the Strasberg classification combines the minor and severe biliary complications (Table 2) (79). Recently, Cho and Strasberg formed a new classification based on the Strasberg classification but combined complications A-E into grades 1-3 based on the severity of the injury (Figure 5) (Cho 2018). The functional Amsterdam classification serves as a proper tool for endoscopist purposes (121). However, a group of surgeons of the European Association for Endoscopic Surgeons built a classification to comprise all of the BDI classifications found (130). We concentrate on major biliary injuries and use the Strasberg and the Cho-Strasberg classifications in this thesis (Table 2; Figure 5).

Anatomical variations are common in the biliary tree and its vascularity. These variations are involved in 30% of complications during cholecystectomy (29). Some of the most typical anomalous structures can be recognized. About 10–15% of patients have a superficial middle hepatic vein in the liver bed (131). Damage to this can result in severe bleeding. However, keeping the dissection plane superficial to the liver bed and close to the bladder, the injury can be avoided (132). In both open and laparoscopic procedures in highly inflamed cases, challenging vasculo-biliary injuries can be associated with the fundus-first technique (81).

The overall mortality 90-days after cholecystectomy is low, 0.15–0.64%. Patients with high age, emergency surgery, or intraoperative complications are at higher risk for death (67, 133). However, the laparoscopic approach per se does not increase the risk of mortality (134). Indeed, the risk of death is three times higher in open cholecystectomy than in LCC (133, 135, 136). Nevertheless, the patient's comorbidity and complexity of the gallbladder disease is likely to explain this higher risk.

Type		Criteria
A		Bile leak from cystic duct or liver bed
B		Partial occlusion of the biliary tree, most frequently from an aberrant right hepatic duct
C		Bile leak from duct (aberrant right hepatic duct) that is not communicating with the CBD
D		Lateral injury of the biliary system, without loss of continuity
E		Circumferential injury of the biliary tree with loss of continuity
	E1	Transection > 2 cm from the confluence of the hepatic ducts
	E2	Transection < 2 cm from the confluence of the hepatic ducts
	E3	Transection involving the confluence of the hepatic ducts with continued right and left ductal communication
	E4	Transection resulting in the destruction of the hepatic confluence (and no communication between left and right hepatic ducts)
	E5	Type C injury in the hilum

Table 2. Strasberg classification system. Abbreviations: CBD – common bile duct

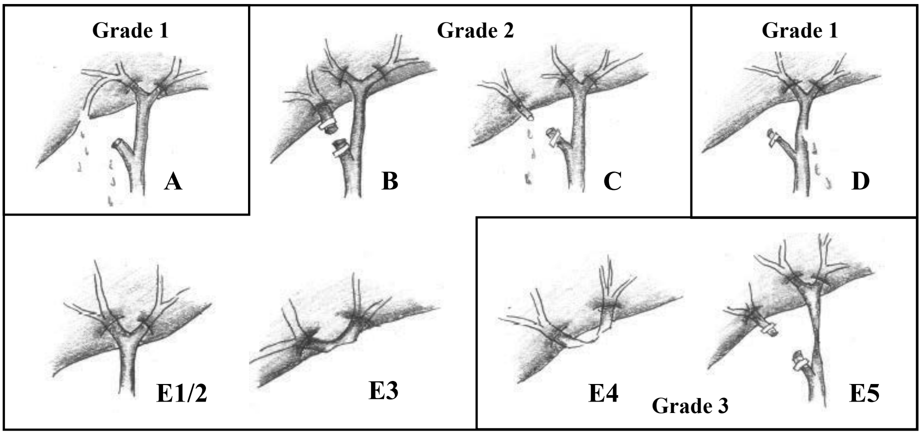
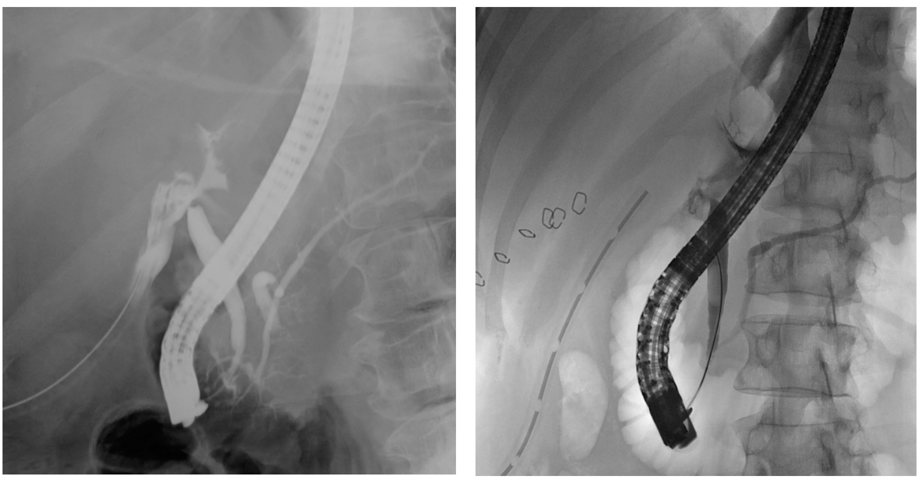


Figure 5. Strasberg classification system illustrated and grouped into three grades by Cho and Strasberg.



A: Elective cholecystectomy for previous cholecystitis resulted in E2 type BDI. This was diagnosed with ERC where the continuity of the choledochus was found to be interrupted. A small amount of contrast agent spreads in the abdomen.

B: Difficult BDI (E3) diagnosed with ERC after converted cholecystectomy for symptomatic cholelithiasis.

Figure 6. BDI diagnosed with endoscopic retrograde cholangiography (ERC). Two patients with a blockage at choledochus. A distal choledochus is filled with contrast agent, but the proximal part of the biliary tree is not visualized.

2.3.3 Surgical reconstruction after biliary complication

The need for surgical reconstruction of biliary complications depends on the severity of the injury. Most of the complications are minor (Strasberg A–D), whit endoscopic or radiologic management being sufficient (119, 121, 137). Whether or not the continuity of the biliary tree is lost, is vital for the decision of management. Surgical reconstruction is essential after a total loss of continuity or a major vessel complication.

Immediate detection of a BDI increases not only the possibility of a successful result after definite repair but also improves the QOL of these patients (138, 139). The BDI is, however, not detected in about half of these operations (140). This oversight increases the risk for severe inflammation, need for intensive care, and failure of definitive repair (141). Further, the need for repetitive operations leading to reduced working ability and prolonged sick leave is a difficult socioeconomic challenge (142).

A hepatobiliary surgeon should perform the surgical reconstruction after a major BDI (116, 137, 143, 144). If the support of a specialist is not available, abdominal drainage and referral to an adequate hospital is recommended. Any inflammation or infection can impair the result of the repair. Therefore, an immediate or early repair is preferred (145). On the other hand, time itself is not harmful, but inflammation is. Therefore, in cases of acute inflammation a reconstruction 4–6 weeks after the complication may be justified (143). In a sizeable retrospective multicenter study, which included 914 patients with BDI, the purpose was to determine optimal timing for definitive BDI repair. They did, however, find that the timing of a definitive repair was irrelevant to the success of the biliary reconstruction (140).

The goal is to achieve a patent anastomosis between a bile duct and the jejunum (Roux-en-Y hepaticojejunostomy or choledochojejunostomy, HJ) or distal part of the bile duct (choledochocholedochostomy). The proper surgical technique depends on the circumstances and on the biliary injury. The principles for the anastomosis performed in surgery are simple: to make a patent connection between two tubes with adequate caliber, mucosa-to-mucosa, and without tension and vascular impairment (146). Circumstances after BDI are mostly not favorable for repair without appropriate preparation. The level of injury determines the number of anastomoses performed. Both the proximal and distal parts of the bile duct are first exposed. The injured part is dissected and removed. Injury at the level of the bifurcation might even demand three different anastomoses between the jejunum and right, left, and right posterior hepatic duct. Otherwise, an anastomosis between the CHD or CBD and CBD or jejunum is performed.

Either the end-to-side or side-to-side technique (Figure 7) can be used to perform the HJ. The latter was presented by the surgeons Hepp and Couinaud in 1956, thus the name Hepp–Couinaud technique (147, 148). This provided a useful, precise technique for the reconstruction of type E1–3 biliary injuries, but in E4–5 injuries supplied a method only for left biliary duct repair. The use of the side-to-side approach, however, is rationalized by providing a wide and well-vascularized anastomosis. However, in the case of tiny ducts, when an incision on the side of the duct would more likely harm it, this technique is not preferred (149).

In long-term follow-up, a stricture may evolve in an anastomosis and consequently lead to biliary cirrhosis. With an end-to-side HJ, the stricture can develop in as many as 30% of patients (138, 141, 150), but with a side-to-side reconstruction, the stricture formation decreases to a few percent (149, 151). Prophylactic stents are used for preventing stricture formation and immediate post-operative complications. However, only if the anastomosis is suboptimal, intrahepatic bile duct stones exist, or the bile duct is clearly inflamed, is this recommended. Even then, the stenting is recommended to only continue for three months (146). The long-term success of biliary reconstruction is highly associated with the circumstances of the initial operation; absence of abdominal infection, use of correct surgical technique and presence of a hepatobiliary surgeon all increase the rate of short-term and long-term success of the repair (143, 146).

Cho and Strasberg (2018) developed a standardized protocol that is also used in this thesis to create an opportunity to evaluate and compare the results of bile duct repair. By this protocol, the studies described in Table 3 have evaluated the results of their reconstruction methods. The definitions for the terms ‘patency’, ‘primary patency,’ and ‘secondary patency’ are later described in section 4.3.

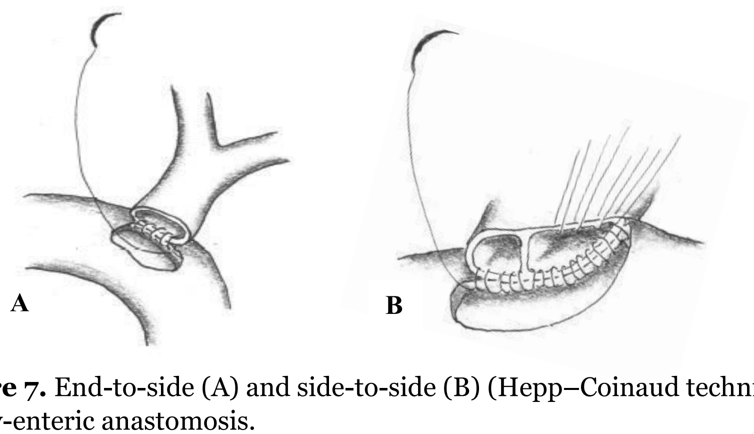


Figure 7. End-to-side (A) and side-to-side (B) (Hepp–Coinaud technique) biliary-enteric anastomosis.

Author	Country; Publication year	Number of patients	Possible comparison	Surgical approach	Primary patency rate	Actuarial primary patency (follow-up median)	Conclusions
Cuendis-Velazquez et al. (152)	Mexico; 2019	40	Mixed groups	Laparoscopic	100%	92.5% (49 months)	Robotic and laparoscopic approach for treatment of major BDI offers a possible choice for standard open surgery
		35		Robotic	100%	100% (16 months)	
Rueda-de-Leon et al. (153)	Mexico; 2019	148	Primary repair/UMIC	Open	77%	63% (10 years)	A standardized reporting system allowed for comparison and this study showed better results of BDI repair in high-income countries
		113	Secondary repair/UMIC	Open	73%**	52%* (10 years)	
		122	Primary repair/HIC	Open	93%	N/A	
Lindemann et al. (154)	South-Africa; 2020	23	Index operation in referral unit	Open	NA	89.7%* (10 years)	Incomplete detection of biliary tree in the preoperative evaluation was the only predictor of loss of patency
		108	Index operation by HB-surgeon	Open	92.6%	81.5% (10 years)	
Martinez-Mier et al. (155)	Mexico; 2020	37	Primary repair/LIC	Open	89%	N/A	Despite differences in referral and preoperative and operational events, good BDI repair outcomes can be achieved
		41	Primary repair/MIC	Open	97%	N/A	

Table 3. Current studies evaluating bile duct repair with a biliary-enteric anastomosis by the proposed standards of Cho and Strasberg (2018) (156). *Actuarial secondary patency rate included all patients failed to maintain or achieve the primary patency; **Secondary patency rate. Abbreviations: BDI – bile duct injury; (U)MIC – (Upper) middle-income country; HIC – High-income country; LIC – Low-income country; N/A – not applicable; HB – hepatobiliary

2.4 MANAGEMENT OF GALLBLADDER MALIGNANCY

2.4.1 Premalignant findings

Premalignant findings are usually incidental. Two apparent pathways have been studied considering precursors for GBC. The evolution of GBC from the premalignant cells is not entirely clear because monitoring of an already removed gallbladder is not possible. However, histopathological studies have revealed "metaplasia-dysplasia-carcinoma" and "adenoma-carcinoma" sequences (50, 55, 157-159).

Gallbladder lithiasis, causing constant irritation to the wall, may generate epithelial dysplasia. Metaplasia is also a frequent finding in gallbladders mutilated by stones. Metaplasia developing to dysplasia is not unequivically proven, however, dysplasia and metaplasia are both seen in the immediate proximity of cancer cells in these samples (50). The increase of intestinal metaplasia and expression of tumor protein p53 is associated with chronically inflamed gallbladder specimens with GBC (159). It is estimated that a dysplasia would theoretically need ten years to proceed into cancer (160).

Gallbladder adenomas are benign neoplasms of the epithelium. They are mainly tubular or less frequently papillary adenomas (158). Adenomas may carry a neoplastic potential, although they are rarely precursors of GBC (55, 157, 161). Patients with a carcinoma originating from an adenoma are older than patients with simple adenomas (50). Moreover, the size of these malignant polypoid adenomas is over ten millimeters (159).

2.4.2 Gallbladder carcinoma

Gallbladder cancer is a rare neoplasia with poor survival. However, it is the most frequent biliary tract malignancy (162). In some countries, GBC has been the primary cause of death for malignant tumors among women (163, 164). In Finland, the incidence is approximately 260 new gallbladder and biliary tract cancers annually, with the estimated 5-year survival being 14% (165). If the GBC occurs on the liver side, the prognosis decreases (166). Therefore, the location of the cancer in the gallbladder has also been considered in the most recent TNM classification (Table 4) (166, 167).

Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
TiS	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum), or Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T2a	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)
T2b	Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures
Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes
Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIIA	T3	N0	M0
IIIB	T1–3	N1	M0
IVA	T4	N0–1	M0
IVB	Any T	N2	M0
IVB	Any T	Any N	M1

Table 4. American Joint Committee on cancer (AJCC) 8th edition TNM staging for GBC (168)

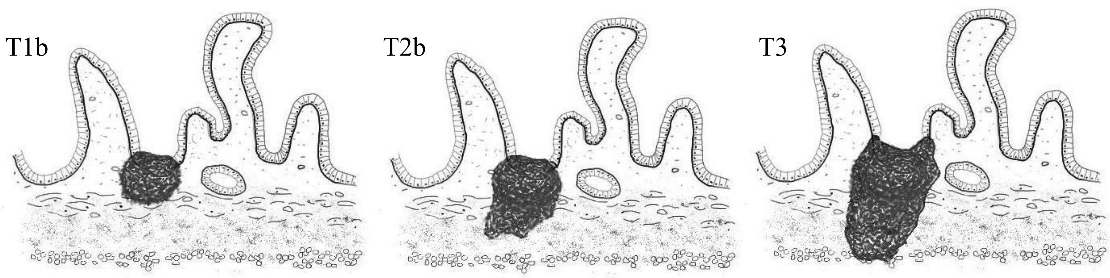


Figure 8: Histologic view of gallbladder cancer invading the wall.

2.4.2.1 Epidemiology and diagnosis

The incidence of GBC varies between countries, as well as regionally. The incidence has been increasing annually in the USA but declining in some European countries (169, 170). It is particularly high in India, Pakistan, and Ecuador. Somewhat elevated rates of the GBC incidence can be found in parts of Europe, female gender being overrepresented in all countries' GBC statistics (171). These neoplastic findings are predominately adenocarcinomas (98%). Adenosquamous, squamous, papillary, and mucinous subtypes, neuroendocrine tumors, lymphomas, or metastases are infrequently detected in the gallbladder specimens (172). Most often GBC originates from the gallbladder fundus, producing no symptoms at the early stage (173). Jaundice and general symptoms such as fever, nausea, and weight loss predict poor survival (174).

Stone disease is highly associated with the risk of GBC. Indeed, patients with gallstones possess a much higher risk of GBC than the average population. Still, the risk also varies by genders and ethnicities (171, 175-177). In the presence of any polypoid lesion of the gallbladder, the Indian ethnicity itself is an independent risk factor for developing GBC (176). Other factors increasing the risk of gallbladder malignancy are obesity (178), tobacco (179), alcohol (180), number or size of gallstones (181), high age (169), PSC (61), and exposure to heavy metal pollution (182). An ultrasound finding of porcelain gallbladder (calcified wall of gallbladder) carries an elevated risk of GBC. However, porcelain gallbladder itself does not cause GBC, rather a long-term inflammation, which causes these calcifying changes of the wall (183). This porcelain gallbladder finding was concluded as an indication for LCC only for patients with symptoms or clinical suspicion for localized GBC (184, 185).

GBC can be diagnosed preoperatively, during cholecystectomy, or incidentally in the histopathologic examination. When discovered incidentally, GBC is more often found at an early stage (15, 186, 187). These patients have had symptoms caused by gallbladder stones, which have led to gallbladder surgery for a benign indication. An incidental GBC is found in 0.2–0.9% of gallbladder specimens and accounts for half of the overall GBC cases (14, 15, 186-188). Pre-operative diagnosis is difficult. Early cancers especially are frequently misinterpreted as chronic cholecystitis upon ultrasound and CT (181). As the GBC progresses further, a mass in the gallbladder lumen or infiltrating tumor in the wall appears. A biopsy may be taken if the tumor is deemed inoperable. Otherwise, a biopsy is not recommended, and the CT provides the basis for diagnosis and the possibility of resection (189, 190).

Author	Country; Publication year	Incidental GBC prevalence (%)	Results	Conclusions
Koshenkov et al. (191)	United States; 2012	67/26,572 (0.25%)	Age over 65, gallbladder wall thickening, and bile duct dilatation were associated with incidental GBC	These three factors are recommended to use in evaluation of incidental GBC risk. Surgeons should more closely to avoid any contamination when operated these patients
Charfi et al. (187)	Tunisia; 2018	155/20,584 (0.8%)	Low GBC rate, but high proportion (67.1%) of T2–3 GBC	If selective HPE is used, risk factors such as patient's age and macroscopic appearance of the specimen is recommended to use in decision
Chin et al. (192)	Malaysia; 2012	3/1375 (0.2%)	Suspicious macroscopic appearance was present in all samples with GBC	A selective policy for HPE is recommended
De Zoysa et al. (193)	Sri Lanka; 2010	4/477 (0.8%)	Suspicious macroscopic appearance was present in all samples with GBC	A more selective approach to gallbladder HPE is safe but also saves time and costs
Deng et al. (194)	China; 2016	46/14,365 (0.32%)	In two samples with Tis and T1a GBC, no macroscopic abnormalities appeared. All other had suspicious lesions	The gallbladder should be sent for histology only if macroscopic examination raises suspicion.

Kalita et al. (195)	India; 2013	25/4115 (0.6%)	7 cases were clinically suspected, another 18 had thickened wall or localized growth in macroscopic examination performed by pathologist	All gallbladder specimens should be submitted to HPE in countries with relative high incidence of GBC
van Vliet et al. (17)	The Netherlands; 2013	6/1375 (0.4%)	Suspicious macroscopic appearance was present in all samples with GBC	A selective policy for HPE is recommended
Corten et al. (18)	The Netherlands; 2020	6/2271 (0.26%)	1083 (47.7%) specimens were sent to HPE. All six GBC cases was found from these. All patients whose gallbladder was not sent to HPE, were followed median 49 months.	Selective HPE after cholecystectomy is oncologically safe and reduces costs
Lohsiriwat et al. (13)	Thailand; 2009	24/4317 (0.56%)	Primary GBC was found in 24 and 3 (0.07%) secondary metastasis of gallbladder specimens. In multivariate analysis, empyema and patient's over 60 years age were significant risk factors	Routine HPE is indicated especially in cases of empyema and patient's age over 60 years

Table 5. Prevalence of incidental gallbladder cancer in a few other studies considering the need of routine histopathologic examination available in PubMed-database. Abbreviations: GBC – gallbladder cancer; HPE – histopathologic examination

2.4.2.2 Surgical treatment

Surgical resection is the only possible curative treatment for GBC currently available. In simple cholecystectomy, only the gallbladder is removed. The extended cholecystectomy includes lymph node dissection and liver resection (Figure 9). In this, segmentectomy IVb/V, a non-anatomical liver resection with 2–3 cm margins (a wedge resection) or hemihepatectomy is performed (196, 197).

Not only does the lymph node status strongly affect the overall survival (OS), but also the amount of the dissected lymph nodes (198). Regional lymph node dissection includes the hepatoduodenal lymph nodes (197). The recommended amount of dissected lymph nodes is at least six (167, 198). Thus, the strongest effect on the prognosis of a patient with GBC is achieved with 4 to 7 dissected lymph nodes (199). Indeed, an even more extensive lymphadenectomy has been proposed. This procedure would include lymph nodes from behind the portal vein, posterior pancreatoduodenal, common hepatic, and right celiac nodes (200). The importance of lymph node dissection is high. It has been proposed that without lymphadenectomy, the survival after radical resection would not differ from the simple cholecystectomy (201). Besides liver and lymph node resection, a resection of the extrahepatic bile duct can be offered for a specific patient group to achieve R0 resection. This extended bile duct resection has, however, also been seen to increase morbidity (202, 203). An example of a current protocol for the management of known or suspected GBC based on an American guideline is given in Table 7 (203). The management of GBC is based on many different guidelines, and no Finnish guidelines exist so far (Table 6).

For iGBC, cholecystectomy itself can be a curative treatment if the HPE reveals *in situ* carcinoma or a T1a tumor. If the cancer invades through the muscle layer (T1b and beyond), further evaluation is needed (203, 204). Staging CT is performed to reveal cancer progress. A multidisciplinary meeting evaluation is recommended to plan additional procedures (205). If the CT scan shows distant lymph node or other metastases, oncologic treatment is preferable. However, in the absence of further metastasis or other contraindications, the patient can proceed to curative-intent resection (Table 6).

Staging laparoscopy for iGBC starts with an exploration of the abdominal cavity (206). If the cancer appears to be disseminated (e.g., to carcinosis), though not revealed by CT, the operation is not recommended to be continued (189). Recovery after the laparoscopy is faster, which accelerates the onset of oncological treatments. Otherwise, the explorative laparoscopy is converted to open and proceeds with an appropriate resection. If the cancer has spread to wounds, it is likely to be disseminated. Therefore, a port site resection does not improve the prognosis (207). The presence of lymphovascular invasion, the stage status, and nodal metastasis decrease the success of curative-intent re-resection and survival after incidental GBC (208, 209)

Symptomatic GBC is often at the locally advanced (T3–4) stage, nodes are involved, or metastasis exists. Therefore, surgical options are mostly restricted. The principles of surgical treatment remain the same as in iGBC, considering extended cholecystectomy. After a multidisciplinary meeting evaluation, and if invasion beyond T1a is not seen, a simple cholecystectomy is recommended (196). No clear consensus exists regarding whether a simple cholecystectomy would also be sufficient for T1b cancer (196, 210). However, even a 3.4-years survival benefit was demonstrated for patients with T1b cancer undergoing extended resection compared with a simple cholecystectomy (211). After the cancer has advanced to the perimuscular connective tissue (T2), the location of the tumor plays a significant role in survival (166). The newest AJCC TNM staging was updated in 2017; the stage T2 was split to consider whether the growing carcinoma is in a peritoneal (T2a) or liver site (T2b) (168). In both cases, current recommendations propose an extended cholecystectomy (196, 197, 203, 212). Surprisingly, a recent study proposed that the hepatic resection might not be essential for curative treatment of T2 GBC in T2a or T2b groups (213). Beyond this, the current guidelines recommend curative resection for patients with nodal involvement until stage T3N1 (196, 203, 212), not necessarily excluding a non-metastatic T4N0-1 GBC (197). None of the guidelines suggest resection for patients with distal nodal metastases (N2) or metastatic (M1) GBC.

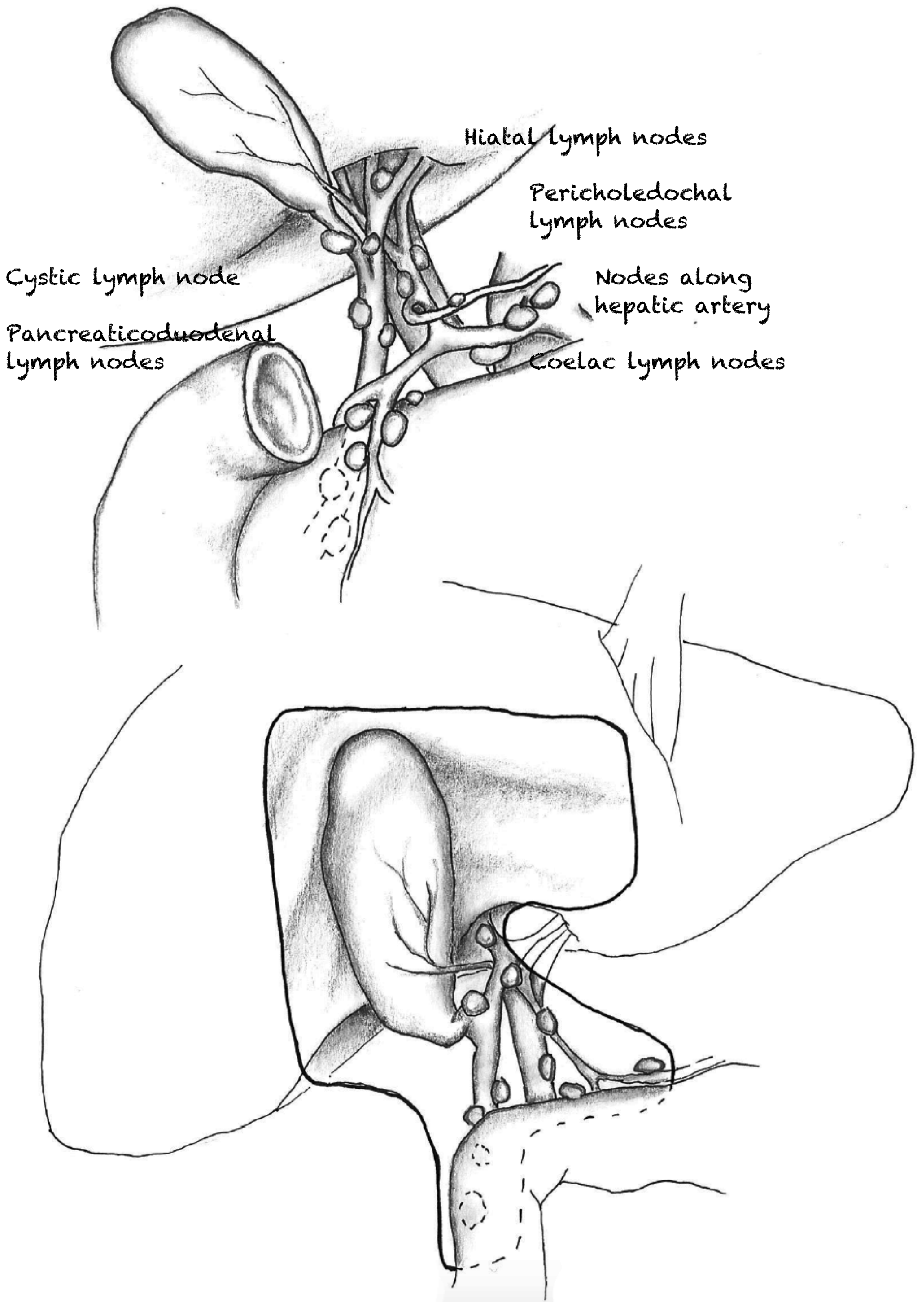


Figure 9. Hilar lymph nodes and dissection plane of extended cholecystectomy.

An estimated two-thirds of patients diagnosed with GBC are operated on either by cholecystectomy or any level of resection after symptomatic disease (214). After iGBC, curative-intent resection is possible in 40–68%, which indicates a great variation between centers (15, 202, 215, 216). After curative-intent resection, the R0 result improves survival significantly (209, 217). However, even in one-third of these patients with R0 resection, the cancer recurs with loco-regional or distant metastasis (218). Indeed, an especially advanced T-stage and the presence of perineural or lymphovascular invasion and tumor differentiation increases this risk (199, 218-220). Since the residual disease is an important factor for predicting the outcome after the re-resection, a Gallbladder Cancer Predictive Risk Score (GCPS) has been developed (Table 8). Ethun et al. suggested utilizing this score for patients with incidentally discovered GBC to predict loco-regional residual and distant disease more precisely than T-stage alone (221). Ramos et al. found GCPS to adequately identify patients with a high risk of distant or regional residual disease, which predicts poor prognosis and could thereby guide the decision of re-resection (222).

The management of locally advanced GBC is a widely discussed subject and so far without a resolution. A few researchers have studied neoadjuvant chemotherapy (NACT) or chemoradiotherapy (NACRT) for patients with locally advanced disease or nodal involvement (223-226). Gemcitabine alone or combined with platinum was found to stabilize or lead to partial response in 77% of patients; 30% proceeded to an attempted resection. However, only ten (14%) patients were able to continue to R0 resection (225). In another study, patients receiving gemcitabine combined with platinum responded better; there, the R0 rate rose to 40% (63 patients) (226). Both studies were able to show significantly better OS despite small study groups. However, providing a benefit for only a third of patients, the routine NACT cannot be recommended for all patients with advanced GBC (227). The most recent NCCN guidelines recommend consideration of NACT if nodal involvement is present (203).

Affiliation	Year	Main purpose of this recommendation	Target group	Curative-intent resection	Adjuvant therapy	Palliative chemotherapy
The Korean Association of HPB Surgery (196)	2014	Surgical treatment guidelines	T1a GBC	Simple cholecystectomy without perforating the gallbladder	-	-
			T1b GBC	Simple or extended cholecystectomy	Not recommended for patients who have undergone radical resection	
			T2 GBC and above*	A wedge resection (2–3 cm) or segmentectomy IVb/V	Gemcitabine or fluoropyrimidine adjuvant can be used	
				Lymphadenectomy includes at least 3 nodes from cystic duct, CBD and hepatoduodenal ligament nodes		
				Selective bile duct resection		
AHPBA (212)	2015	Clinical practice guidelines	Incidental GBC	Re-resection for T1b-T3N0-1 GBC	T2-4N1 R0 resections adjuvant chemo and/or chemoradiotherapy is recommended	Gemcitabine with or without cisplatin or capecitabine
				Routine port-site/wound excision is not indicated		
				Consider neoadjuvant therapy before re-resection of T3-4N1 GBC		
			T1-4N0-1M0 GBC in imaging or in staging laparoscopy	Extended cholecystectomy, including at least 6 nodes from any suspected areas		
				Only selective bile duct resection		
				Only selective major hepatectomy		
ESMO (197)	2016	Clinical practice guidelines	Incidental GBC	Re-resection for patients with T1b-T4 GBC	5-Fluorouracil or capecitabine chemo(radio)therapy for lymph node–positive and R1-resections	Gemcitabine with cisplatin
				Port-site resection if the bag was not used in primary operation		
				Consider staging laparoscopy and simultaneous liver resection		
			T1-4N0-1M0 GBC in imaging	Extended cholecystectomy with or without bile duct excision		
				Infundibular T4 GBC requires bile duct, duodenal, and probably pancreatic resection		

ASCO (228)	2019	Adjuvant therapy guidelines	All R0 resections	-	Capecitabine for 6 months	-
			R1 resection	-	Chemoradiotherapy may be beneficial	-
NCCN (203)	2020	Clinical practice guidelines	Incidental GBC	If incidentally detected during the surgery, diagnostic laparoscopy or simultaneous radical surgery is recommended	Capecitabine for R0- and R1-resections Consider fluoropyrimidine-chemoradiation for R1-resections	Gemcitabine with cisplatin
				Re-resection for patients with T1b-T3N1 GBC		
				Consider neoadjuvant therapy before re-resection of locoregionally advanced or N1 GBC		
			In imaging diagnosed GBC	Recommendation of resection is equal to incidental GBC		

Table 6. Current guidelines for treatment of gallbladder cancer. *No recommendation of N1 or M1 statuses. Abbreviations: ESMO – European Society for Medical Oncology; GBC – Gallbladder cancer; HPB – hepato-pancreato-biliary; AHPBA – American Hepato-Pancreato-Biliary Association; ASCO – American Society of Clinical Oncology; NCCN – The National Comprehensive Cancer Network

Current circumstance	Key points of management
Preoperative mass identified	• Contrasted CT of chest, abdomen, and pelvis • Liver function tests and tumor markers • Consider SL
Incidental finding at surgery	• Frozen section of gallbladder if suspicious for cancer • Intraoperative staging with resection of any suspicious lymph nodes and cystic duct node • Definitive surgery should be delayed until full imaging and pathologic workup is complete • Contrasted CT of chest, abdomen, and pelvis
Incidental findings on pathology	• Observation recommended for T1a patients with R0 resection • Contrasted CT/MRI of chest, abdomen, and pelvis for T1b or greater • Consider SL for T1b or greater • Consider neoadjuvant therapy in N1 disease
Unresectable (on SL or imaging)	• Biopsy if tissue not available • Genetic testing

Table 7 Detailed workup of known or suspected gallbladder cancer according to NCCN guidelines (203). Abbreviations: CT – computed tomography; MRI – magnetic resonance imaging; SL – staging laparoscopy

T-Stage	Tis/T1a T1b T2 T3/4	0 1 2 3
Grade	G1 (Well-diff) G2 (Mod-diff) G3 (Poor-diff)	1 2 3
LVI	Negative Positive	1 2
PNI	Negative Positive	1 2
TOTAL RISK	**Loco-regional residual**	**Distant disease**
Low (3-4)	0%	0%
Intermediate (5-7)	24%	3%
High (8-10)	61%	32%

Table 8. Gallbladder Cancer Predictive Risk Score (229). Abbreviations: LVI, lympho-vascular invasion; PNI, perineural invasion

2.4.2.3 Oncologic treatment

Some if the guidelines recommend adjuvant therapy with or without radiation (CRT) after curative intent resection in both R0 and R1 resections (Table 6) (203, 212). The range of regimens available is extensive, and no individual drug was superior to others prior to the BILCAP trial (189, 230). According to earlier recommendations, adjuvant chemotherapy was mostly based on fluoropyrimidine or gemcitabine. The BILCAP trial, however, was a multicenter study that found capecitabine to improve the OS by several months when treating patients with biliary tract cancer (230). According to ASCO Clinical Practice Guidelines, the capecitabine adjuvant chemotherapy is now suggested to be offered to all patients with resected biliary tract cancer including patients with GBC beyond stage T1b for 6 months (228). The current guideline of NCCN suggest an adjuvant CRT for patients with positive nodes or R1 resection (203). This treatment with CRT showed a slightly better survival advantage when given as adjuvant for patients with T3 or node-positive GBC (231, 232).

The strength of adjuvant chemotherapy can be demonstrated especially in patients with an advanced stage or nodal involvement (232, 233). Chemotherapy, especially with gemcitabine or gemcitabine combined to cisplatin, can show this positive effect (164). These cytostatic drugs were first discovered to be efficient for biliary tract and pancreatic cancer, but given the many similarities between these cancers, they were detected to be valid against GBC as well (234, 235). Indeed, adjuvant therapy, also combined with simple cholecystectomy, could be beneficial for patients unfit for the most aggressive radical curative surgery (233). This can offer a possibility for high-risk patients' care.

If resection is not possible, chemotherapy can provide a survival benefit for patients with metastatic or locally advanced, inoperable, GBC. Valle et al. found a statistically significant benefit for patients with biliary tract cancer treated with gemcitabine/cisplatin compared with gemcitabine alone (236). Dierks et al. controlled this protocol for treatment with gemcitabine/cisplatin. They found a significant increase in the OS compared to the best supportive care (237). However, the number of patients with GBC was low in these studies, which concentrated on biliary tract cancers overall.

The advanced and unresectable disease quickly infiltrates the liver or around the hepatic duct. Occasionally symptoms emerge after the GBC blocks the bowel, but biliary obstruction manifests frequently. As a best supportive care, an endoscopist can insert a stent into the obstructed bile duct or bowel (238). This treatment offers the patient an open biliary tree and bowel to enable possible palliative oncologic treatment. Survival of advanced GBC is poor, and with the best supportive care reaches just a few months (173, 239).

3 AIMS OF THIS STUDY

This thesis aims to study laparoscopic cholecystectomy considering the safety and feasibility of new technology and surgical complications in cholecystectomy. It also aims to study the management of a malignant finding of the gallbladder. Specific aims of this study were:

Study I
to compare the three-dimensional and two-dimensional laparoscopic cholecystectomy, whether the three-dimensional technique is superior considering the operation time and safety,

Study II
to study the effect of bile duct injury on quality-of-life and report the results of biliary reconstructions,

Study III
to clarify the need of histopathologic examination of the gallbladder specimen after simple cholecystectomy for gallbladder stone disease and to report the amount of incidental gallbladder cancers, and

Study IV
to determine the incidence, treatment, and survival of gallbladder cancer in southern Finland.

4 MATERIALS AND METHODS

4.1 Study design and research settings

This study was carried out at the Helsinki University Hospital (HUH) Abdominal Center during 2015–2020. The Abdominal Center and Department of Transplant and Liver surgery functions as a secondary and tertiary referral unit for 1.2 and 1.9 million inhabitants, respectively. As the largest hepatobiliary center in Finland, the Department of Transplant and Liver surgery offers a referral center to the whole country.

Study I was a randomized clinical trial. Study II was a retrospective, case–control cohort study. Studies III and IV were retrospective; in addition, Study IV was a population-based study. The HUH institutional review board approved all studies. Studies I and II were approved by the HUH ethical board and Studies II and IV by the Finnish Institute for Health and Welfare. Written consent was obtained from patients participating in Studies I and II.

4.2 Patients

This thesis included 2338 patients with benign gallbladder disease and 294 patients diagnosed with gallbladder malignancy. All patients with benign gallbladder disease were operated on in the HUH Abdominal Center (Study I and III) or Department of Transplant and Liver Surgery (Study II). Study IV included all GBC patients treated at FICAN (National Cancer Center Finland) South.

Study I. This randomized controlled single-blinded trial was carried out at the Surgical Hospital (until December 2015) and Jorvi Hospital (from January 2016) day surgery unit between February 2015 and April 2017. Patients were referred to the HUH Abdominal Center for elective LCC and were assessed for eligibility for this trial. Patients were excluded if a surgeon had an inappropriate level of experience (< 5 previous operations) with 3D laparoscopy if another operation was planned to be performed simultaneously, or the risk of conversion was estimated to be high. Altogether, 209 patients were randomized to either the 2D or 3D arm. Patients were blinded to their randomization group. All 15 surgeons who participated in this study were tested for stereo acuity with the Randot® Stereotest (Stereo Optical, Chicago, Illinois, USA). Patients were contacted 30 days after the procedure for follow-up.

Study II. 52 patients with major BDI were identified from a prospectively maintained database at the HUH Department of Transplant and Liver surgery. Patients were treated at this clinic during 2000–2016. For these patients, to compare the QOL between patients with and without BDI, controls were searched for from hospital patient databases by matching them on age (up to a 10-year difference), sex, the date (up to 3-month difference) and urgency of an operation. All patients with BDI and controls were contacted by sending three questionnaires (GIQLI – gastrointestinal QOL index, SF-36 – Short Form Health Survey and an additional non-validated questionnaire including information on education, working status, opinion of the provided information before the LCC and possible discomfort and medications after the primary operation).

Study III. All patients whose gallbladder had been removed for benign reasons were included in the study. These patients were operated on in the Surgical Hospital, Meilahti Hospital, Jorvi Hospital, and Peijas Hospital from November 2010 to May 2012. Patients were identified from the electronic patient database by procedure codes JKA20 and JKA21, for open and laparoscopic cholecystectomy, respectively. Altogether, 2034 patients were included.

Study IV. This retrospective population-based study included all patients with GBC diagnosed in the FICAN South area. Patients with GBC were gathered from the Finnish Cancer Register (FCR). After exclusion, 294 patients with GBC were found between 2006–2017. The 12-year period was divided into 3 equal periods to be able to see any changes in incidence, survival or treatment patterns. Follow-up data were available for 291 patients, including 21 patients diagnosed with GBC only at autopsy.

4.3 Definitions

3D Laparoscopic cholecystectomy in Study I was conducted with a Wolf® 2D/3D laparoscopic HD (high-definition) device. In this, a non-deflectable 30° 10-mm scope was used. The surgeon was standing on the patient's left side, and the monitor was on the right. The surgeon and assistant wore passive polarized glasses to perceive a 3D-view. The assistant was standing on the surgeon's left. The surgeon was allowed to switch to a 2D mode during, for example, trocar insertion, if needed. The standard laparoscopic four-port technique was used in starting the preparation from the neck of the gallbladder and aiming at CVS. The gallbladder was removed from its' bed, and a plastic bag was used to remove the gallbladder from the abdominal cavity. The operation time was calculated from the incision to wound closure.

Conventional laparoscopic cholecystectomy is the gold-standard procedure for cholecystectomy. The four-port technique was used in all LCC of this thesis. In Study I, the instrument was standardized, and therefore a Wolf® 2D/3D laparoscopic HD devise was used. Since the system can display 2D and 3D views, it was switched to 2D mode during this randomization. Surgeons did not wear polarizing glasses during a 2D operation. They were also not allowed to switch on the 3D position. Otherwise, the operation was accomplished as described above.

Converted cholecystectomy was used if the surgeon considered an open procedure safer than continuing with the laparoscopic technique. In this, laparoscopic instrumentation is removed and proceeded with an open technique. An open cholecystectomy was described earlier in section 2.3 Gallbladder surgery.

Hepaticojejunostomy was performed with the Roux-en-Y technique. In this, the small bowel was divided, and the jejunum lifted close to the liver hilum and sutured end-to-side with the bile duct(s) (Figure 5 A). An enteroanastomosis between the disconnected proximal jejunum and the middle or distal part of the jejunum (jejunojejunostomy) was performed.

Patency delineates as an open biliary tree after surgical reconstruction. By definition, a bile duct then appears without the need for stents or manifested episodes of jaundice or cholangitis (156).

Index treatment is the first surgical reconstruction that was attempted to restore the biliary tree continuity (156). In this, the procedure was either an end-to-end anastomosis between the proximal and distal bile duct or a hepaticojejunostomy. The salvage procedure, for example, with a laparotomy and drainage, meant an additional operation designed to create favorable conditions for future reconstructive procedures.

Primary and secondary patency was defined as an open biliary tract after surgical reconstruction. The primary patency was achieved if the patient did not need any further operation or was free from stents and drainages after 90 days from primary index treatment. If the patient achieved and maintained the primary patency after that, the result was graded as a grade A result. However, if the patient could not achieve or maintain the primary patency, the result was defined as grades B, C, or D, depending on whether the patient was able to obtain the secondary patency (156).

The actuarial primary patency rate represents the grade A result after the biliary reconstruction of BDI (156). It is calculated as a Kaplan–Meier curve and can visualize the patency rate's change as a function of time. The actuarial secondary patency rate is the same as the aforementioned Kaplan–

Meier curve, but is calculated for patients undergoing a secondary bile duct repair.

Lymphadenectomy included lymph nodes around the choledochus, hepatic artery, and liver hilum.

Liver resection was performed in cases where the BDI was associated with significant vascular injury, which had damaged the liver. In the extended cholecystectomy or the re-resection after incidental GBC, a wedge resection or sections IV and V was performed with a possible concomitant lymphadenectomy.

4.4 Statistical methods

All data extracted from an electronic database or directly from patients (Studies I and II) were collected and analyzed with Statistical Package for the Social Sciences (SPSS Statistics ver. 22–24 IBM, Armonk, NY, USA). To reveal possible changes in the GBC incidence (Study IV), R statistical software including Epi and epitools packages was used.

Study I. A two-tailed power analysis was performed by using 80% power, 0.05 alpha. Ten minute differences between the 2D and 3D groups was considered clinically significant. Patients were randomized with a 1:1 allocation to either group. The CONSORT flowchart can be found in the original article. Differences between groups with continuous variables were tested with the Mann–Whitney U test and categorical variables with Fisher's exact test. P values <0.05 were considered statistically significant.

Study II. Newly proposed standards for reporting the outcome after biliary reconstruction were used (Cho 2018). The terms ‘patency,’ ‘actuarial primary patency,’ ‘primary and secondary patency,’ and ‘index treatment’ are defined above following these standards. Kaplan–Meier analysis was used to calculate the actuarial primary patency rate at 1-, 3-, and 5-years follow-up and actuarial secondary patency rate at one year and end of follow-up. A log-rank test was used to compare groups. If the patient died before an index treatment was possible, the patency could not be calculated. Differences between groups with continuous variables were tested with the Mann–Whitney U test and categorical variables with the Fisher’s exact test or Chi-square. P-values <0.05 were considered statistically significant.

Study III. The FCR was used to crosscheck patients whose gallbladder was not sent to histopathologic examination, verifying that no GBC was missed from these unexamined specimens.

Study IV. Survival estimates after GBC diagnosis were based on Kaplan–Meier analysis. Groups were compared with the log-rank test. Differences between groups with continuous variables were tested with the Mann–Whitney U test and categorical variables with Fisher's exact test. P-values <0.05 were considered statistically significant. To determine the change in the incidence of GBC, crude incidence rates (IR) were calculated. Further, the crude and age-adjusted incidence rate ratios (IRR) and their 95% confidence intervals (CI) were assessed from the Poisson models without and with age, respectively.

5 RESULTS

As shown in Table 9, this thesis included 2444 patients operated on primarily for a benign reason, mainly for symptomatic cholecystolithiasis (61.1%). Patients with incidental GBC in Study IV were significantly older ($p < 0.001$) than in the other studies. Study IV patients were also operated on more often (47.9% vs. 23.8%) for acute cholecystitis than in Study III which included all patients operated on for primarily benign reasons within 1.6 years. Additionally, Study IV included 195 patients diagnosed with GBC by imaging or at autopsy (n=21).

	Study I	Study II	Study III	Study IV
N	105+104	52+ 53	2034*	103**
Age, median/IQR	48.5 (38-57.3)	54.7 (44.6-67.2)	53 (41-64.6)	72.9 (65.4-81.1)
Sex, n (%)				
Male	58 (27.8%)	37 (35.2%)	661 (32.5%)	30 (30.0%)
Female	151 (72.2%)	68 (64.2%)	1373 (67.5%)	70 (70.0%)
Indication for surgery, n (%)				
Symptomatic gallstones	198 (94.7%)	56 (53.3%)	1189 (58.5%)	43 (43.0%)
Acute cholecystitis	0	18 (17.1%)	484 (23.8%)	49 (49.0%)
Previous cholecystitis	2 (1.0%)	17 (16.2%)	136 (6.7%)	0
Pancreatitis	1 (0.5%)	6 (5.7%)	136 (6.7%)	3 (3.0%)
Choledocholithiasis/cholangitis	2 (1.0%)	6 (5.7%)	77 (3.8%)	0
Asymptomatic gallstones	2 (1.0%)	2 (1.9%)	12 (0.6%)	0
Gallbladder wall polyp or another lesion	4 (1.9%)	0	0	1 (1.0%)
Other	0	0	0	4 (4.0%)
Level of urgency, n (%)				
Elective	209 (100%)	84 (80%)	1488 (73.2%)	53 (53.0%)
Emergency	0	21 (20%)	546 (26.8%)	47 (47.0%)
Operative approach, n (%)				
Laparoscopic	208 (99,5%)	71 (67.6%)	1838 (58.5%)	61 (61.0%)
Converted cholecystectomy	1 (0.5%)	31 (29.5%)	117 (5.8%)	20 (20.0%)
Open cholecystectomy		3 (2.9%)	79 (3.9%)	19 (19.0%)
Follow-up, years, median (IQR)	30 days	7.5 y (5.8-9.6)	2.9 y (0.1-4.1)	1.4 y (0.6-3.5)

Table 9 Basic characteristics of all patients for whom gallbladder was *primarily operated on for benign reasons*. *ten patients with an incidental GBC; **35% of Study IV population. Abbreviations: IQR – Interquartile range

5.1 Comparison of 3D and 2D laparoscopy in cholecystectomy (I)

Basic demographics. The study included 105 patients randomized to the 3D arm and 104 patients to the 2D arm. The median age was 48.5 years, and the median body mass index (BMI) was 27.8. There were no differences between 3D and 2D groups according to basic characteristics. The primary operative characteristics of all patients in this study are provided in Table 5. The patients were mainly healthy women (72.2%) with an American Society of Anesthesiologists' (ASA) physical status classification score of 1–2 in 92.4%, and a Charlson's comorbidity index (CCI) score of 0 in 53.1%. The indication for LCC was predominantly symptomatic gallstone disease (94.7%). Three attendings and 12 residents operated on patients. Stereoacuity was perfect (10) in 6 surgeons, who performed operations on 154 (73.7%) patients.

Operation time was the primary outcome measure. The overall average operation time was 48 min. For residents, this was 61 min, and for attendings 42 minutes. One operation was converted to open in the 3D group. The operation time did not differ between 3D and 2D groups (49 min vs. 48 min, p=0.703), nor did it differ by subgroup analysis including subgroups by surgeon status (attendings: 42.5 min vs. 42 min, p=0.703; residents: 62 min vs. 60 min, p=0.596), 3D or LCC experience, resident surgeon's gender or stereovision, or patients' BMI.

Complications during and 30-days after the operation were evaluated. Intraoperative complications occurred in 29 (13.9%) patients. These complications were minor (gallbladder rupture or intraoperative bleeding managed with diathermy or hemostatic). No bile duct injuries occurred. Postoperative complications were reported using the Clavien-Dindo classification (CDi). A total of 43 (22.5%) patients out of 191 patients, who responded to 30-day contact for follow-up, had a CDi I–II complication. No other postoperative complications occurred. Neither postoperative nor intraoperative complications differed between the 3D and 2D groups.

5.2 Biliary tract injuries (II)

Basic demographics. The study included 52 patients with a major (Strasberg E) BDI and 53 patients with an uneventful cholecystectomy who responded adequately to questionnaires. Their basic characteristics are combined in Table 5. Briefly, the median age of patients with BDI was 53 years, and 57.7% (n=30) were women. Patients with BDI were operated on for symptomatic gallstone disease in half of the cases (n=26). Seven (13.5%) patients with BDI had had an acute cholecystitis, and in a quarter (n=13), the patient had had cholecystitis earlier. The operation was emergent in ten

(19.2%) of patients with BDI. Except for one operation, all were initially laparoscopic, but in 30 (57.4%) cases were converted to open.

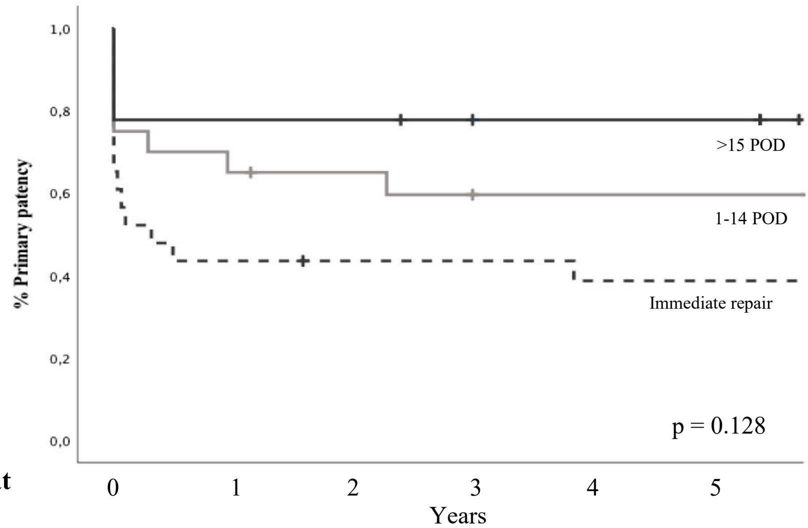
5.2.1 Surgical reconstruction after bile duct injury

The BDI was detected intraoperatively in 29 (55.8%) cases. Patients with BDI most often had Strasberg type E1 BDI with distributions detailed in Table 10. BDIs were further graded into subgroups, according to Cho et al. (2018), where Strasberg type E1–3 BDI belongs to Grade 2 and types E4 and E5 to Grade 3 (Figure 5).

BDI classification	E1 E2 E3 E4 E5	19 (36.5%) 18 (34.6%) 6 (11.5%) 8 (15.4%) 1 (1.9%)
BDI Grade	2 3	43 (82.7%) 9 (17.3%)
Damage detection	Intraoperative 1st – 2nd POD 3rd POD – 1 week Later	29 (55.8%) 6 (11.5%) 12 (23.1%) 5 (9.6%)
Damage repair	Immediate Early (1st-14th POD) Late (15th- POD)	23 (44.2%) 20 (38.5%) 9 (17.3%)
Index treatment surgeon	Abdominal or general surgeon HB surgeon	17 (32.7%) 35 (67.3%)

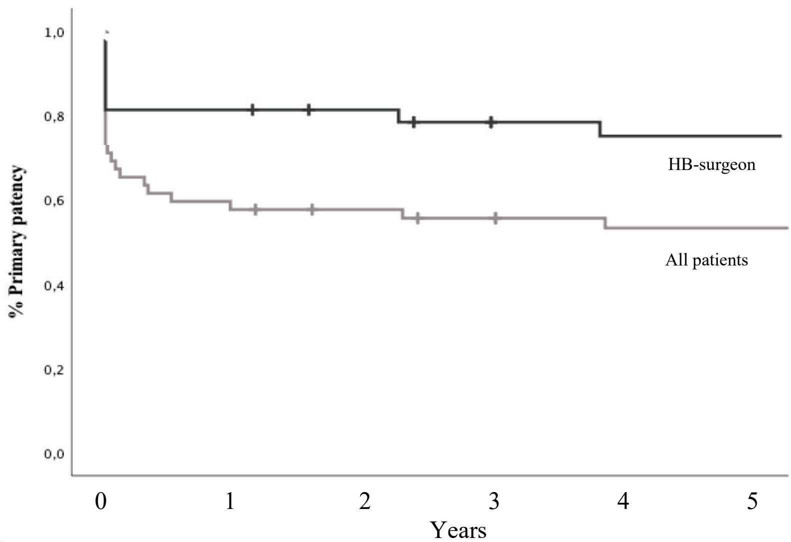
Table 10. Detailed information of the BDI and the repair. Abbreviations: BDI – Bile duct injury; POD – post-operative day; HB – hepatobiliary

The primary patency rate at one year was 43.5%, 65%, and 77.8% if the index treatment was performed immediately, during the first two weeks or later, respectively (Figure 10). The estimated primary patency rates were similarly 43.5%, 59.6%, and 77.8% at three years. The actuarial long-term primary patency after 1, 3, and 5 years was 83%, 80%, 76% for repairs by the hepatobiliary surgeon, and 58%, 57%, and 53% for all repairs, respectively (Figure 11).



Patients at risk	0	1	2	3	4	5
Immediate repair	23	10	9	9	8	8
1st-14th POD	20	13	12	11	10	10
After 15th POD	9	7	7	6	5	5

Figure 10. Primary patency for patients with primary repair performed immediately, between 1-14 days postoperatively or over two weeks after the injury. POD – post-operative day



Patients at risk	0	1	2	3	4	5
Primary repair by HB-surgeon	35	29	27	25	22	22
All BDI-patients	52	30	28	26	23	23

Figure 11. Primary patency for patients treated primarily by hepatobiliary (HB) surgeon (dark grey) and all patients with Strasberg type E bile duct injury (BDI) (light grey).

5.2.2 Quality of life after bile duct injury

At the time of this study, 46 patients with BDI were alive; 35 (75%) patients responded to questionnaires. The median follow-up was 90 months. Women responded to these surveys more often than men (71.4%, n=25). For the BDI-patients who responded (n=35), matched controls (n=103) were identified and sent questionnaires, and 53 (51%) returned adequately filled-in questionnaires. Patients who responded had similar educational (p=0.226) and working (p=0.25) statuses. Patients who did not have a BDI were more often satisfied with preoperatively provided information about risks (22 vs. 7; 41.5% vs. 20%; p=0.025)

When the QOL was tested with GIQLI and SF-36 questionnaires by each grade (A–D) of patency, it did not differ when compared with controls (Figure 12). The BDI did not appear to be different between BDI patients and controls overall (Figure 13; A), nor did it differ with respect to the obtained patency (Figure 13; B).

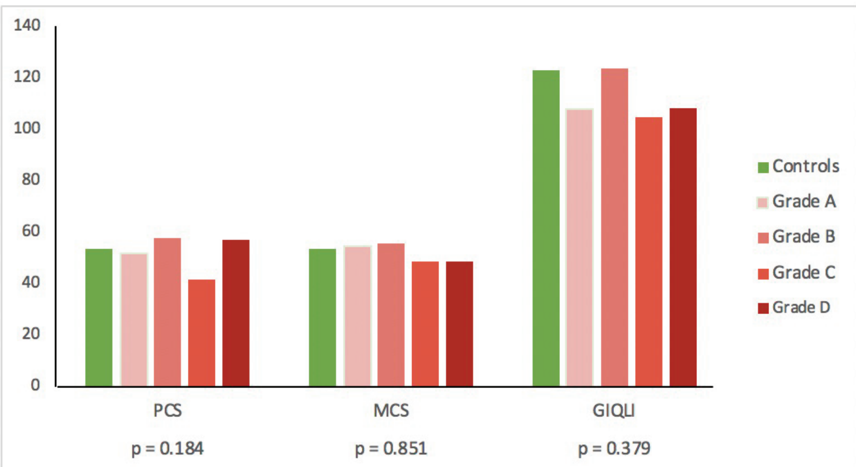
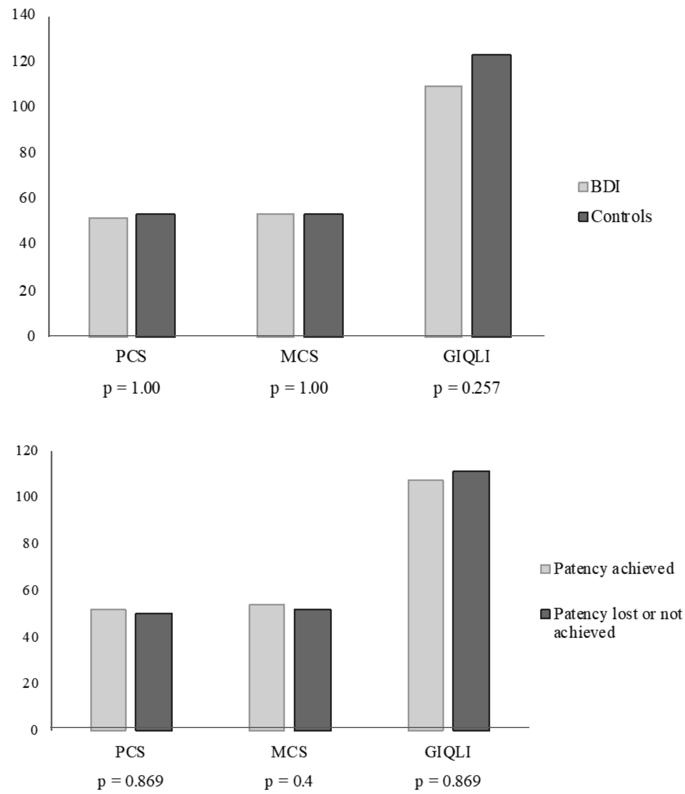


Figure 12. Quality of life after uncomplicated cholecystectomy (Controls) and BDI reconstruction by the BDI grading (A–D) in median 90 months (IQR 69.7–116.0) follow-up. (Median (IQR) PCS: Controls 53.4 (46.8–57.7), Grade A 51.7 (43.6–57.6), Grade B 57.8 (41.0–60.6), Grade C 41.4 (35.8–51.1), Grade D 57.0 (42.0–60.5). Median (IQR) MCS: Controls 53.4 (45.2–56.6), Grade A 54.4 (40.7–57.2), Grade B 55.6 (51.1–57.4), Grade C 48.6 (39.3–61.0), Grade D 48.4 (40.0–52.6). Median (IQR) GIQLI: Controls 123 (105.0–129.5), Grade A 108 (83.5–131.5), Grade B 124 (107.0–129.0), Grade C 105 (80.5–125.5), Grade D 108.5 (81.0–130.0)). Abbreviations: BDI – bile duct injury; PCS – Physical component summary; MCS – Mental component summary; GIQLI - gastrointestinal quality-of-life index. Originally published in Surgical Endoscopy (Study II)



A

B

Figure 13. Quality of life after repair of a major BDI and uncomplicated cholecystectomy (Controls) (**A**) (Median PCS 51.7 vs. 53.4; MCS 53.3 vs. 53.4; GIQLI 109.0 vs. 123.0) and when the patency was achieved and maintained or lost or not achieved (**B**) (PCS 51.7 vs. 50.6; MCS 54.4 vs. 551.7; GIQLI 108.0 vs. 111.5). Abbreviations: BDI – bile duct injury; PCS – Physical component summary; MCS – Mental component summary; GIQLI - gastrointestinal quality-of-life survey

5.3 Necessity of histopathological examination after cholecystectomy (III)

Macroscopic findings. The basic demographics are listed in Table 5**.** Surgeons indicated that most of gallbladders removed for benign reasons were normal (n=1464; 70%). An obvious tumor was seen in 4 (0.2%), a polyp in 6 (0.3%), and a thickened or necrotic wall in 505 (24.8%) samples. Of 118 gallbladders not sent to HPE, 6 displayed thickened or necrotic walls. These patients were crosschecked with the FCR, and no GBC was found.

Microscopic findings. HPE was performed for 1916 (94%) specimens. Minor dysplasia was apparent in 20 (1%) and major dysplasia in 3 (0.2%) samples. Ten samples showed a GBC, almost all (90%) had adenocarcinoma. Each of these gallbladders had an abnormal wall on macroscopic examination.

Patients with GBC. Of 2034 patients, 10 (0.5%) patients had an incidental GBC. Seven patients were women. The median age was 74 years; one patient was 49 years old. Each patient underwent some imaging (US n=9, CT n=1, magnetic resonance imaging (MRI) n=3) and was diagnosed with either a gallstone disease (n=6) or acute cholecystitis (n=4). None of them were suspected to have a malignancy. After the operation, a tumor was seen in three, a local hardness in one, a thickened wall in five, and acute cholecystitis in one specimen. Five patients were able to proceed to the liver resection. Three of these patients were alive and disease-free at the end of follow-up. An estimated survival for patients diagnosed with an incidental GBC at 1 and 3 years was 79% and 37.5% (Figure 14).

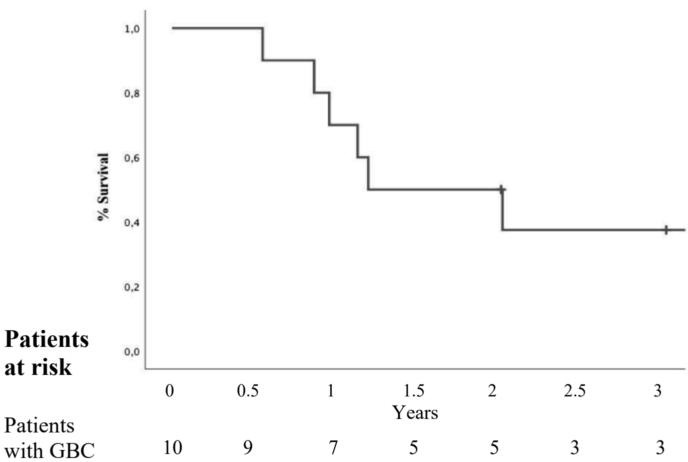


Figure 14. Kaplan–Meier curve for survival for patients with incidental GBC in Study III

5.4 Incidence and management of gallbladder malignancy (IV)

Incidence. During the 12-year study period, 273 patients were treated for GBC and 21 were diagnosed at autopsy. Patient medical records were available for 270 patients. The crude overall incidence of GBC in the FICAN south was 1.32/100,000 inhabitants. The crude GBC incidences were 1.50, 1.28, and 1.18/100,000 inhabitants at periods A, B, and C, respectively. Comparing age-adjusted IRRs of periods B and C to period A, a decrease in the incidence appeared (age-adjusted IRR 0.95, 95% CI 0.92-0.98; p=0.010)

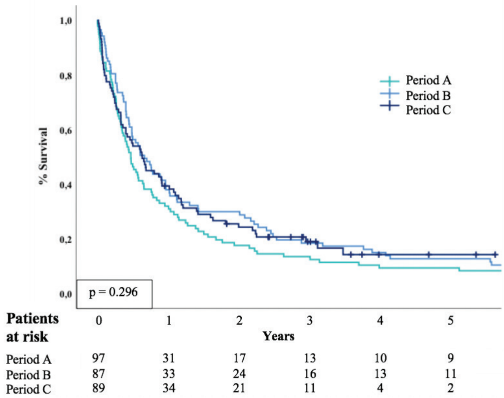
Treatment. Of 294 patients with GBC, 103 cancers (35%) were detected after primary cholecystectomy. These patients were often older (>70 years) and operated on for acute cholecystitis than in Studies I–III (Table 5). The treatment changed during the three study periods; the number of patients treated with any surgical procedure increased over time (Period A N=29, 30.9%; Period B N=44, 50.6%; Period C N=46, 51.7%, p=0.006). Similarly, the number of patients receiving only the best supportive care decreased (Period A N=41, 44.7%; Period B N=26, 29.9%; Period C N=24, 27.0%, p=0.039). However, the number of patients proceeding to curative-intent surgery did not change (N=14, 14.9%; N=18, 20.7%; N=19, 21.3%; p=0.3).

A simple cholecystectomy was a curative operation for four patients (pT0-1N0M0). After primary cholecystectomy, the curative intent operation was performed for 31 out of 103 (30.1%) patients. The reoperation was complementary lymphadenectomy (n=2), liver bed resection with lymphadenectomy (n=18), or liver bed resection with lymphadenectomy and incision resection (n=11). The direct curative-intent operation was performed for 16 (5.5%) patients: extended cholecystectomy (n=8) combined with bile duct resection (n=2), simple cholecystectomy and liver bed resection (n=2), or lymphadenectomy (n=2), or bile duct resection (n=1), or bile duct resection and lymphadenectomy (n=1).

Gemcitabine (n=15) was the most often used adjuvant therapy after curative-intent surgery. Additionally, patients were treated with capecitabine (n=4) and combination chemotherapy (n=1). Moreover, one (1.5%) patient received radiotherapy. Patients who did not proceed to a curative-intent surgical procedure were treated with gemcitabine (n=75), capecitabine (n=5), and combination chemotherapy (n=5), but also received radiation therapy (n=3). Five (1.9%) patients were treated with a combination of chemoradiation. During the three study periods, no changes in treatment patterns with curative-intent procedures or oncologic therapy were apparent.

Survival. The prognosis of GBC has not improved during the 12-year study period. Kaplan–Meier curves for survival among all patients, patients with curative-intent resection, and patients who did not proceed to curative resection but received chemo- or radiation therapy, are shown in Figures 13–15. Further, the estimated 1-, 3-, and 5-year survivals are in Tables 11–13, divided in three periods. The estimated overall 1- and 5-year survival for all patients with GBC were 36.2% and 11.6%, respectively.

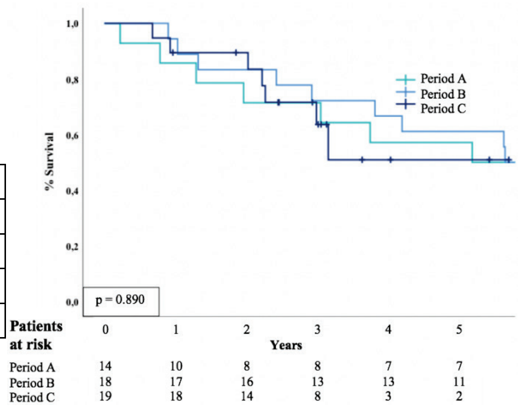
Figure 15. Kaplan–Meier curve for overall survival among all patients with GBC.



Survival, %	Period A	Period B	Period C
95% CI	126.7-223.3	161.7-330.3	158.0-310.2
1-year	32.0%	37.9%	39.3%
3-year	13.4%	18.4%	18.9%
5-year	9.3%	17.2%	14.2%

Table 11. Estimated overall survival for all patients

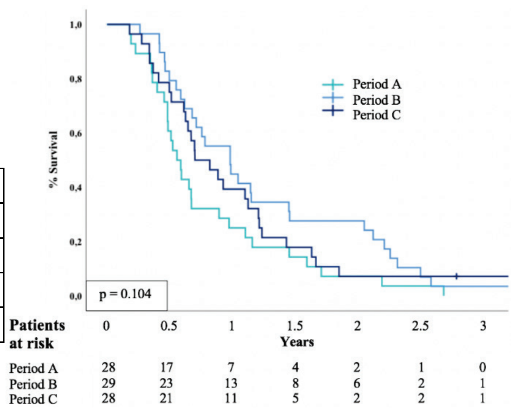
Figure 16. Kaplan–Meier curve for overall survival among patients with curative-intent surgery.



Survival, %	Period A	Period B	Period C
95% CI	N/A	N/A	N/A
1-year	85.7%	88.9%	89.5%
3-year	71.4%	72.2%	63.6%
5-year	57.1%	61.1%	50.9%

Table 12. Estimated overall survival for patients with curative-intent resection

Figure 17. Kaplan–Meier curve for overall survival among patients with palliative and oncologic chemotherapy.



Survival, %	Period A	Period B	Period C
95% CI	163.1-240.9	224.1-487.9	152.9-355.2
1-year	28.6%	44.8%	39.3%
3-year	0%	3.4%	7.1%
5-year	0%	0%	0%

Table 13. Estimated overall survival for patients with palliative chemotherapy

6 DISCUSSION

6.1 Three-dimensional view in laparoscopic cholecystectomy

In Study I, we showed that 3D laparoscopy is not safer or more efficient than 2D laparoscopy in cholecystectomy. Hanna et al. and Currò et al. were also unable to demonstrate the superiority of 3D laparoscopy in terms of speed or safety (95, 113). For nearly four decades, surgeons have performed procedures laparoscopically, most commonly by removing the appendix or gallbladder. It is understandable that the three-dimensional visibility is not superior to the customary two-dimensionality in such operations where, for example, suturing is not needed. However, in potentially technically demanding procedures, such as radical prostatectomy, mini gastric bypass, laparoscopic inguinal hernia repair (TAPP), and splenic hilar lymphadenectomy, the benefits of 3D technology are reflected in increased safety or efficacy (105, 109, 240, 241). We can assume that the 3D view improves the depth perception in such a way that in procedures that require these features, the benefits of this 3D technology become apparent, thereby accelerating the procedure and reducing errors, making operations safer.

Although the operation time as a primary outcome measure did not differ between groups, the surgeons were nearly 100% satisfied with the 3D laparoscopic view. This has also been the result of previous studies, albeit from two decades ago, when 3D technology was still evolving (95). The loss of binocular vision in the 2D laparoscopy can increase errors by impairing hand–eye coordination and eliminating depth perception. As described earlier, a large proportion of biliary complications is due to misperception of biliary structures. However, we were not able to show differences in complication rates between 3D or 2D LCC. Fortunately, major BDIs are rare and no lesions appeared in this study. It does not seem advisable to use a 3D laparoscope for LCC based on this study, given the cost of 3D technology, the current size of the optics (10 mm), and the limited surgical benefit.

6.2 Bile duct injury in laparoscopic cholecystectomy

Current guidelines suggest LCC for the treatment of symptomatic gallstone disease, including also most patients with complicated gallstone disease (7, 78). Chronic cholecystitis increases the possibility of BDI by causing difficult adhesions and changes the structure of the gallbladder wall. Even in non-inflamed circumstances, a BDI is possible due to the many anatomical variations. In Study II, half of the patients with a major BDI were operated on electively for symptomatic cholelithiasis. The other patients had a variety of conditions requiring urgent care. A small proportion of these injuries could have been avoided if conservative treatment had evaluated possible. Conservative treatment for acute calculous cholecystitis is indeed a treatment of choice in elderly patients deemed unfit for surgery (80). However, an even more restrained line has been highlighted in a systematic review that suggests conservative treatment even for patients with mild disease. Only a small proportion of these patients go on to develop symptomatic gallstone disease after mild inflammation, which could justify a more restrictive strategy (242).

Even without complications, up to 40% of patients who undergo surgery for typical symptoms of cholelithiasis may remain symptomatic (243, 244). Persistent pain after uncomplicated LCC increases healthcare costs and patient concerns for their own well-being (244). Van Dijk et al. conducted a multicenter trial to study whether a restricted strategy was efficient in decreasing the number of LCCs in patients with uncomplicated symptomatic gallstone disease and to reduce pain after LCC (245). Though they were not able to show a difference in pain reduction between study groups after LCC, they did find a lower number of cholecystectomies in the restrictive strategy group. In our study (I), after a short 30-day follow-up 13% of patients reported pain that affected normal life. This does not indicate an incorrect patient selection assuming the pain decreases over time in a longer follow-up. Consequently, as in our Study II, patients with a major BDI had an equal QOL compared to patients with uneventful cholecystectomy, suggesting that QOL may even after a major complication normalize in long-term follow-up (11). However, QOL is very multifactorial and the effects of a BDI on QOL is still not clear (12, 142, 246-249).

As shown in various previous studies, we noted better results after primary reconstruction of a major BDI when the reconstruction was performed by a hepatobiliary surgeon (143, 144). Comparison between hepato-biliary centers has been difficult when lacking a systematic and uniform reporting system for biliary reconstructions. In 2018, Cho's and Strasberg's group published a recommendation according to which we also reported the results of our BDI repairs (156). We found three other clinics where this reporting system was used, in Mexico and South Africa. The primary patency was achieved in 83 to 100% in these studies (152-154). In our Study II, the primary patency rate for patients operated primarily by an HB surgeon was 83% but actuarial primary patency at 36 months follow-up decreased to 80%. Since this study also included patients referred from other centers after primary treatment had failed, the overall actuarial primary patency was 58% at 1-year follow-up. It should be noted that the number or results of patients who have successfully undergone biliary reconstruction in other surgical units in Finland were not considered in this study.

Notable is that the highest primary patency rate was achieved with a robot-assisted technique (follow-up 16 months) in the Mexican highly detailed retrospective study (152). The BDI repair has traditionally been performed with an open technique, but previous results also make laparoscopic lesion repair something to be considered but only under conditions that are favorable and when the technique is controlled (152, 250). A recent meta-analysis draws a cautious conclusion in favor of delayed repair. Better results may be achieved with a favorable level of nutrition, the possibility to diagnose a simultaneous vascular injury and by reducing major inflammation (251). As seen in Figure 8, the 'actuarial primary patency' was higher in patients treated on a delayed schedule. However, it should be noted that in this dataset, a third (N=17) of patients had undergone the index treatment prior to referral. Therefore, no far-reaching conclusions can be drawn in this regard.

6.3 Examination of removed gallbladder

GBC is a very rare malignancy that has a highly variable incidence between countries. The routine HPE has been justified by a poor overall prognosis and a better prognosis in early detected GBC (13, 16, 195). On the other hand, iGBC has an even lower incidence varying between 0.17–0.5%, making HPE an unnecessary resource utilization for most of the samples (252, 253). Therefore, routine HPE can be questioned (254).

Similarly, Talreja et al. or Tayeb et al. did not find gallbladders with GBC that had a normal wall in macroscopic evaluation (255, 256). However, as the policy changes, one could question the clinician's ability to assess abnormal mucosal changes (195). It is more likely that when the routine manner is removed, the clinician's threshold for a referral will be lowered for even the slightest suspicious change, and no GBC is missed (254, 256). On the other hand, in Study III, 70% of samples were evaluated as normal by the surgeon, but only 60% by the pathologist. It is the case that the surgeon's method of reporting an abnormality (such as cholesterolosis) interpreted in such a retrospective manner may differ significantly from the pathologist's method.

Resource utilization is one of the main subjects of concern in modern medicine. The cost–benefit of HPE of the gallbladder specimen has recently been studied in several clinics in the Netherlands (17, 18, 257). Savings from selective gallbladder HPE are estimated at 1.6 million EUR, and in Finland, the same action would produce an estimated 0.5 million EUR in savings per year. Based on Study III results, we recommended selective HPE to the HUH operational units. By this, only gallbladders with an inflamed (chronically or acutely) or abnormal wall were recommended to be sent for HPE.

6.4 Management of gallbladder cancer

Study IV demonstrates that GBC's incidence has decreased in Finland but not in the same way at different ages. A more detailed analysis in Study IV suggested that GBC's age-standardized incidence in those over 50 and under 70 years of age has been declining since 2006. Changes in lifestyle and in the metropolitan population due to migration from other parts of Finland and from abroad may contribute to this relative decline. However, our study period and study population were relatively low, but an absolute reduction of 6.8 cases per million person-years was still detected.

In a SEER-database-based study, the number of GBC patients doubled after the start of the current millennium (169). The changes in the treatment of symptomatic gallstones may partly explain the difference in the number of GBCs diagnosed in studies in which the study period staddles both millennia. When MIS established its place in the treatment of gallstone disease, LCCs became the treatment of choice. It is possible that the change in the diagnostics and achievability of a cholecystectomy increased the incidence of GBC. However, if the gallbladder is removed earlier, cancer does not even develop, which would cause a decline in the incidence. In Study IV, all GBC cases were diagnosed during the era of MIS, and only a third of diagnoses were established after cholecystectomy, so other reasons for the GBC incidence decline undoubtedly exist. We could speculate on the impact of lifestyle changes, migration, or healthcare changes, but our Study IV provides no insight into these.

As earlier mentioned, surgical resection is the only possibility for curative treatment of GBC. However, the rate of resections varies greatly in different studies. In India, the resection rate was reported to be 20%, in the Netherlands 23%, in Sweden 37%, in Canada 46%, and in the United States overall 55% (169, 173, 258-260). In our study, the resection rate was 19%. Such large variability is likely to be explained by varying research settings, but differences in treatment practices between countries need to be considered. For instance, patients with a stage over T1a GBC treated only with simple cholecystectomy were included in the resected patients in the Swedish study (258).

The studies from the Netherlands and the United States did not specify the type of resection, and indeed, in the American database, the overall 5-year survival only reached 13% despite the high resection rate (169, 259). Thus, it could be suspected that all patients treated with a simple cholecystectomy alone were also included in the resections in the American study. In the Canadian study, the high resection rate resulted in a 25% 5-year OS compared to 12% in our study (260). Dixon et al. found that a more aggressive approach to GBC surgery increased 5-year survival fivefold (217).

Therefore, it may be that a more open-minded evaluation of patients with GBC should be considered. Another retrospective study revealed that even with residual disease appearance in the re-exploration, the survival benefit is apparent after complete R0 re-resection (215).

An aggressive increase of resections and neoadjuvant therapy for selected patients with GBC could result in better outcomes. The majority (63%) of patients with GBC in Study IV were at stage IIIB or beyond, possibly the one reason for the low resection rate. However, neoadjuvant therapy was not used during the study period. According to the systematic review of Hakeem et al., neoadjuvant therapy could be beneficial for 66% of patients with stage IIIA or greater (227). However, not all patients necessarily proceed to a curative-intent procedure.

After the BILCAP study, biliary tract cancer treatment recommendations included adjuvant chemotherapy with capecitabine (228, 230). Although only a small proportion of this heterogeneous population with biliary tract cancers in the BILCAP study were GBC patients, a per-protocol analysis showed a 17-month improvement in survival. Our study included patients before the BILCAP study, and only four patients received capecitabine adjuvant therapy. However, the adjuvant therapy was offered for 21 patients of 51 resected patients (simple cholecystectomy was sufficient for 4 patients). On the other hand, these patients were more often at an advanced stage and had significantly reduced 5-year survivals than other resected patients.

6.5 Strengths and limitations

Study I showed that the 3D laparoscopic system could not provide clear benefits in LCC compared to the 2D system. This is one of the largest RCT cohorts considering 3D and 2D laparoscopic surgery in cholecystectomy. However, this study included only the patients undergoing elective cholecystectomy and who were eligible for day surgery. Since the severe complications of LCC are rare, it is, however, unlikely that the research setting in more difficult conditions would make a difference in the appearance of complications in 3D or 2D surgery.

QOL after BDI is widely studied, but our Study II was able to dive deeper and compare QOL between patients who achieved patency with different levels and the controls. The study group consisted only of patients with major E-type BDI and their controls, which makes the study population more uniform but, at the same time, limits the generalizability of the results. Furthermore, the study group's limited size may restrict the result of the QOL questionnaires. Not to mention, possible selection among patients with uncomplicated cholecystectomy should also be considered. Thus, with the moderately small data (n = 53, 51% of the respondents), we cannot completely rule out the role of chance. In the long-term follow-up, the changes in patients' perception after a severe illness or complication may affect how some physical changes reflect on their experience of life quality (11, 12). The QOL may be affected by patients' shift in perspective, often referred to as reconceptualization (261). Encountering a severe disease might change a person's values and expectations differently from a condition perceived as benign.

In Study II, we used a recently standardized reporting system for BDI that can later contribute significantly to the possibilities to compare results from different centers. Our result of patency is comparable with other centers who published their results using the BDI repair with an open technique.

Studies III and IV were purely retrospective, which may limit the accuracy of the data. The larger retrospective data was in Study III, which despite of the study design, was able to demonstrate the redundancy of HPE in macroscopically normal gallbladders. Patients whose gallbladder was not sent to HPE were crosschecked from the FCR for possible developed malignancy. Thus, we were able to safely recommend that only macroscopically aberrant gallbladders should be sent for HPE.

There are no other population-based studies considering GBC in Finland other than our Study IV. The study period was as wide as possible to have enough patients and still have available medical records. However, since the GBC is (fortunately) rare, only 270 patients with GBC were available and the study might be underpowered to show changes in some variables. Although the FCR is considered to have good accuracy, under-reporting, according to a Swedish study, may occur, especially in connection with biliary tract cancers (262). Besides, especially in locally advanced GBC, reported cancer might be interpreted as originating from the bile duct, gallbladder, or liver, causing miss-reporting. However, such a change as in the Swedish study's reporting activity hardly occurred in our 12-year Study IV period, and the observed decrease in incidence is genuine.

6.6 Future prospects

Gallstone disease is undoubtedly one of the conditions that is an increasing burden to healthcare. As recommended, an operative approach to symptomatic cholecystolithiasis is currently the most common treatment. Given the potential for surgical complications and the potential for persistent symptoms after surgery, patients most likely to benefit from LCC should be identified.

This same problem of increasing gallstone disease is also associated with the possibility of increased GBC. However, this does not seem to be the case in Southern Finland. Despite this, the treatment results have not improved. This cancer with poor prognosis should be studied both nationwide and in multicenter studies to possibly identify key factors for survival in order to improve the prognosis of these patients.

7 CONCLUSIONS

With the results of the studies of the present thesis, the conclusions are as follows:

Study I
The three-dimensional laparoscopic technique does not improve the efficacy or safety of LCC in the elective day-surgery;

Study II
With the appearance of a major BDI, immediate consultation with a hepatobiliary surgeon is recommended to obtain a favorable repair result. However, even with this significant complication, the QOL is equal after uncomplicated LCC in long-term follow-up;

Study III
Macroscopically normal gallbladders that have been operated on during normal circumstances do not need a histopathologic examination to confirm the benign finding of the gallbladder wall;

Study IV
The incidence of GBC has decreased in southern Finland. Although surgical and oncological treatment in GBC patients has increased, patient prognosis has not improved during the recent decades.

8 ACKNOWLEDGMENTS

This study was carried out at the Abdominal Center of the Helsinki University Hospital and the University of Helsinki. As an author, I gratefully acknowledge the Martti I. Turunen Foundation, Mary and Georg C Ehrnrooth's foundation, Vatsatautien Tutkimussäätiö Foundation, and Helsinki University Hospital Research Fund for their financial support for this thesis.

I express my gratitude to Professor Pauli Puolakkainen for the possibility of accomplishing this thesis and accepting me as a resident surgeon to this clinic. I am also thankful for the adjunct professor, chief of gastrointestinal surgery Leena Halme for her ability to see the right moments for research leave and her encouraging attitude not only as a member of the thesis committee but also as the surgical head. As a surgical resident, I have felt it was possible to combine clinical work and research. I also thank another member of my thesis committee, Professor Johanna Laukkarinen, for her support and wise words during this process.

I was privileged to have adjunct professor Ville Sallinen as my thesis supervisor. He has carefully guided every step on this path. I am incredibly grateful to him for all the supportive and clarifying conversations that provided guidance and his tenacious attitude towards research. My second supervisor, adjunct professor Tom Scheinin, also deserves appreciation for his support and discussions. I have learned an enormous amount from my supervisors, both from research and clinical work.

My warm thanks are also directed to adjunct professor Joonas Kauppila and adjunct professor Jukka Karvonen for reviewing this thesis. Further, I am thankful to Professor Kjetil Søreide for accepting the challenge to be my opponent. An enormous amount of wisdom has surrounded my book.

I want to thank my co-authors, Jukka Harju, Heikki Mäkisalo, Arno Nordin, Panu Mentula, Jukka Sirén, Katriina Peltola, and Anna But. Further, medicine candidate, co-author Sini Takala deserves my warm gratitude for her careful work and flexible collaboration in gallbladder cancer research. This thesis would not have been possible without the help of the administrative assistant Nina Ask at the Department of Transplant and Liver surgery. I am also highly grateful for the researcher, editor, and English instuctor Alyce Whipp at the University of Helsinki.

Over the years, numerous scientific, interdisciplinary, and unscientific discussions with tremendous friends and colleagues have facilitated the research work. My dearest friend, Hanna, hopefully, we will be able to return to those long, mind-relaxing walks again. Colleagues in surgery, Anna, Mervi, Lauri, Irina, Pauliina, and other colleagues during residency, so many memorable, funny and serious moments we have spent together in Kesähippalot, Puukkojuhlat, and Davos, among others. My colleagues, dear friends Laura, Henna, and Maija, I hope I can be as supportive of you in future life stages as you have been during this challenge for me. Sunday brunches and Saturday sauna evenings will hopefully continue after the pandemic.

Last but not least, my warmest acknowledgements goes to my family. Big hugs belong to my sister, dad, and mom, whose strength is admirable. Thank you, Anne, for the intelligent conversations outside of my familiar box. To friends and family who keep life in balance when my head feels like its falling apart in the world of research. My warmest gratitude belongs to Niklas. With your support, you made this thesis possible by building my confidence and certainty over all the years we've lived together. My dear daughters Ida and Emilia, you take care of reminding me of the most important things. I am grateful for the assistance which the artistically highly gifted Ida was able to offer me in creating the book's cover image. Most of all, I could not be more delighted watching you both grow into happy, thinking, and strong people.

9 REFERENCES

1. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: Cholelithiasis and cancer. *Gut Liver*, 2012; 6:172-187.
2. Järvelin J, Martikainen V. Non-psychiatric specialized health care 2018. database reports. Accessed Dec 19, 2019. https://thl.fi/en/web/thlfi-en/statistics/statistics-by-topic/ .
3. Digital N. Surgery and the NHS in numbers. *hospital episode statistics (HES) 2013-2014*. Accessed Dec 19, 2019. https://www.rcseng.ac.uk/news-and-events/media-centre/media-background-briefings-and-statistics/surgery-and-the-nhs-in-numbers/ .
4. McDermott K, Freeman W, Elixhauser A. Overview of operating room procedures during inpatient stays in U.S. hospitals, 2014. Accessed Apr 15, 2020. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb233-Operating-Room-Procedures-United-States-2014.pdf .
5. Björnsson E, Gustafsson J, Borkman J, Kilander A. Fate of patients with obstructive jaundice. *J Hosp Med*, 2008; 3:117-123.
6. Siddique K, Ali Q, Mirza S, Jamil A, Ehsan A, Latif S, Malik AZ. Evaluation of the aetiological spectrum of obstructive jaundice. *J Ayub Med Coll Abbottabad*, 2008; 20:62-66.
7. Tazuma S, Unno M, Igarashi Y, Inui K, Uchiyama K, Kai M, Tsuyuguchi T, Maguchi H, Mori T, Yamaguchi K, Ryozawa S, Nimura Y, Fujita N, Kubota K, Shoda J, Tabata M, Mine T, Sugano K, Watanabe M, Shimosegawa T. Evidence-based clinical practice guidelines for cholelithiasis 2016. *J Gastroenterol*, 2017; 52:276-300.
8. Spaner SJ, Warnock GL. A brief history of endoscopy, laparoscopy, and laparoscopic surgery. *J Laparoendosc Adv Surg Tech A*, 1997; 7:369-373.
9. Keus F, de Jong JA, Gooszen HG, van Laarhoven CJ. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. *Cochrane Database Syst Rev*, 2006; (4):CD006231. doi:CD006231.
10. Strasberg SM, Brunt LM. Rationale and use of the critical view of safety in laparoscopic cholecystectomy. *J Am Coll Surg*, 2010; 211:132-138.
11. Mbah N, Brown RE, St Hill CR, Bower MR, Ellis SF, Scoggins CR, McMasters KM, Martin RC. Impact of post-operative complications on quality of life after pancreatectomy. *JOP*, 2012; 13:387-393.
12. Dominguez-Rosado I, Mercado MA, Kauffman C, Ramirez-del Val F, Elnecavé-Olaiz A, Zamora-Valdés D. Quality of life in bile duct injury: 1-, 5-, and 10-year outcomes after surgical repair. *J Gastrointest Surg*, 2014; 18:2089-2094.

13. Lohsiriwat V, Vongjirad A, Lohsiriwat D. Value of routine histopathologic examination of three common surgical specimens: Appendix, gallbladder, and hemorrhoid. *World J Surg*, 2009; 33:2189-2193.
14. Basak F, Hasbahceci M, Canbak T, Sisik A, Acar A, Yucel M, Bas G, Alimoglu O. Incidental findings during routine pathological evaluation of gallbladder specimens: Review of 1,747 elective laparoscopic cholecystectomy cases. *Ann R Coll Surg Engl*, 2016; 98:280-283.
15. Choi KS, Choi SB, Park P, Kim WB, Choi SY. Clinical characteristics of incidental or unsuspected gallbladder cancers diagnosed during or after cholecystectomy: A systematic review and meta-analysis. *World J Gastroenterol*, 2015; 21:1315-1323.
16. Ramraje SN, Pawar VI. Routine histopathologic examination of two common surgical specimens-appendix and gallbladder: Is it a waste of expertise and hospital resources? *Indian J Surg*, 2014; 76:127-130.
17. van Vliet JL, van Gulik TM, Verbeek PC. Is it necessary to send gallbladder specimens for routine histopathological examination after cholecystectomy? the use of macroscopic examination. *Dig Surg*, 2013; 30:472-475.
18. Corten, B. J. G. A., Leclercq WKG, Roumen RMH, van Zwam PH, Dejong CH, Slooter GD. Histological examination of the gallbladder following routine cholecystectomy? A selective analysis is justified. *Eur J Surg Oncol*, 2020; 46:572-576.
19. Acalovschi M, Lammert F. The growing global burden of gallstone disease. Accessed Jan 15, 2020. https://www.worldgastroenterology.org/publications/ .
20. Hsu CE, Lee KT, Chang CS, Chiu HC, Chao FT, Shi HY. Cholecystectomy prevalence and treatment cost: An 8-year study in taiwan. *Surg Endosc*, 2010; 24:3127-3133.
21. Rawla P, Sunkara T, Thandra KC, et al. Epidemiology of gallbladder cancer. *Clinical and experimental hepatology*, 2019;5:93-102.
22. Aerts R, Penninckx F. The burden of gallstone disease in europe. *Aliment Pharmacol Ther*, 2003; 18 Suppl 3:49-53.
23. Keplinger KM, Bloomston M. Anatomy and embryology of the biliary tract. *Surg Clin North Am*, 2014; 94:203-217.
24. Housset C, Chrétien Y, Debray D, Chignard N. Functions of the gallbladder. *Comprehensive physiology*, 2016; 6:1549-1577.
25. Stelow EB, Hong SM. Histology for pathologists: Gallbladder and extra hepatic biliary system Wolters Kluwer Health, 2019.
26. Lamah M, Karanjia ND, Dickson GH. Anatomical variations of the extrahepatic biliary tree: Review of the world literature. *Clin Anat*, 2001; 14:167-172.
27. Moosman DA, Collier FA. Prevention of traumatic injury to the bile ducts; a study of the structures of the cystohepatic angle encountered in

cholecystectomy and supraduodenal choledochostomy. *Am J Surg*, 1951; 82:132-143.
28. Andall RG, Matusz P, du Plessis M, Ward R, Tubbs RS, Loukas M. The clinical anatomy of cystic artery variations: A review of over 9800 cases. *Surg Radiol Anat*, 2016; 38:529-539.
29. Khayat MF, Al-Amoodi MS, Aldaqal SM, Sibiany A. Abnormal anatomical variations of extra-hepatic biliary tract, and their relation to biliary tract injuries and stones formation. *Gastroenterology Res*, 2014; 7:12-16.
30. Laitio M. Morphology and histochemistry of non-tumorous gallbladder epithelium. A series of 103 cases. *Pathol Res Pract*, 1980; 167:335-345.
31. Arola J. Gastroenterologia ja hepatologia: Sappirakon ja sappiteiden rakenne ja toiminta Kustannus Oy Duodecim, 2018.
32. Ash-Miles J, FRCR, Roach H, FRCR, Virjee J, FRCR, Callaway M, FRCR. More than just stones: A pictorial review of common and less common gallbladder pathologies. *Current Problems in Diagnostic Radiology*, 2008; 37:189-202.
33. Dairi S, Demeusy A, Sill AM, Patel ST, Kowdley GC, Cunningham SC. Implications of gallbladder cholesterolosis and cholesterol polyps? *J Surg Res*, 2016; 200:467-472.
34. Golse N, Lewin M, Rode A, Sebagh M, Mabrut JY. Gallbladder adenomyomatosis: Diagnosis and management. *J Visc Surg*, 2017; 154:345-353.
35. Kim JH, Jeong IH, Han JH, Kim JH, Hwang JC, Yoo BM, Kim JH, Kim MW, Kim WH. Clinical/pathological analysis of gallbladder adenomyomatosis; type and pathogenesis. *Hepatogastroenterology*, 2010; 57:420-425.
36. Lammert F, Gurusamy K, Ko CW, Miquel JF, Méndez-Sánchez N, Portincasa P, van Erpecum KJ, van Laarhoven CJ, Wang DQ. Gallstones. *Nat Rev Dis Primers*, 2016; 2:16024.
37. Lee JM, Boll DT. Disease of the gallbladder and biliary tree. In: Hodler J, Kubik-Huch RA, von Schulthess GK, eds. *Diseases of the Abdomen and Pelvis 2018-2021: Diagnostic Imaging - IDKD Book*Cham (CH): The Author(s), 2018, p. 49-56.
38. Chow WH, Johansen C, Gridley G, Mellemkjaer L, Olsen JH, Fraumeni JF,Jr. Gallstones, cholecystectomy and risk of cancers of the liver, biliary tract and pancreas. *Br J Cancer*, 1999; 79:640-644.
39. Nordenstedt H, Mattsson F, El-Serag H, Lagergren J. Gallstones and cholecystectomy in relation to risk of intra- and extrahepatic cholangiocarcinoma. *Br J Cancer*, 2012; 106:1011-1015.
40. Diehl AK. Gallstone size and the risk of gallbladder cancer. *JAMA*, 1983; 250:2323-2326.
41. Dutta U, Bush N, Kalsi D, Popli P, Kapoor VK. Epidemiology of gallbladder cancer in india. *Chin Clin Oncol*, 2019; 8:33.

42. Hyun JJ, Lee HS, Kim CD, Dong SH, Lee SO, Ryu JK, Lee DH, Jeong S, Kim TN, Lee J, Koh DH, Park ET, Lee IS, Yoo BM, Kim JH. Efficacy of magnesium trihydrate of ursodeoxycholic acid and chenodeoxycholic acid for gallstone dissolution: A prospective multicenter trial. *Gut Liver*, 2015; 9:547-555.
43. Morison R. Gallstones. *Edinburgh M.J.*, 1905; 18.
44. Foley EF. Cholecystitis and cholelithiasis. *Med Clin North Am*, 1953; 1:145-154.
45. Byrne JJ. Acute cholecystitis. *The American Journal of Surgery*, 1959;97:156-172.
46. Wang AJ, Wang TE, Lin CC, Lin SC, Shih SC. Clinical predictors of severe gallbladder complications in acute acalculous cholecystitis. *World J Gastroenterol*, 2003; 9:2821-2823.
47. Chawla A, Bosco JI, Lim TC, Srinivasan S, Teh HS, Shenoy JN. Imaging of acute cholecystitis and cholecystitis-associated complications in the emergency setting. *Singapore Med J*, 2015; 56:438-43; quiz 444.
48. Garcia-Sancho Tellez L, Rodriguez-Montes JA, Fernandez de Lis S, Garcia-Sancho Martin L. Acute emphysematous cholecystitis. report of twenty cases. *Hepatogastroenterology*, 1999; 46:2144-2148.
49. Yoshimatsu Y, Takai T, Abe Y, Nakagawa T. The presence of venous gas does not affect the prognosis in emphysematous cystitis. *Intern Med*, 2017; 56:637-640.
50. Roa I, de Aretxabala X, Araya JC, Roa J. Preneoplastic lesions in gallbladder cancer. *J Surg Oncol*, 2006; 93:615-623.
51. Guzman-Valdivia G. Xanthogranulomatous cholecystitis: 15 years' experience. *World J Surg*, 2004; 28:254-257.
52. Nacif LS, Hessheimer AJ, Rodriguez Gomez S, Montironi C, Fondevila C. Infiltrative xanthogranulomatous cholecystitis mimicking aggressive gallbladder carcinoma: A diagnostic and therapeutic dilemma. *World J Gastroenterol*, 2017; 23:8671-8678.
53. Uchiyama K, Ozawa S, Ueno M, Hayami S, Hirono S, Ina S, Kawai M, Tani M, Yamaue H. Xanthogranulomatous cholecystitis: The use of preoperative CT findings to differentiate it from gallbladder carcinoma. *J Hepatobiliary Pancreat Surg*, 2009; 16:333-338.
54. Pandey A, Kumar D, Masood S, Chauhan S, Kumar S. Is final histopathological examination the only diagnostic criteria for xanthogranulomatous cholecystitis? *Niger J Surg*, 2019; 25:177-182.
55. Cairns V, Neal CP, Dennison AR, Garcea G. Risk and cost-effectiveness of surveillance followed by cholecystectomy for gallbladder polyps. *Arch Surg*, 2012; 147:1078-1083.
56. Martin E, Gill R, Debru E. Diagnostic accuracy of transabdominal ultrasonography for gallbladder polyps: Systematic review. *Can J Surg*, 2018; 61:200-207.

57. Metman MJH, Olthof PB, van der Wal, J. B. C., van Gulik TM, Roos D, Dekker JWT. Clinical relevance of gallbladder polyps; is cholecystectomy always necessary? *HPB (Oxford)*, 2019.
58. Terzioglu SG, Kilic MO, Sapmaz A, Karaca AS. Predictive factors of neoplastic gallbladder polyps: Outcomes of 278 patients. *Turk J Gastroenterol*, 2017; 28:202-206.
59. McCain RS, Diamond A, Jones C, Coleman HG. Current practices and future prospects for the management of gallbladder polyps: A topical review. *World J Gastroenterol*, 2018; 24:2844-2852.
60. Lee SR, Kim HO, Shin JH. Reasonable cholecystectomy of gallbladder polyp - 10 years of experience. *Asian J Surg*, 2019; 42:332-337.
61. Horsley-Silva JL, Rodriguez EA, Franco DL, Lindor KD. An update on cancer risk and surveillance in primary sclerosing cholangitis. *Liver International*, 2017; 37:1103-1109.
62. Jones MW, Deppen JG. Open cholecystectomy. In: *StatPearls*Treasure Island (FL): StatPearls Publishing LLC, 2019.
63. To KB, Cherry-Bukowiec JR, Englesbe MJ, Terjimanian MN, Shijie C, Campbell DA,Jr, Napolitano LM. Emergent versus elective cholecystectomy: Conversion rates and outcomes. *Surg Infect (Larchmt)*, 2013; 14:512-519.
64. Agrusa A, Romano G, Frazzetta G, Chianetta D, Sorce V, Di Buono G, Gulotta G. Role and outcomes of laparoscopic cholecystectomy in the elderly. *Int J Surg*, 2014; 12 Suppl 2:S37-S39.
65. Zaidi MY, Maithel SK. Updates on gallbladder cancer management. *Curr Oncol Rep*, 2018; 20:21-3.
66. Roslyn JJ, Binns GS, Hughes EF, Saunders-Kirkwood K, Zinner MJ, Cates JA. Open cholecystectomy. A contemporary analysis of 42,474 patients. *Ann Surg*, 1993; 218:129-137.
67. Sandblom G, Videhult P, Crona Guterstam Y, Svenner A, Sadr-Azodi O. Mortality after a cholecystectomy: A population-based study. *HPB (Oxford)*, 2015; 17:239-243.
68. Licciardello A, Arena M, Nicosia A, Di Stefano B, Cali G, Arena G, Minutolo V. Preoperative risk factors for conversion from laparoscopic to open cholecystectomy. *Eur Rev Med Pharmacol Sci*, 2014; 18:60-68.
69. Ballal M, David G, Willmott S, Corless DJ, Deakin M, Slavin JP. Conversion after laparoscopic cholecystectomy in england. *Surg Endosc*, 2009; 23:2338-2344.
70. Philip Rothman J, Burcharth J, Pommergaard HC, Viereck S, Rosenberg J. Preoperative risk factors for conversion of laparoscopic cholecystectomy to open surgery - A systematic review and meta-analysis of observational studies. *Dig Surg*, 2016; 33:414-423.
71. Sakpal SV, Bindra SS, Chamberlain RS. Laparoscopic cholecystectomy conversion rates two decades later. *JSLS*, 2010; 14:476-483.

72. Tang CL, Schlich T. Surgical innovation and the multiple meanings of randomized controlled trials: The first RCT on minimally invasive cholecystectomy (1980-2000). *J Hist Med Allied Sci*, 2017; 72:117-141.
73. Muhe E. Laparoscopic cholecystectomy--late results. *Langenbecks Arch Chir Suppl Kongressbd*, 1991:416-423.
74. Litynski GS. Erich muhe and the rejection of laparoscopic cholecystectomy (1985): A surgeon ahead of his time. *JSLS*, 1998; 2:341-346.
75. Singh M, Prasad N. The anatomy of rouviere's sulcus as seen during laparoscopic cholecystectomy: A proposed classification. *J Minim Access Surg*, 2017; 13:89-95.
76. van de Graaf, F. W., Zaimi I, Stassen LPS, Lange JF. Safe laparoscopic cholecystectomy: A systematic review of bile duct injury prevention. *Int J Surg*, 2018; 60:164-172.
77. Hugh TB, Kelly MD, Mekisic A. Rouviere's sulcus: A useful landmark in laparoscopic cholecystectomy. *Br J Surg*, 1997; 84:1253-1254.
78. Wakabayashi G, Iwashita Y, Hibi T, Takada T, Strasberg SM, Asbun HJ, Endo I, Umezawa A, Asai K, Suzuki K, Mori Y, Okamoto K, Pitt HA, Han HS, Hwang TL, Yoon YS, Yoon DS, Choi IS, Huang WS, Gimenez ME, Garden OJ, Gouma DJ, Belli G, Dervenis C, Jagannath P, Chan ACW, Lau WY, Liu KH, Su CH, Misawa T, Nakamura M, Horiguchi A, Tagaya N, Fujioka S, Higuchi R, Shikata S, Noguchi Y, Ukai T, Yokoe M, Cherqui D, Honda G, Sugioka A, de Santibanes E, Supe AN, Tokumura H, Kimura T, Yoshida M, Mayumi T, Kitano S, Inomata M, Hirata K, Sumiyama Y, Inui K, Yamamoto M. Tokyo guidelines 2018: Surgical management of acute cholecystitis: Safe steps in laparoscopic cholecystectomy for acute cholecystitis (with videos). *J Hepatobiliary Pancreat Sci*, 2018; 25:73-86.
79. Strasberg SM, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. *J Am Coll Surg*, 1995; 180:101-125.
80. Mayumi T, Okamoto K, Takada T, Strasberg SM, Solomkin JS, Schlossberg D, Pitt HA, Yoshida M, Gomi H, Miura F, Garden OJ, Kiriyama S, Yokoe M, Endo I, Asbun HJ, Iwashita Y, Hibi T, Umezawa A, Suzuki K, Itoi T, Hata J, Han HS, Hwang TL, Dervenis C, Asai K, Mori Y, Huang WS, Belli G, Mukai S, Jagannath P, Cherqui D, Kozaka K, Baron TH, de Santibanes E, Higuchi R, Wada K, Gouma DJ, Deziel DJ, Liau KH, Wakabayashi G, Padbury R, Jonas E, Supe AN, Singh H, Gabata T, Chan ACW, Lau WY, Fan ST, Chen MF, Ker CG, Yoon YS, Choi IS, Kim MH, Yoon DS, Kitano S, Inomata M, Hirata K, Inui K, Sumiyama Y, Yamamoto M. Tokyo guidelines 2018: Management bundles for acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci*, 2018; 25:96-100.

81. Strasberg SM, Gouma DJ. 'Extreme' vasculobiliary injuries: Association with fundus-down cholecystectomy in severely inflamed gallbladders. *HPB (Oxford)*, 2012; 14:1-8.
82. Törnqvist B, Strömberg C, Akre O, Enochsson L, Nilsson M. Selective intraoperative cholangiography and risk of bile duct injury during cholecystectomy. *Br J Surg*, 2015; 102:952-958.
83. Conrad C, Wakabayashi G, Asbun HJ, Dallemagne B, Demartines N, Diana M, Fuks D, Gimenez ME, Goumard C, Kaneko H, Memeo R, Resende A, Scatton O, Schneck AS, Soubrane O, Tanabe M, van den Bos J, Weiss H, Yamamoto M, Marescaux J, Pessaux P. IRCAD recommendation on safe laparoscopic cholecystectomy. *J Hepatobiliary Pancreat Sci*, 2017; 24:603-615.
84. Buess G, Becerra-Garcia F, Misra MC. Instruments for transluminal laparoscopic surgery or "NOTES". *Minim Invasive Ther Allied Technol*, 2008; 17:331-335.
85. Rao PP, Bhagwat SM, Rane A, Rao PP. The feasibility of single port laparoscopic cholecystectomy: A pilot study of 20 cases. *HPB (Oxford)*, 2008; 10:336-340.
86. Leung KF, Lee KW, Cheung TY, Leung LC, Lau KW. Laparoscopic cholecystectomy: Two-port technique. *Endoscopy*, 1996; 28:505-507.
87. Bartnicka J, Zietkiewicz AA, Kowalski GJ. Advantages and disadvantages of 1-incision, 2-incision, 3-incision, and 4-incision laparoscopic cholecystectomy: A workflow comparison study. *Surg Laparosc Endosc Percutan Tech*, 2016; 26:313-318.
88. Sallinen V, Mentula P, Scheinin T. Laparoskooppinen kolekystektomia. *Duodecim*, 2019; 6:565-573.
89. Peters JH, Ellison EC, Innes JT, Liss JL, Nichols KE, Lomano JM, Roby SR, Front ME, Carey LC. Safety and efficacy of laparoscopic cholecystectomy. A prospective analysis of 100 initial patients. *Ann Surg*, 1991; 213:3-12.
90. Zollinger RM, Ellison EC. Zollinger's atlas of surgical operations . United States: McGraw-Hill Companies, Inc, 2011.
91. Wheatstone C. Contributions to the physiology of vision. part the first. on some remarkable, and hitherto unobserved, phenomena of binocular vision. *Philosophical Transactions of the Royal Society London*, 1838; 128:371-394.
92. Satava RM. 3-D vision technology applied to advanced minimally invasive surgery systems. *Surg Endosc*, 1993; 7:429-431.
93. Bogdanova R, Boulanger P, Zheng B. Depth perception of surgeons in minimally invasive surgery. *Surg Innov*, 2016; 23:515–524.
94. Sinha RY, Raje SR, Rao GA. Three-dimensional laparoscopy: Principles and practice. *J Minim Access Surg*, 2017; 13:165-169.
95. Hanna GB, Shimi SM, Cuschieri A. Randomised study of influence of two-dimensional versus three-dimensional imaging on performance of laparoscopic cholecystectomy. *Lancet*, 1998; 351:248–251.

96. Patankar SB, Padasalagi GR. Three-dimensional versus two-dimensional laparoscopy in urology: A randomized study. *Indian J Urol*, 2017; 33:226–229.
97. Sörensen SMD, Konge L, Bjerrum F. 3D vision accelerates laparoscopic proficiency and skills are transferable to 2D conditions: A randomized trial. *Am J Surg*, 2017; 214:63–68.
98. Spille J, Wenners A, von Hehn U, Maass N, Pecks U, Mettler L, Alkatout I. 2D versus 3D in laparoscopic surgery by beginners and experts: A randomized controlled trial on a pelvitrainer in objectively graded surgical steps. *J Surg Educ*, 2017; 74:867–877.
99. Buia A, Stockhausen F, Filmann N, Hanisch E. 3D vs. 2D imaging in laparoscopic surgery-an advantage? results of standardised black box training in laparoscopic surgery. *Langenbecks Arch Surg*, 2017; 402:167–171.
100. Poudel S, Kurashima Y, Watanabe Y, Ebihara Y, Tamoto E, Murakami S, Nakamura T, Tsuchikawa T, Okamura K, Shichinohe T, Hirano S. Impact of 3D in the training of basic laparoscopic skills and its transferability to 2D environment: A prospective randomized controlled trial. *Surg Endosc Interv Tech*, 2017; 31:1111–1118.
101. Sakata S, Grove PM, Hill A, Watson MO, Stevenson ARL. Impact of simulated three-dimensional perception on precision of depth judgements, technical performance and perceived workload in laparoscopy. *Br J Surg*, 2017; 104:1097–1106.
102. Matsunaga R, Nishizawa Y, Saito N, Kobayashi A, Ohdaira T, Ito M. Quantitative evaluation of 3D imaging in laparoscopic surgery. *Surg Today*, 2017; 47:440–444.
103. Fergo C, Burcharth J, Pommergaard HC, Rosenberg J. Age is highly associated with stereo blindness among surgeons: A cross-sectional study. *Surg Endosc*, 2016; 30:4889-4894.
104. Bloch E, Uddin N, Gannon L, Rantell K, Jain S. The effects of absence of stereopsis on performance of a simulated surgical task in two-dimensional and three-dimensional viewing conditions. *Br J Ophthalmol*, 2015; 99:240–245.
105. Curro G, La Malfa G, Caizzone A, Rampulla V, Navarra G. Three-dimensional (3D) versus two-dimensional (2D) laparoscopic bariatric surgery: A single-surgeon prospective randomized comparative study. *Obes Surg*, 2015; 25:2120-2124.
106. Leon P, Rivellini R, Giudici F, Sciuto A, Pirozzi F, Corcione F. 3D vision provides shorter operative time and more accurate intraoperative surgical performance in laparoscopic hiatal hernia repair compared with 2D vision. *Surg Innov*, 2017; 24:155–161.
107. Lu J, Zheng CH, Zheng HL, Li P, Xie JW, Wang JB, Lin JX, Chen QY, Cao LL, Lin M, Tu RH, Huang CM. Randomized, controlled trial comparing clinical outcomes of 3D and 2D laparoscopic surgery for gastric cancer: An interim report. *Surg Endosc*, 2017; 31:2939-2945.

108. Arezzo A, Vettoretto N, Francis NK, Bonino MA, Curtis NJ, Amparore D, Arolfo S, Barberio M, Boni L, Brodie R, Bouvy N, Cassinotti E, Carus T, Checcucci E, Custers P, Diana M, Jansen M, Jaspers J, Marom G, Momose K, Müller-Stich BP, Nakajima K, Nickel F, Perretta S, Porpiglia F, Sánchez-Margallo F, Sánchez-Margallo JA, Schijven M, Silecchia G, Passera R, Mintz Y. The use of 3D laparoscopic imaging systems in surgery: EAES consensus development conference 2018. *Surg Endosc*, 2019; 33:3251-3274.
109. Liu J, Zhou H, Qin H, Ru H, Huang J, Liang S, Mo X, Tang W. Comparative study of clinical efficacy using three-dimensional and two-dimensional laparoscopies in the treatment of distal gastric cancer. *Onco Targets Ther*, 2018; 11:301-306.
110. Curtis NJ, Conti JA, Dalton R, Rockall TA, Allison AS, Ockrim JB, Jourdan IC, Torkington J, Phillips S, Allison J, Hanna GB, Francis NK. 2D versus 3D laparoscopic total mesorectal excision: A developmental multicentre randomised controlled trial. *Surg Endosc*, 2019.
111. Bilgen K, Ustun M, Karakahya M, Isik S, Sengul S, Cetinkunar S, Kucukpinar TH. Comparison of 3D imaging and 2D imaging for performance time of laparoscopic cholecystectomy. *Surg Laparosc Endosc Percutan Tech*, 2013; 23:180–183.
112. Sahu D, Mathew MJ, Reddy PK. 3D laparoscopy - help or hype; initial experience of A tertiary health centre. *J Clin Diagn Res*, 2014; 8:NC01-3.
113. Curro G, La Malfa G, Lazzara S, Caizzone A, Fortugno A, Navarra G. Three-dimensional versus two-dimensional laparoscopic cholecystectomy: Is surgeon experience relevant? *J Laparoendosc Adv Surg Tech A*, 2015; 25:566–570.
114. Zeng N, Fang C, Yang J, Xiang N, Zhu W, Liu J, Chen Q, Liang H, Huang W. Application of three-dimensional laparoscopic cholecystectomy for complicated gallstone disease. *Nan Fang Yi Ke Da Xue Xue Bao*, 2016; 36:145-147.
115. Schwab KE, Curtis NJ, Whyte MB, Smith RV, Rockall TA, Ballard K, Jourdan IC. 3D laparoscopy does not reduce operative duration or errors in day-case laparoscopic cholecystectomy: A randomised controlled trial. *Surg Endosc*, 2020; 34:1745-1753.
116. AbdelRafee A, El-Shobari M, Askar W, Sultan AM, El Nakeeb A. Long-term follow-up of 120 patients after hepaticojejunostomy for treatment of post-cholecystectomy bile duct injuries: A retrospective cohort study. *International Journal of Surgery*, 2015; 18:205-210.
117. Hariharan D, Psaltis E, Scholefield JH, Lobo DN. Quality of life and medico-legal implications following iatrogenic bile duct injuries. *World J Surg*, 2017; 41:90-99.
118. Nuzzo G, Giuliante F, Giovannini I, Ardito F, D'Acapito F, Vellone M, Murazio M, Capelli G. Bile duct injury during laparoscopic

cholecystectomy: Results of an italian national survey on 56 591 cholecystectomies. *Arch Surg*, 2005; 140:986-992.
119. Karvonen J, Gullichsen R, Laine S, Salminen P, Grönroos J,M. Bile duct injuries during laparoscopic cholecystectomy: Primary and long-term results from a single institution. *Surg Endosc*, 2007; 21:1069-1073.
120. Tantia O, Jain M, Khanna S, Sen B. Iatrogenic biliary injury: 13,305 cholecystectomies experienced by a single surgical team over more than 13 years. *Surg Endosc*, 2008; 22:1077-1086.
121. Rainio M, Lindstrom O, Udd M, Haapamaki C, Nordin A, Kylanpaa L. Endoscopic therapy of biliary injury after cholecystectomy. *Dig Dis Sci*, 2018; 63:474-480.
122. Pottakkat B, Vijayahari R, Prakash A, Singh RK, Behari A, Kumar A, Kapoor VK, Saxena R. Incidence, pattern and management of bile duct injuries during cholecystectomy: Experience from a single center. *Dig Surg*, 2010; 27:375-379.
123. Gupta V, Gupta V, Joshi P, Kumar S, Kulkarni R, Chopra N, Pavankumar G, Chandra A. Management of post cholecystectomy vascular injuries. *Surgeon*, 2018.
124. Way LW, Stewart L, Gantert W, Liu K, Lee CM, Whang K, Hunter JG. Causes and prevention of laparoscopic bile duct injuries: Analysis of 252 cases from a human factors and cognitive psychology perspective. *Ann Surg*, 2003; 237:460-469.
125. Chapman WC, Abecassis M, Jarnagin W, Mulvihill S, Strasberg SM. Bile duct injuries 12 years after the introduction of laparoscopic cholecystectomy. *J Gastrointest Surg*, 2003; 7:412-416.
126. Bergman JJ, van den Brink, G. R., Rauws EA, de Wit L, Obertop H, Huibregtse K, Tytgat GN, Gouma DJ. Treatment of bile duct lesions after laparoscopic cholecystectomy. *Gut*, 1996; 38:141-147.
127. Bismuth H, Majno PE. Biliary strictures: Classification based on the principles of surgical treatment. *World J Surg*, 2001; 25:1241-1244.
128. Stewart L, Robinson TN, Lee CM, Liu K, Whang K, Way LW. Right hepatic artery injury associated with laparoscopic bile duct injury: Incidence, mechanism, and consequences. *J Gastrointest Surg*, 2004; 8:523-1.
129. Chun K. Recent classifications of the common bile duct injury. *Korean J Hepatobiliary Pancreat Surg*, 2014; 18:69-72.
130. Fingerhut A, Dziri C, Garden OJ, Gouma D, Millat B, Neugebauer E, Paganini A, Targarona E. ATOM, the all-inclusive, nominal EAES classification of bile duct injuries during cholecystectomy. *Surg Endosc*, 2013; 27:4608-4619.
131. Ball CG, MacLean AR, Kirkpatrick AW, Bathe OF, Sutherland F, Debru E, Dixon E. Hepatic vein injury during laparoscopic cholecystectomy: The unappreciated proximity of the middle hepatic vein to the gallbladder bed. *J Gastrointest Surg*, 2006; 10:1151-1155.

132. Grimes N, Mark D, McKie L, Scoffield J, Kirk G, Taylor M, Diamond T. Anomalous biliary and vascular anatomy-potential pitfalls during cholecystectomy. *Clin Anat*, 2017; 30:1103-1106.
133. Rosenmüller M, Haapamäki M,M., Nordin P, Stenlund H, Nilsson E. Cholecystectomy in sweden 2000-2003: A nationwide study on procedures, patient characteristics, and mortality. *BMC gastroenterology*, 2007; 7:35.
134. McMahon AJ, Fischbacher CM, Frame SH, MacLeod MC. Impact of laparoscopic cholecystectomy: A population-based study. *Lancet*, 2000; 356:1632-1637.
135. Zacks SL, Sandler RS, Rutledge R, Brown RS,Jr. A population-based cohort study comparing laparoscopic cholecystectomy and open cholecystectomy. *Am J Gastroenterol*, 2002; 97:334-340.
136. Coccolini F, Catena F, Pisano M, Gheza F, Fagiuoli S, Di Saverio S, Leandro G, Montori G, Ceresoli M, Corbella D, Sartelli M, Sugrue M, Ansaloni L. Open versus laparoscopic cholecystectomy in acute cholecystitis. systematic review and meta-analysis. *Int J Surg*, 2015; 18:196-204.
137. Pottakkat B, Vijayahari R, Prakash A, Singh RK, Behari A, Kumar A, Kapoor VK, Saxena R. Incidence, pattern and management of bile duct injuries during cholecystectomy: Experience from a single center. *Dig Surg*, 2010; 27:375-379.
138. de Reuver PR, Rauws EA, Bruno MJ, Lameris JS, Busch OR, van Gulik TM, Gouma DJ. Survival in bile duct injury patients after laparoscopic cholecystectomy: A multidisciplinary approach of gastroenterologists, radiologists, and surgeons. *Surgery*, 2007; 142:1-9.
139. Rystedt JM, Montgomery AK. Quality-of-life after bile duct injury: Intraoperative detection is crucial. A national case-control study. *HPB (Oxford)*, 2016; 18:1010-1016.
140. A European-African HepatoPancreatoBiliary Association (E-AHPBA) Research Collaborative Study management group, Other members of the European-African HepatoPancreatoBiliary Association Research Collaborative. Post cholecystectomy bile duct injury: Early, intermediate or late repair with hepaticojejunostomy - an E-AHPBA multi-center study. *HPB (Oxford)*, 2019.
141. Booij KAC, Coelen RJ, de Reuver PR, Besselink MG, van Delden OM, Rauws EA, Busch OR, van Gulik TM, Gouma DJ. Long-term follow-up and risk factors for strictures after hepaticojejunostomy for bile duct injury: An analysis of surgical and percutaneous treatment in a tertiary center. *Surgery*, 2018; 163:1121-1127.
142. Booij KA, Reuver PR, Dieren Sv, Delden OMv, Rauws EA, Busch OR, Gulik TMv, Gouma DJ. Long-term impact of bile duct injury on morbidity, mortality, quality of life, and work related limitations. *Annals of Surgery*, 2018; 268:143-150.

143. Stewart L, Way LW. Laparoscopic bile duct injuries: Timing of surgical repair does not influence success rate. A multivariate analysis of factors influencing surgical outcomes. *HPB (Oxford)*, 2009; 11:516-522.
144. Perera MT, Silva MA, Hegab B, Muralidharan V, Bramhall SR, Mayer AD, Buckels JA, Mirza DF. Specialist early and immediate repair of post-laparoscopic cholecystectomy bile duct injuries is associated with an improved long-term outcome. *Ann Surg*, 2011; 253:553-560.
145. Pekolj J, Alvarez FA, Palavecino M, Sanchez Claria R, Mazza O, de Santibanes E. Intraoperative management and repair of bile duct injuries sustained during 10,123 laparoscopic cholecystectomies in a high-volume referral center. *J Am Coll Surg*, 2013; 216:894-901.
146. Feng X, Dong J. Surgical management for bile duct injury. *Biosci Trends*, 2017; 11:399-405.
147. Hepp J, Couinaud C. Approach to and use of the left hepatic duct in reparation of the common bile duct. *Presse Med*, 1956; 64:947-948.
148. Hepp J. Hepaticojejunostomy using the left biliary trunk for iatrogenic biliary lesions: The french connection. *World J Surg*, 1985; 9:507-511.
149. Winslow ER, Fialkowski EA, Linehan DC, Hawkins WG, Picus DD, Strasberg SM. "Sideways": Results of repair of biliary injuries using a policy of side-to-side hepatico-jejunostomy. *Ann Surg*, 2009; 249:426-434.
150. Huang CS, Lein HH, Tai FC, Wu CH. Long-term results of major bile duct injury associated with laparoscopic cholecystectomy. *Surg Endosc*, 2003; 17:1362-1367.
151. Mercado MA, Chan C, Orozco H, Villalta JM, Barajas-Olivas A, Erana J, Dominguez I. Long-term evaluation of biliary reconstruction after partial resection of segments IV and V in iatrogenic injuries. *J Gastrointest Surg*, 2006; 10:77-82.
152. Cuendis-Velazquez A, Trejo-Avila M, Bada-Yllan O, Cardenas-Lailson E, Morales-Chavez C, Fernandez-Alvarez L, Romero-Loera S, Rojano-Rodriguez M, Valenzuela-Salazar C, Moreno-Portillo M. A new era of bile duct repair: Robotic-assisted versus laparoscopic hepaticojejunostomy. *J Gastrointest Surg*, 2019; 23:451-459.
153. Rueda-De-Leon A, Dominguez-Rosado I, Contreras AG, Vilatoba M, Mercado MA. Disparities in bile duct injury care. *Surg Endosc*, 2019.
154. Lindemann J, Krige JEJ, Kotze U, Jonas E. Factors leading to loss of patency after biliary reconstruction of major laparoscopic cholecystectomy bile duct injuries: An observational study with long-term outcomes. *HPB (Oxford)*, 2020.
155. Martínez-Mier G, Moreno-Ley PI, Esquivel-Torres S, Gonzalez-Grajeda JL, Mendez-Rico D. Differences in post-cholecystectomy bile duct injury care: A comparative analysis of 2 different health-care public institutions in a low- and middle-income country: Southeast mexico. *Dig Surg*, 2020:1-8.

156. Cho JY, Baron TH, Carr-Locke DL, Chapman WC, Costamagna G, de Santibanes E, Dominguez Rosado I, Garden OJ, Gouma D, Lillemoe KD, Angel Mercado M, Mullady DK, Padbury R, Picus D, Pitt HA, Sherman S, Shlansky-Goldberg R, Tornqvist B, Strasberg SM. Proposed standards for reporting outcomes of treating biliary injuries. *HPB (Oxford)*, 2018; 20:370-378.
157. Kozuka S, Tsubone N, Yasui A, Hachisuka K. Relation of adenoma to carcinoma in the gallbladder. *Cancer*, 1982; 50:2226-2234.
158. Albores-Saavedra J, Chable-Montero F, Gonzalez-Romo MA, Ramirez Jaramillo M, Henson DE. Adenomas of the gallbladder. morphologic features, expression of gastric and intestinal mucins, and incidence of high-grade dysplasia/carcinoma in situ and invasive carcinoma. *Hum Pathol*, 2012; 43:1506-1513.
159. Hughes NR, Bhathal PS. Adenocarcinoma of gallbladder: An immunohistochemical profile and comparison with cholangiocarcinoma. *J Clin Pathol*, 2013; 66:212-217.
160. Roa I, Araya JC, Villaseca M, De Aretxabala X, Riedemann P, Endoh K, Roa J. Preneoplastic lesions and gallbladder cancer: An estimate of the period required for progression. *Gastroenterology*, 1996; 111:232-236.
161. Spaziani E, Di Filippo A, Picchio M, Lucarelli P, Pattaro G, De Angelis F, Francioni P, Vestri A, Petrozza V, Narilli F, Drudi FM, Stagnitti F. Prevalence of adenoma of gallbladder, ultrasonographic and histological assessment in a retrospective series of 450 cholecystectomy. *Ann Ital Chir*, 2013; 84:159-4.
162. World Health Organization. Cancer WIAfRo. global cancer observatory: Cancer today. 2018. . Accessed 26th June, 2019. http://gco.iarc.fr/ .
163. Medina E, Kaempffer AM. Cancer mortality in chile: Epidemiological considerations. *Rev Med Chil*, 2001; 129:1195-1202.
164. de Aretxabala X, Roa I, Berrios M, Hepp J, Gallardo J, Cordova A, Roa JC, Leon J, Maluenda F. Chemoradiotherapy in gallbladder cancer. *J Surg Oncol*, 2006; 93:699-704.
165. Pitkäniemi J, Malila N, Virtanen A, et al. Syöpä 2018. tilastoraportti suomen syöpätilanteesta.
166. Shindoh J, de Aretxabala X, Aloia TA, Roa JC, Roa I, Zimmitti G, Javle M, Conrad C, Maru DM, Aoki T, Vigano L, Ribero D, Kokudo N, Capussotti L, Vauthey JN. Tumor location is a strong predictor of tumor progression and survival in T2 gallbladder cancer: An international multicenter study. *Ann Surg*, 2015; 261:733-739.
167. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The eighth edition AJCC cancer staging manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA: a cancer journal for clinicians*, 2017; 67:93-99.

168. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK et al. American joint committee on cancer (AJCC). cancer staging manual New York: Springer, 2017.
169. Lau CSM, Zywot A, Mahendraraj K, Chamberlain RS. Gallbladder carcinoma in the united states: A population based clinical outcomes study involving 22,343 patients from the surveillance, epidemiology, and end result database (1973-2013). *HPB Surg*, 2017; 2017:1532835.
170. Torre LA, Siegel RL, Islami F, Bray F, Jemal A. Worldwide burden of and trends in mortality from gallbladder and other biliary tract cancers. *Clin Gastroenterol Hepatol*, 2018; 16:427-437.
171. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: Geographical distribution and risk factors. *Int J Cancer*, 2006; 118:1591-1602.
172. Hundal R, Shaffer EA. Gallbladder cancer: Epidemiology and outcome. *Clin Epidemiol*, 2014; 6:99-109.
173. Singh SK, Talwar R, Kannan N, Tyagi AK, Jaiswal P, Kumar A. Patterns of presentation, treatment, and survival rates of gallbladder cancer: A prospective study at a tertiary care centre. *J Gastrointest Cancer*, 2018; 49:268-274.
174. D'Angelica M, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol*, 2009; 16:806-816.
175. Lowenfels AB, Lindström CG, Conway MJ, Hastings PR. Gallstones and risk of gallbladder cancer. *J Natl Cancer Inst*, 1985; 75:77-80.
176. Aldouri AQ, Malik HZ, Waytt J, Khan S, Ranganathan K, Kummaraganti S, Hamilton W, Dexter S, Menon K, Lodge JP, Prasad KR, Toogood GJ. The risk of gallbladder cancer from polyps in a large multiethnic series. *Eur J Surg Oncol*, 2009; 35:48-51.
177. Elmasry M, Lindop D, Dunne DFJ, et al. The risk of malignancy in ultrasound detected gallbladder polyps: A systematic review. *International Journal of Surgery*, 2016;33:28-35.
178. Henley SJ, Weir HK, Jim MA, Watson M, Richardson LC. Gallbladder cancer incidence and mortality, united states 1999-2011. *Cancer Epidemiol Biomarkers Prev*, 2015; 24:1319-1326.
179. Aune D, Vatten LJ, Boffetta P. Tobacco smoking and the risk of gallbladder disease. *Eur J Epidemiol*, 2016; 31:643-653.
180. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, Scotti L, Jenab M, Turati F, Pasquali E, Pelucchi C, Galeone C, Bellocco R, Negri E, Corrao G, Boffetta P, Vecchia C. Alcohol consumption and site-specific cancer risk: A comprehensive dose-response meta-analysis. *Br J Cancer*, 2014; 112:580-593.
181. Singh BP, Khan WF, Rathore YS, Pol MM. Incidental carcinoma gallbladder: Incidence, risk factors, and factors affecting survival-5-year experience from a tertiary care institute. *J Gastrointest Cancer*, 2019.

182. Shukla VK, Prakash A, Tripathi BD, Reddy DC, Singh S. Biliary heavy metal concentrations in carcinoma of the gall bladder: Case-control study. *BMJ*, 1998; 317:1288-1289.
183. Wernberg JA, Lucarelli DD. Gallbladder cancer. *Surg Clin North Am*, 2014; 94:343-360.
184. Schnelldorfer T. Porcelain gallbladder: A benign process or concern for malignancy? *J Gastrointest Surg*, 2013; 17:1161-1168.
185. Khan ZS, Livingston EH, Huerta S. Reassessing the need for prophylactic surgery in patients with porcelain gallbladder: Case series and systematic review of the literature. *Arch Surg*, 2011; 146:1143-1147.
186. Shih SP, Schulick RD, Cameron JL, Lillemoe KD, Pitt HA, Choti MA, Campbell KA, Yeo CJ, Talamini MA. Gallbladder cancer: The role of laparoscopy and radical resection. *Ann Surg*, 2007; 245:893-901.
187. Charfi S, Gouiaa N, Mnif H, Chtourou L, Tahri N, Abid B, Mzali R, Boudawara TS. Histopathological findings in cholecystectomies specimens: A single institution study of 20 584 cases. *Hepatobiliary Pancreat Dis Int*, 2018; 17:345-348.
188. Akyurek N, Irkorucu O, Salman B, Erdem O, Sare M, Tatlicioglu E. Unexpected gallbladder cancer during laparoscopic cholecystectomy. *J Hepatobiliary Pancreat Surg*, 2004; 11:357-361.
189. Hickman L, Contreras C. Gallbladder cancer: Diagnosis, surgical management, and adjuvant therapies. *Surg Clin North Am*, 2019; 99:337-355.
190. Li B, Xu XX, Du Y, Yang HF, Li Y, Zhang Q, Xiao DM, Huang YY, Meng J, Wang WX. Computed tomography for assessing resectability of gallbladder carcinoma: A systematic review and meta-analysis. *Clin Imaging*, 2013; 37:327-333.
191. Koshenkov VP, Koru-Sengul T, Franceschi D, Dipasco PJ, Rodgers SE. Predictors of incidental gallbladder cancer in patients undergoing cholecystectomy for benign gallbladder disease. *J Surg Oncol*, 2013; 107:118-123.
192. Chin KF, Mohammad AA, Khoo YY, Krishnasamy T. The impact of routine histopathological examination on cholecystectomy specimens from an asian demographic. *Ann R Coll Surg Engl*, 2012; 94:165-169.
193. De Zoysa MI, De Silva SK, Illeperuma A. Is routine histological examination of gall bladder specimens justifiable? *Ceylon Med J*, 2010; 55:13-16.
194. Deng YL, Xiong XZ, Zhou Y, Shrestha A, Li FY, Cheng NS. Selective histology of cholecystectomy specimens--is it justified? *J Surg Res*, 2015; 193:196-201.
195. Kalita D, Pant L, Singh S, Jain G, Kudesia M, Gupta K, Kaur C. Impact of routine histopathological examination of gall bladder specimens on early detection of malignancy - a study of 4,115 cholecystectomy specimens. *Asian Pac J Cancer Prev*, 2013; 14:3315-3318.

196. Lee SE, Kim KS, Kim WB, Kim IG, Nah YW, Ryu DH, Park JS, Yoon MH, Cho JY, Hong TH, Hwang DW, Choi DW, Korean Association of Hepato-Biliary and Pancreas Surgery. Practical guidelines for the surgical treatment of gallbladder cancer. *J Korean Med Sci*, 2014; 29:1333-1340.
197. Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D, ESMO Guidelines Committee. Biliary cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 2016; 27:v28-v37.
198. Fan DX, Xu RW, Li YC, Zhao BQ, Sun MY. Impact of the number of examined lymph nodes on outcomes in patients with lymph node-negative gallbladder carcinoma. *World J Gastroenterol*, 2018; 24:2886-2892.
199. Tsilimigras DI, Hyer JM, Paredes AZ, Moris D, Beal EW, Merath K, Mehta R, Ejaz A, Cloyd JM, Pawlik TM. The optimal number of lymph nodes to evaluate among patients undergoing surgery for gallbladder cancer: Correlating the number of nodes removed with survival in 6531 patients. *J Surg Oncol*, 2019.
200. Noie T, Kubota K, Abe H, Kimura W, Harihara Y, Takayama T, Makuuchi M. Proposal on the extent of lymph node dissection for gallbladder carcinoma. *Hepatogastroenterology*, 1999; 46:2122-2127.
201. Jensen EH, Abraham A, Jarosek S, et al. Lymph node evaluation is associated with improved survival after surgery for early stage gallbladder cancer. *Surgery*, 2009;146:706-713.
202. Fuks D, Regimbeau JM, Le Treut YP, Bachellier P, Raventos A, Pruvot FR, Chiche L, Farges O. Incidental gallbladder cancer by the AFC-GBC-2009 study group. *World J Surg*, 2011; 35:1887-1897.
203. Benson AB, D'Angelica MI, Abbot DE, Abrams TA et al. NCCN clinical practice guidelines in oncology: Hepatobiliary cancers. version 5.2020. , 2020.
204. Shirai Y, Sakata J, Wakai T, Ohashi T, Hatakeyama K. "Extended" radical cholecystectomy for gallbladder cancer: Long-term outcomes, indications and limitations. *World J Gastroenterol*, 2012; 18:4736-4743.
205. Bergquist JR, Shah HN, Habermann EB, Hernandez MC, Ivanics T, Kendrick ML, Smoot RL, Nagorney DM, Borad MJ, McWilliams RR, Truty MJ. Adjuvant systemic therapy after resection of node positive gallbladder cancer: Time for a well-designed trial? (results of a US-national retrospective cohort study). *Int J Surg*, 2018; 52:171-179.
206. Butte JM, Gonen M, Allen PJ, D'Angelica MI, Kingham TP, Fong Y, Dematteo RP, Blumgart L, Jarnagin WR. The role of laparoscopic staging in patients with incidental gallbladder cancer. *HPB (Oxford)*, 2011; 13:463-472.
207. Fuks D, Regimbeau JM, Pessaux P, Bachellier P, Raventos A, Mantion G, Gigot JF, Chiche L, Pascal G, Azoulay D, Laurent A, Letoublon C,

Boleslawski E, Rivoire M, Mabrut JY, Adham M, Le Treut YP, Delpero JR, Navarro F, Ayav A, Boudjema K, Nuzzo G, Scotte M, Farges O. Is port-site resection necessary in the surgical management of gallbladder cancer? *J Visc Surg*, 2013; 150:277-284.
208. Im JH, Lee WJ, Kang CM, Hwang HK, Seong J. Prognostic factors and patterns of loco-regional failure in patients with R0 resected gallbladder cancer. *HPB (Oxford)*, 2019.
209. Cavallaro A, Piccolo G, Panebianco V, Lo Menzo E, Berretta M, Zanghi A, Di Vita M, Cappellani A. Incidental gallbladder cancer during laparoscopic cholecystectomy: Managing an unexpected finding. *World J Gastroenterol*, 2012; 18:4019-4027.
210. Ouchi K, Mikuni J, Kakugawa Y, Organizing Committee, The 30th Annual Congress of the Japanese Society of Biliary Surgery. Laparoscopic cholecystectomy for gallbladder carcinoma: Results of a japanese survey of 498 patients. *J Hepatobiliary Pancreat Surg*, 2002; 9:256-260.
211. Abramson MA, Pandharipande P, Ruan D, Gold JS, Whang EE. Radical resection for T1b gallbladder cancer: A decision analysis. *HPB (Oxford)*, 2009; 11:656-663.
212. Aloia TA, Jarufe N, Javle M, Maithel SK, Roa JC, Adsay V, Coimbra FJ, Jarnagin WR. Gallbladder cancer: Expert consensus statement. *HPB (Oxford)*, 2015; 17:681-690.
213. Cho JK, Lee W, Jang JY, Kim HG, Kim JM, Kwag SJ, Park JH, Kim JY, Park T, Jeong SH, Ju YT, Jung EJ, Lee YJ, Hong SC, Jeong CY. Validation of the oncologic effect of hepatic resection for T2 gallbladder cancer: A retrospective study. *World J Surg Oncol*, 2019; 17:8-6.
214. Rahman R, Simoes EJ, Schmaltz C, Jackson CS, Ibdah JA. Trend analysis and survival of primary gallbladder cancer in the united states: A 1973-2009 population-based study. *Cancer Med*, 2017; 6:874-880.
215. Butte JM, Waugh E, Meneses M, Parada H, De La Fuente, H A. Incidental gallbladder cancer: Analysis of surgical findings and survival. *J Surg Oncol*, 2010; 102:620-625.
216. Yip VS, Gomez D, Brown S, Byrne C, White D, Fenwick SW, Poston GJ, Malik HZ. Management of incidental and suspicious gallbladder cancer: Focus on early referral to a tertiary centre. *HPB (Oxford)*, 2014; 16:641-647.
217. Dixon E, Vollmer CM,Jr, Sahajpal A, Cattral M, Grant D, Doig C, Hemming A, Taylor B, Langer B, Greig P, Gallinger S. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: A 12-year study at a north american center. *Ann Surg*, 2005; 241:385-394.
218. Margonis GA, Gani F, Buettner S, Amini N, Sasaki K, Andreatos N, Ethun CG, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Maithel SK, Pawlik TM. Rates

and patterns of recurrence after curative intent resection for gallbladder cancer: A multi-institution analysis from the US extra-hepatic biliary malignancy consortium. *HPB (Oxford)*, 2016; 18:872-878.
219. Ethun CG, Postlewait LM, Le N, Pawlik TM, Buettner S, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Jin LX, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Kooby DA, Maithel SK. Association of optimal time interval to re-resection for incidental gallbladder cancer with overall survival: A multi-institution analysis from the US extrahepatic biliary malignancy consortium. *JAMA Surg*, 2017; 152:143-149.
220. Patkar S, Ostwal V, Ramaswamy A, Engineer R, Chopra S, Shetty N, Dusane R, Shrikhande SV, Goel M. Emerging role of multimodality treatment in gall bladder cancer: Outcomes following 510 consecutive resections in a tertiary referral center. *J Surg Oncol*, 2018; 117:372-379.
221. Ethun CG, Postlewait LM, Le N, Pawlik TM, Buettner S, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Jin LX, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Merchant N, Cardona K, Maithel SK. A novel pathology-based preoperative risk score to predict locoregional residual and distant disease and survival for incidental gallbladder cancer: A 10-institution study from the U.S. extrahepatic biliary malignancy consortium. *Ann Surg Oncol*, 2017; 24:1343-1350.
222. Ramos E, Lluis N, Llado L, Torras J, Busquets J, Rafecas A, Serrano T, Mils K, Leiva D, Fabregat J. Prognostic value and risk stratification of residual disease in patients with incidental gallbladder cancer. *World J Surg Oncol*, 2020; 18:18-2.
223. Sirohi B, Mitra A, Jagannath P, Singh A, Ramadvar M, Kulkarni S, Goel M, Shrikhande SV. Neoadjuvant chemotherapy in patients with locally advanced gallbladder cancer. *Future Oncol*, 2015; 11:1501-1509.
224. Agrawal S, Mohan L, Mourya C, Neyaz Z, Saxena R. Radiological downstaging with neoadjuvant therapy in unresectable gall bladder cancer cases. *Asian Pac J Cancer Prev*, 2016; 17:2137-2140.
225. Creasy JM, Goldman DA, Dudeja V, Lowery MA, Cercek A, Balachandran VP, Allen PJ, DeMatteo RP, Kingham TP, D'Angelica MI, Jarnagin WR. Systemic chemotherapy combined with resection for locally advanced gallbladder carcinoma: Surgical and survival outcomes. *J Am Coll Surg*, 2017; 224:906-916.
226. Chaudhari VA, Ostwal V, Patkar S, Sahu A, Toshniwal A, Ramaswamy A, Shetty NS, Shrikhande SV, Goel M. Outcome of neoadjuvant chemotherapy in "locally advanced/borderline resectable" gallbladder cancer: The need to define indications. *HPB (Oxford)*, 2018; 20:841-847.
227. Hakeem AR, Papulas M, Menon KV. The role of neoadjuvant chemotherapy or chemoradiotherapy for advanced gallbladder cancer -

A systematic review. *European Journal of Oncologic Surgery*, 2019;45:83-91.
228. Shroff RT, Kennedy EB, Bachini M, Bekaii-Saab T, Crane C, Edeline J, El-Khoueiry A, Feng M, Katz MHG, Primrose J, Soares HP, Valle J, Maithel SK. Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline. *J Clin Oncol*, 2019; 37:1015-1027.
229. Tran TB, Norton JA, Ethun CG, Pawlik TM, Buettner S, Schmidt C, Beal EW, Hawkins WG, Fields RC, Krasnick BA, Weber SM, Salem A, Martin RCG, Scoggins CR, Shen P, Mogal HD, Idrees K, Isom CA, Hatzaras I, Shenoy R, Maithel SK, Poultsides GA. Gallbladder cancer presenting with jaundice: Uniformly fatal or still potentially curable? *Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract*, 2017; 21:1245-1253.
230. Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, Anthony A, Corrie P, Falk S, Finch-Jones M, Wasan H, Ross P, Wall L, Wadsley J, Evans JTR, Stocken D, Praseedom R, Ma YT, Davidson B, Neoptolemos JP, Iveson T, Raftery J, Zhu S, Cunningham D, Garden OJ, Stubbs C, Valle JW, Bridgewater J, BILCAP study group. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): A randomised, controlled, multicentre, phase 3 study. *Lancet Oncol*, 2019; 20:663-673.
231. Mantripragada KC, Hamid F, Shafqat H, Olszewski AJ. Adjuvant therapy for resected gallbladder cancer: Analysis of the national cancer data base. *J Natl Cancer Inst*, 2016; 109:10.1093/jnci/djw202. Print 2017 Feb.
232. Kim Y, Amini N, Wilson A, Margonis GA, Ethun CG, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Cardona K, Maithel SK, Pawlik TM. Impact of chemotherapy and external-beam radiation therapy on outcomes among patients with resected gallbladder cancer: A multi-institutional analysis. *Ann Surg Oncol*, 2016; 23:2998-3008.
233. Kasumova GG, Tabatabaie O, Najarian RM, Callery MP, Ng SC, Bullock AJ, Fisher RA, Tseng JF. Surgical management of gallbladder cancer: Simple versus extended cholecystectomy and the role of adjuvant therapy. *Ann Surg*, 2017; 266:625-631.
234. Soreide K, Harrison EM, Wigmore SJ. Research gaps and unanswered questions in gallbladder cancer. *HPB (Oxford)*, 2018; 20:685-686.
235. Mason KA, Milas L, Hunter NR, Elshaikh M, Buchmiller L, Kishi K, Hittelman K, Ang KK. Maximizing therapeutic gain with gemcitabine and fractionated radiation. *Int J Radiat Oncol Biol Phys*, 1999; 44:1125-1135.
236. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J, ABC-02 Trial Investigators. Cisplatin plus gemcitabine

versus gemcitabine for biliary tract cancer. *N Engl J Med*, 2010; 362:1273-1281.
237. Dierks J, Gaspersz MP, Belkouz A, van Vugt, J. L. A., Coelen RJS, de Groot, J. W. B., Ten Tije AJ, Meijer WG, Pruijt JFM, van Voorthuizen T, van Spronsen DJ, Rentinck M, Ten Oever D, Smit JM, Otten HM, van Gulik TM, Wilmink JW, Groot Koerkamp B, Klumpen H. Translating the ABC-02 trial into daily practice: Outcome of palliative treatment in patients with unresectable biliary tract cancer treated with gemcitabine and cisplatin. *Acta Oncol*, 2018; 57:807-812.
238. Saluja SS, Gulati M, Garg PK, Pal H, Pal S, Sahni P, Chattopadhyay TK. Endoscopic or percutaneous biliary drainage for gallbladder cancer: A randomized trial and quality of life assessment. *Clinical Gastroenterology and Hepatology*, 2008; 6:944-950.
239. Sharma A, Dwary AD, Mohanti BK, Deo SV, Pal S, Sreenivas V, Raina V, Shukla NK, Thulkar S, Garg P, Chaudhary SP. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: A randomized controlled study. *J Clin Oncol*, 2010; 28:4581-4586.
240. Dirie NI, Wang Q, Wang S. Two-dimensional versus three-dimensional laparoscopic systems in urology: A systematic review and meta-analysis. *J Endourol*, 2018; 32:781-790.
241. Koppatz HE, Harju JI, Sirén JE, Mentula PJ, Scheinin TM, Sallinen VJ. Three-dimensional versus two-dimensional high-definition laparoscopy in transabdominal preperitoneal inguinal hernia repair: A prospective randomized controlled study. *Surg Endosc*, 2019.
242. Loozen CS, Oor JE, van Ramshorst B, van Santvoort HC, Boerma D. Conservative treatment of acute cholecystitis: A systematic review and pooled analysis. *Surg Endosc*, 2017; 31:504-515.
243. Vetrhus M, Berhane T, Søreide O, Søndenaa K. Pain persists in many patients five years after removal of the gallbladder: Observations from two randomized controlled trials of symptomatic, noncomplicated gallstone disease and acute cholecystitis. *J Gastrointest Surg*, 2005; 9:826-831.
244. Wennmacker SZ, Dijkgraaf MGW, Westert GP, Drenth JPH, van Laarhoven, C. J. H. M., de Reuver PR. Persistent abdominal pain after laparoscopic cholecystectomy is associated with increased healthcare consumption and sick leave. *Surgery*, 2018; 163:661-666.
245. van Dijk AH, Wennmacker SZ, de Reuver PR, Latenstein CSS, Buyne O, Donkervoort SC, Eijsbouts QAJ, Heisterkamp J, Hof KI, Janssen J, Nieuwenhuijs VB, Schaap HM, Steenvoorde P, Stockmann, H. B. A. C., Boerma D, Westert GP, Drenth JPH, Dijkgraaf MGW, Boermeester MA, van Laarhoven, C. J. H. M. Restrictive strategy versus usual care for cholecystectomy in patients with gallstones and abdominal pain (SECURE): A multicentre, randomised, parallel-arm, non-inferiority trial. *Lancet*, 2019; 393:2322-2330.

246. Sturesson C, Hemmingsson O, Månsson C, Sandström P, Strömberg C, Taflin H, Rystedt J. Quality-of-life after bile duct injury repaired by hepaticojejunostomy: A national cohort study. *Scand J Gastroenterol*, 2020:1-6.
247. Karvonen J, Gronroos JM, Makitalo L, Koivisto M, Salminen P. Quality of life after iatrogenic bile duct injury - a case control study. *Minim Invasive Ther Allied Technol*, 2013; 22:177-180.
248. Hogan AM, Hoti E, Winter DC, Ridgway PF, Maguire D, Geoghegan JG, Traynor O. Quality of life after iatrogenic bile duct injury: A case control study. *Ann Surg*, 2009; 249:292-295.
249. Sarmiento JM, Farnell MB, Nagorney DM, Hodge DO, Harrington JR. Quality-of-life assessment of surgical reconstruction after laparoscopic cholecystectomy-induced bile duct injuries: What happens at 5 years and beyond? *Arch Surg*, 2004; 139:483-9.
250. Guerra F, Coletta D, Gavioli M, Coco D, Patriti A. Minimally invasive surgery for the management of major bile duct injury due to cholecystectomy. *J Hepatobiliary Pancreat Sci*, 2020; 27:157-163.
251. Wang X, Yu WL, Fu XH, Zhu B, Zhao T, Zhang YJ. Early versus delayed surgical repair and referral for patients with bile duct injury: A systematic review and meta-analysis. *Ann Surg*, 2020; 271:449-459.
252. Bazoua G, Hamza N, Lazim T. Do we need histology for a normal-looking gallbladder? *J Hepatobiliary Pancreat Surg*, 2007; 14:564-568.
253. Darmas B, Mahmud S, Abbas A, Baker AL. Is there any justification for the routine histological examination of straightforward cholecystectomy specimens? *Ann R Coll Surg Engl*, 2007; 89:238-241.
254. Firat YD, Idiz UO, Cakir C, Yardimci E, Yazici P, Bektasoglu H, Bozkurt E, Ucak R, Gucin Z, Uresin T, Hasbahceci M. Prospective multi-center study of surgeon's assessment of the gallbladder compared to histopathological examination to detect incidental malignancy. *Langenbecks Arch Surg*, 2019; 404:573-579.
255. Talreja V, Ali A, Khawaja R, Rani K, Samnani SS, Farid FN. Surgically resected gall bladder: Is histopathology needed for all? *Surg Res Pract*, 2016; 2016:9319147.
256. Tayeb M, Rauf F, Ahmad K, Khan FM. Is it necessary to submit grossly normal looking gall bladder specimens for histopathological examination? *Asian Pac J Cancer Prev*, 2015; 16:1535-1538.
257. Olthof PB, Metman MJH, de Krijger RR, Scheepers JJ, Roos D, Dekker JWT. Routine pathology and postoperative follow-up are not cost-effective in cholecystectomy for benign gallbladder disease. *World J Surg*, 2018.
258. Lindner P, Holmberg E, Hafstrom L. Gallbladder cancer - no improvement in survival over time in a swedish population. *Acta Oncol*, 2018; 57:1482-1489.

259. de Savornin Lohman E, de Bitter T, Verhoeven R, van der Geest L, Hagendoorn J, Haj Mohammad N, Daams F, Klümpen HJ, van Gulik T, Erdmann J, de Boer M, Hoogwater F, Koerkamp BG, Braat A, Verheij J, Nagtegaal I, van Laarhoven C, van den Boezem P, van der Post R, de Reuver P. Trends in treatment and survival of gallbladder cancer in the netherlands; identifying gaps and opportunities from a nation-wide cohort. *Cancers (Basel)*, 2020; 12:918. doi: 10.3390/cancers12040918.
260. Akhtar-Danesh N, Akhtar-Danseh GG, Seow H, Shakeel S, Finley C. Treatment modality and trends in survival for gallbladder cancer: A population-based study. *J Gastrointest Cancer*, 2020.
261. Rapkin BD, Schwartz CE. Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift. *Health Qual Life Outcomes*, 2004; 2:14-14.
262. Kilander C, Mattsson F, Ljung R, Lagergren J, Sadr-Azodi O. Systematic underreporting of the population-based incidence of pancreatic and biliary tract cancers. *Acta Oncol*, 2014; 53:822-829.