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BILE DUCT STONES, STRICTURES AND IATROGENIC LESIONS: STUDIES ON EARLY DIAGNOSIS AND TREATMENT

by

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To Matilda, Elias and Anne

ABSTRACT

Jukka Karvonen

Bile duct stones, strictures and iatrogenic lesions: studies on early diagnosis and treatment.

From the Department of Surgery, University of Turku, Turku, Finland.
Annales Universitatis Turkuensis, Medica-Odontologica, 2009, Turku, Finland.

Aims: This study was carried out to investigate the role of common liver function tests, and the degree of common bile duct dilatation in the differential diagnosis of extrahepatic cholestasis, as well as the occurrence, diagnosis and treatment of iatrogenic bile duct injuries. In bile duct injuries, special attention was paid to gender and severity distribution and long-term results.

Patients and methods: All consecutive patients with diagnosed common bile duct stones or malignant strictures in ERCP between August 2000 and November 2003. Common liver function tests were measured in the morning before ERCP on all of these 212 patients, and their common bile duct diameter was measured from ERCP films.
Between January 1995 and April 2002, 3736 laparoscopic cholecystectomies were performed and a total of 32 bile duct injuries were diagnosed. All pre-, per-, and postoperative data were collected retrospectively; and the patients were also interviewed by phone.

Results: Plasma bilirubin proved to be the best discriminator between CBD stones and malignant strictures ($p \leq 0.001$ compared to other liver function tests and degree of common bile duct dilatation). The same effect was seen in Receiver Operating Characteristics curves (AUC 0.867). With a plasma bilirubin cut-off value of 145 µmol/l, four out of five patients could be classified correctly. The degree of common bile duct dilatation proved to be worthless in differential diagnostics.
After laparoscopic cholecystectomy the total risk for bile duct injury was 0.86%, including cystic duct leaks. 86% of severe injuries and 88% of injuries requiring operative treatment were diagnosed in females. All the cystic duct leakages and 87% of the strictures were treated endoscopically. Good long-term results were seen in 84% of the whole study population.

Conclusions: Plasma bilirubin is the most effective liver function test in differential diagnosis between CBD stones and malignant strictures. The only value of common bile duct dilatation is its ability to verify the presence of extrahepatic cholestasis.
Female gender was associated with higher number of iatrogenic bile duct injuries, and in particular, most of the major complications occur in females. Most of the cystic duct leaks and common bile duct strictures can be treated endoscopically. The long-term results in our institution are at an internationally acceptable level.

Keywords: Amsterdam criteria, bile duct injury, bile duct stone, bile duct stricture, common bile duct, complication, ERCP, extrahepatic cholestasis, laparoscopic cholecystectomy, liver function test, Receiver Operating Characteristics

TIIVISTELMÄ

Jukka Karvonen
Sappitiekivet, sappitieahtaumat ja sappitievauriot: tutkimuksia varhaisdiagnostiikasta ja hoidosta.
Kirurgian klinikka, Turun Yliopisto, Turku
Annales Universitatis Turkuensis, Medica-Odontologica, 2009, Turku.

Tavoite: Väitöskirjatyön tarkoituksena oli tutkia tavallisten maksan toimintakokeiden ja pääsappitiehyen leveyden merkitystä ekstrahepaattisen kolestaasin erotusdiagnostiikassa sekä iatrogeenisten sappitievaurioiden esiintyvyyttä, diagnostiikkaa ja hoitoa. Erityisesti vaurioiden sukupuoli- ja vaikeusastejakauma sekä hoidon pitkäaikaistulokset olivat kiinnostuksen kohteena.

Aineisto ja menetelmät: Aikavälillä elokuusta 2000 marraskuuhun 2003 kerättiin kaikki peräkkäiset potilaat, joilla todettiin sappitiekivet tai maligni sappitiestriktuura ERCP:ssä. Kaikilta näiltä 212 potilaalta tutkittiin tavalliset maksantoimintakokeet ERCP:tä edeltävänä aamuna ja lisäksi pääsappitien suurin leveys mitattiin ERCP-kuvista.
Vuoden 1995 alusta huhtikuun loppuun 2002 välisenä aikana tehtiin 3736 laparoskooppista kolekystektomiaa, joissa todettiin 32 iatrogeenista sappitievaurioita. Pre-, per- ja postoperatiiviset tiedot kerättiin retrospektiivisesti ja lisäksi elossa olevat potilaat haastateltiin puhelimitse.

Tulokset: Plasman kokonaisbilirubiini osoittautui parhaaksi tutkimukseksi sappitiekivien ja malignien striktuuroiden välisessä erotusdiagnostiikassa ($p \leq 0.001$ verrattuna muihin maksan toimintakokeisiin ja pääsappitien leveyteen). Sama vaikutelma todettiin ROC analyysissä (AUC 0.867). Päätösraja-analyysissä paras tehokkuus saavutettiin bilirubiiniarvolla 145 µmol/l, jolloin neljä viidestä potilaasta pystyttiin ryhmittelemään oikein. Pääsappitien leveydellä ei todettu olevan merkitystä erotusdiagnostiikassa.
Iatrogeenisten sappitievaurioiden esiintyvyys oli 0.86% mukaan lukien kystikustumpin lekaasit. 86% vakavista vaurioista ja 88% operatiivista hoitoa vaativista vaurioista todettiin naisilla. Kaikki kystikustumpin lekaasit ja 87% sappitieahtaumista hoidettiin endoskooppisesti. Koko aineistossa hoidon pitkäaikaistulokset olivat hyvät 84%:lla.

Johtopäätökset: Plasman bilirubiini on kliinisesti merkittävin maksan toimintakoe sappitiekivien ja malignien striktuuroiden välisessä erotusdiagnostiikassa. Sappitiedilataation ainoa merkitys on ekstrahepaattisen kolestaasin olemassaolon osoittaminen.
Naisilla oli enemmän iatrogeenisia sappitievaurioita, erityisesti vakavien vaurioiden osuus oli suurempi kuin miehillä. Suurin osa kystikustumpin lekaaseista ja sappitieahtaumista voidaan hoitaa endoskooppisin menetelmin. Sappitievaurioiden hoidon osalta tulokset ovat kansainvälisesti vertailukelpoisia sairaanhoitopiirissämme.

Avainsanat: Amsterdamin luokitus, ekstrahepaattinen kolestaasi, ERCP, komplikaatio, laparoskooppinen kolekystektomia, maksan toimintakoe, ROC-analyysi, sappitie, sappitieahtauma, sappitiekivi, sappitievaurio, sukupuoli

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ABBREVIATIONS

ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
BDI	bile duct injury
BMI	body mass index
CA 19-9	carbohydrate antigen 19-9
CBD	common bile duct
CCK	cholecystokinin
CEA	carcinoembryonic antigen
CT	computed tomography
CP	chronic pancreatitis
CV	coefficient of variation
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
GGT	gammaglutamyl transferase
HDL	high-density lipoprotein
HJS	hepaticojejunostomy
IOC	intraoperative cholangiography
LC	laparoscopic cholecystectomy
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
OC	open cholecystectomy
PBM	pancreatobiliary maljunction
PSC	primary sclerosing cholangitis
PTC	percutaneous transhepatic cholangiography
ROC	Receiver Operating Characteristics
TUCH	Turku University Central Hospital
US	ultrasound

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals.

I Grönroos JM, Hämäläinen MT, Karvonen J, Gullichsen R, Laine S: Is male gender a risk factor for bile duct injury during laparoscopic cholecystectomy? Langenbecks Arch Surg 2003;388(4):261-4

II Karvonen J, Kairisto V, Grönroos JM: Stone or stricture as a cause of extrahepatic cholestasis - do liver function tests predict the diagnosis? Clin Chem Lab Med 2006;44(12):1453-6

III Karvonen J, Gullichsen R, Laine S, Salminen P, Grönroos JM: Bile duct injuries during laparoscopic cholecystectomy: primary and long-term results from a single institution. Surg Endosc 2007;21(7):1069-73

IV Karvonen J, Kairisto V, Grönroos JM: The diameter of common bile duct does not predict the cause of extrahepatic cholestasis. Surg Laparosc Endosc Percutan Tech 2009;19(1):25-8

1. INTRODUCTION

Cholestasis is a clinical challenge. In an advanced form of cholestasis, the patients are jaundiced, which is almost always caused by hyperbilirubinemia, and is characterized by yellow pigmentation of skin and sclera. Cholestasis can be roughly divided into non-obstructive and obstructive form. The mechanisms causing non-obstructive cholestasis include overproduction of bilirubin, e.g. in hemolysis, decreased hepatic uptake or decreased conjugation. Obstructive cholestasis is caused either by impaired hepatocellular excretion of bilirubin (intrahepatic cholestasis) or, usually, by mechanical obstruction of the major extrahepatic bile ducts. Typically, mechanical obstruction is caused either by a bile duct stone or a stricture; of these, stricture most often refers to a malignancy (Vlahcevic et al. 1996, Rosalki et al. 1999).

Laboratory tests including the activities of alanine aminotransferase (ALT), alkaline phosphatase (AP) and γ-glutamyl transferase (GGT) and concentration of bilirubin are used to determine the presence and severity of cholestasis. Only one previous study has examined the value of common liver function tests in differential diagnosis of extrahepatic cholestasis (Pasanen et al. 1993).

Another diagnostic tool often available for differential diagnosis in the early phase is abdominal ultrasonography (US) which, in case of extrahepatic cholestasis, is the method of choice in the early phase in showing dilated bile ducts and in evaluating the degree of ductal dilatation (Cooperberg et al. 1980, Stott et al. 1991). However, it mostly fails to show definitely whether the cause of obstruction is a tumour or a stone (Blackbourne et al. 1994). With the recent advances of computed tomography (CT), it has become an equal diagnostic tool compared to magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) in differential diagnosis of extrahepatic cholestasis. Both of them detected the presence and level of obstruction with accuracy nearing 100% (Romagnuolo et al. 2003). The only difference favouring MRI and MRCP is in diagnosing for small (<1cm) tumours or stones under 0.5 cm in diameter (Andersson et al. 2005, Kondo et al. 2005). In the literature, there are no previous reports on the role of the degree of bile duct dilatation in predicting the diagnosis in extrahepatic cholestasis.

Iatrogenic bile duct injury (BDI) is a devastating complication that results in lasting morbidity, increased costs, may have a serious impact on the patient's physical and mental quality of life, and may even be fatal (Boerma et al. 2001, de Reuver et al. 2008). In the era of open surgery, the male gender has been reported to make several abdominal operations technically more demanding, and, accordingly, male patients were reported to have more than twice the risk for BDI when compared to women in cholecystectomy (Fletcher et al. 1999).

Soon after the introduction in the late 1980's, laparoscopic cholecystectomy (LC) became the gold standard for treatment of symptomatic gallstone disease, but it is associated with a higher incidence of BDIs than open cholecystectomy (OC). Many studies have shown that the incidence has risen from 0.1-0.2% (Roslyn et al. 1993) to as high as 0.8-1.4% (Adamsen et al. 1997, MacFadyen et al. 1998). A certain decrease in the incidence is seen due to the learning curve effect, but the overall number of complications is still at least twofold compared to OC (Flum et al. 2003, Nuzzo et al. 2005). Management of BDI depends on the timing of the recognition of injury, extent of injury and availability of experienced endoscopist, radiologist and hepatobiliary surgeon. The main goal of treatment is the restoration of bile conduit with the least possible complications and a minimum number of procedures. The outcome varies considerably and is highly dependent on the type of injury and its treatment (Regoly-Merei et al. 1998, Lillemoe et al. 2000, Gouma et al. 2002, Savassi-Rocha et al. 2003).

This thesis was designed to study the early diagnosis and treatment of the common bile duct (CBD) disorders, i.e. stones, malignant strictures and iatrogenic lesions. In particular, the interest was focused on topics of which there are no or only few earlier studies in the literature.

2. REVIEW OF THE LITERATURE

2.1. Anatomy of the biliary tract

The development of the human biliary tract begins in the third week of gestation from the embryonic hepatic diverticulum which develops from the foregut. The diverticulum divides into two parts, hepatic and biliary. The primitive bile ducts further divide into caudal and cranial parts. Gallbladder, cystic duct, and CBD develop from the caudal part, and the intrahepatic bile ducts, and the common hepatic duct develop from the cranial part (Nakanuma et al. 1997).

The smallest bile ducts are tiny bile canaliculi, which are formed by adjacent hepatocytes and are missing true wall structures. These canaliculis form a network which are connected to small bile ductules via canals of Hering. The bile ductules anastomose freely and increase in size to form trabecular ducts, intrahepatic ducts, and eventually the right and left hepatic duct. At the hilum of the liver, these ducts join to form the common hepatic duct (Gilloteaux 1997). About 3-4 cm after leaving the liver, the cystic duct joins the common hepatic duct to form the CBD. The length of the CBD varies between 5 and 15 cm, depending on where the common hepatic duct and cystic duct are merged, and the normal width is 4-10 mm (Niederau et al. 1984, Bowie 2000, Daradkeh et al. 2005). The CBD is divided into supraduodenal, retroduodenal, pancreatic, and intraduodenal segments. The distal part of the CBD comes into contact with the main pancreatic duct and in about 70% of cases unites to form the major duodenal papilla or papilla of Vater. The intraduodenal part of the CBD and the papilla of Vater are surrounded by a complex network of longitudinal and circular muscle fibers, which form the sphincter of the hepatopancreatic ampulla, or, the sphincter of Oddi (Nakanuma et al. 1997). The gross anatomy of the extrahepatic biliary tract is described in Figure 1.

The gallbladder is a pear-shaped sac with a capacity of 30-50 ml. It lies in the gallbladder fossa at the junction of the right and left lobes of the liver. The hepatic surface of the gallbladder attaches to the liver by the loose connective tissue of the fibrous capsule of the liver. The gallbladder is divided into three parts: fundus, body, and neck. The wall is 1-2 mm thick, depending on whether the gallbladder is relaxed or not (Gadzijev 2002). The cystic duct connects the neck of gallbladder to the common hepatic duct. It is 1-4 cm long and 5-8 mm wide. The cystic duct typically presents two types of structures: spirally arranged outgrowth of mucosa which forms the valve of Heister, and a smooth part (Bird et al. 2006).

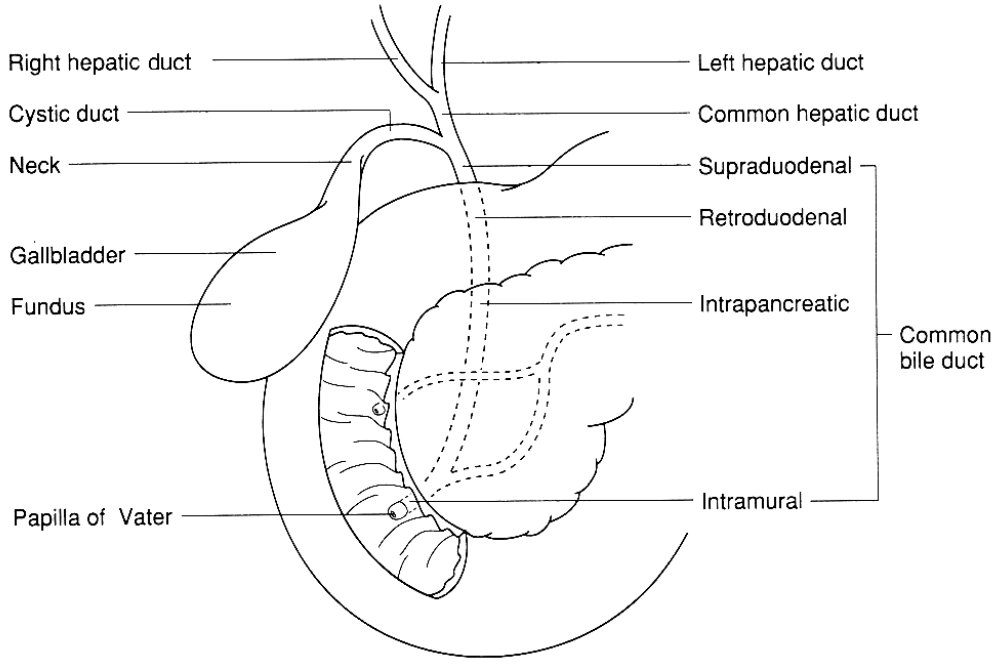

Figure 1. Gross anatomy of the extrahepatic biliary tract. Modified from (Crist et al. 1996)

2.1.1. Circulation, lymphatic drainage and innervation of the biliary tract

The extrahepatic biliary tract gets its arterial blood supply from the tributaries of the common hepatic artery: the cystic artery supplies the gallbladder, the cystic duct, and the proximal part of CBD, the right hepatic artery supplies the middle part, and the posterior superior pancreatoduodenal and gastroduodenal arteries supply the retroduodenal part of the duct (Northover et al. 1979).

The veins from the hepatic ducts and proximal part of the CBD enter the liver directly. The distal part of the CBD drains to the posterior superior pancreatoduodenal vein which empties into the portal vein or one of its tributaries.

The lymphatic vessels from the biliary tract pass to the cystic lymph nodes near the neck of the gallbladder, the nodes of the omental foramen, the hepatic lymph nodes, and eventually to the lymph nodes around the celiac trunk. The lymphatic vessels of the gallbladder and the biliary tract anastomose superiorly with those of the liver and inferiorly with those of the pancreas and duodenum (Gadzijev 2002).

The sympathetic nerves of the extrahepatic biliary tract come from the celiac plexus, the parasympathetic nerves come from the vagus nerve and the sensory

nerves come from the right phrenic nerve. They pass along the hepatic artery, the portal vein, and CBD.

2.1.2. Anatomical variations of the biliary tree

The normal biliary anatomy is thought to be present in about half of individuals. Anatomical variations are most common in the confluence area, typically concerning the right posterior hepatic duct and its drainage site; these variations are present in approximately 25% of the population. Another common variation is the so-called trifurcation where the right anterior and posterior ducts drain separately into the common hepatic duct, and is present in 11% of the population (Puente et al. 1983, Hirao et al. 2000).

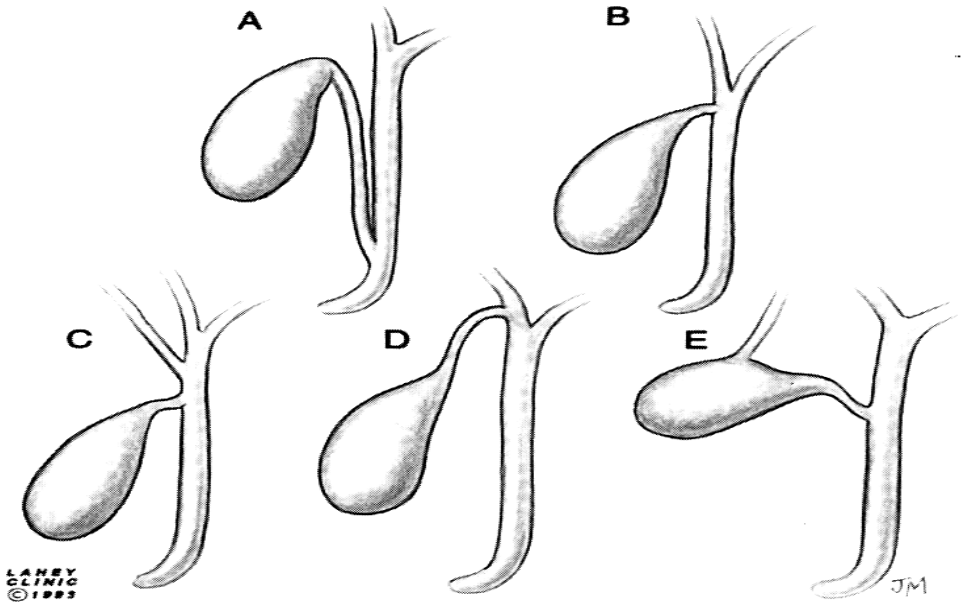

Figure 2. The common variants in bile duct anatomy. A, long cystic duct with low fusion. B, high fusion. C, accessory hepatic duct (trifurcation). D, cystic duct entering right hepatic duct. E, cholecystohepatic duct. With permission, (Martin et al. 1994).

There are three common variants in the anatomy of the cystic duct region: low cystic duct insertion with distal third of the CBD (9%); medial insertion, where the cystic duct drains into the left side of CBD (10-17%); and a parallel course and less angular entry into CBD (1.5-25%) (Puente et al. 1983, Taourel et al. 1996). The potential other routes for the cystic duct drain into the biliary tree are numerous, and it is estimated that only one third of the population has a so-called normal cystic duct anatomy (Adkins et al. 2000). The most common duct anomalies and the cystic union types are described in figures 2 and 3.

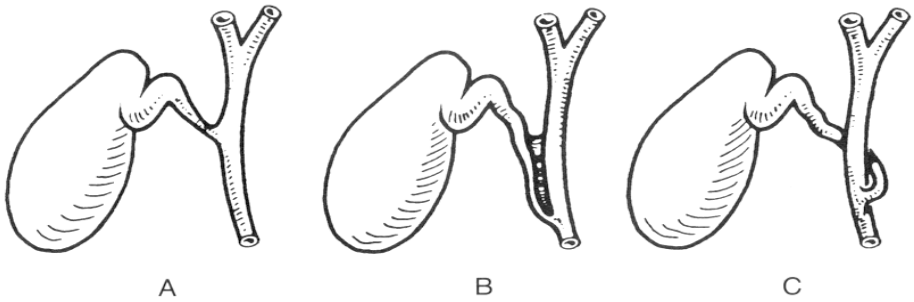

Figure 3. The common cystic duct unions. A, angular (75%). B, parallel (20%). C, spiral/medial (5%). With permission, (Adkins et al. 2000).

True anatomical variations of the gallbladder are extremely rare. Agenesis, duplication and left-sided position are described in literature. The operating surgeon needs only to be aware of these entities as they have only a limited clinical significance.

2.2. Physiology of the biliary tract

Bile is a complex mixture of organic and inorganic components. The main organic components are bile acids, phospholipids, cholesterol, and bile pigments. Bile acids account for about 50% of the organic components. Four bile acids are present in the bile and they are synthetized from cholesterol. Cholic and chenodeoxycholic are the primary bile acids and are synthesized in the liver. Within the lumen of the intestine, bacteria dehydroxylate secondary bile acids, deoxycholic and lithocholic acids. All four are returned to the liver in the portal blood and secreted into the bile.

Phospholipids, primarily lecithins, account for about 30-40% of the organic components. Cholesterol makes up approximately 4% of the organic material in the bile. Bile pigments, mainly bilirubin, account for about 2% of the organic compounds.

The major parts of the biliary tract which participate actively in the control of bile flow are the gallbladder and the sphincter of Oddi. Bile is continuously produced by the hepatocytes in the liver, and under a normal physiological condition, the bile flow averages about 500-1000 ml per day. The secretion of bile acids carries water and electrolytes into the bile by osmotic filtration, additional water and electrolytes are added by the cells lining the ducts

(Nakanuma et al. 1997). This latter secretory component is stimulated by secretin. The hepatic end of the biliary system is closed; thus the secretion generates hydrostatic pressure within the ducts. During the interdigestive period, the gallbladder is flaccid and the sphincter of Oddi is closed; this permits the bile flow into the gallbladder. The gallbladder does not simply fill passively, periodical contractions, mediated mainly by motilin, partially empty the concentrated bile, which permits the diluted bile to enter the gallbladder (Qvist et al. 1995). During the interdigestive period, vasoactive intestinal peptide and nitric oxide possibly promote the relaxation of the gallbladder wall to allow the filling (Lonovics et al. 1998). Between meals, bile is actively concentrated by the gallbladder epithelium as much as tenfold. Na^+, Cl^-, and HCO_3^- are reabsorbed, and water follows down the osmotic gradient. The gallbladder also secretes mucus and slightly acidifies the bile. After the meal, the major stimulus for gallbladder contraction is cholecystokinin (CCK) released by fat and protein digestion products within the lumen of the duodenum. The gallbladder contraction is also stimulated by vagal activity during all phases of digestion. CCK has two principal actions: relaxation of the sphincter of Oddi and contraction of the smooth muscle within the gallbladder wall. Several other hormones, released from different sources, may modulate the effect of CCK, affect the relaxation of the sphincter of Oddi, or the motility of the gallbladder (Lonovics et al. 1998). During normal postprandial gallbladder emptying, 50-90% of the contents is expelled (Vlahcevic et al. 1996).

2.3. Pathophysiology of the biliary tract

Cholestasis is a clinical and biochemical syndrome resulting from impaired bile flow. Jaundice is an advanced state of cholestasis characterized by yellowing of the skin and sclera due to excess circulating bilirubin. The most common causes of extrahepatic cholestasis are presented in Figure 4.

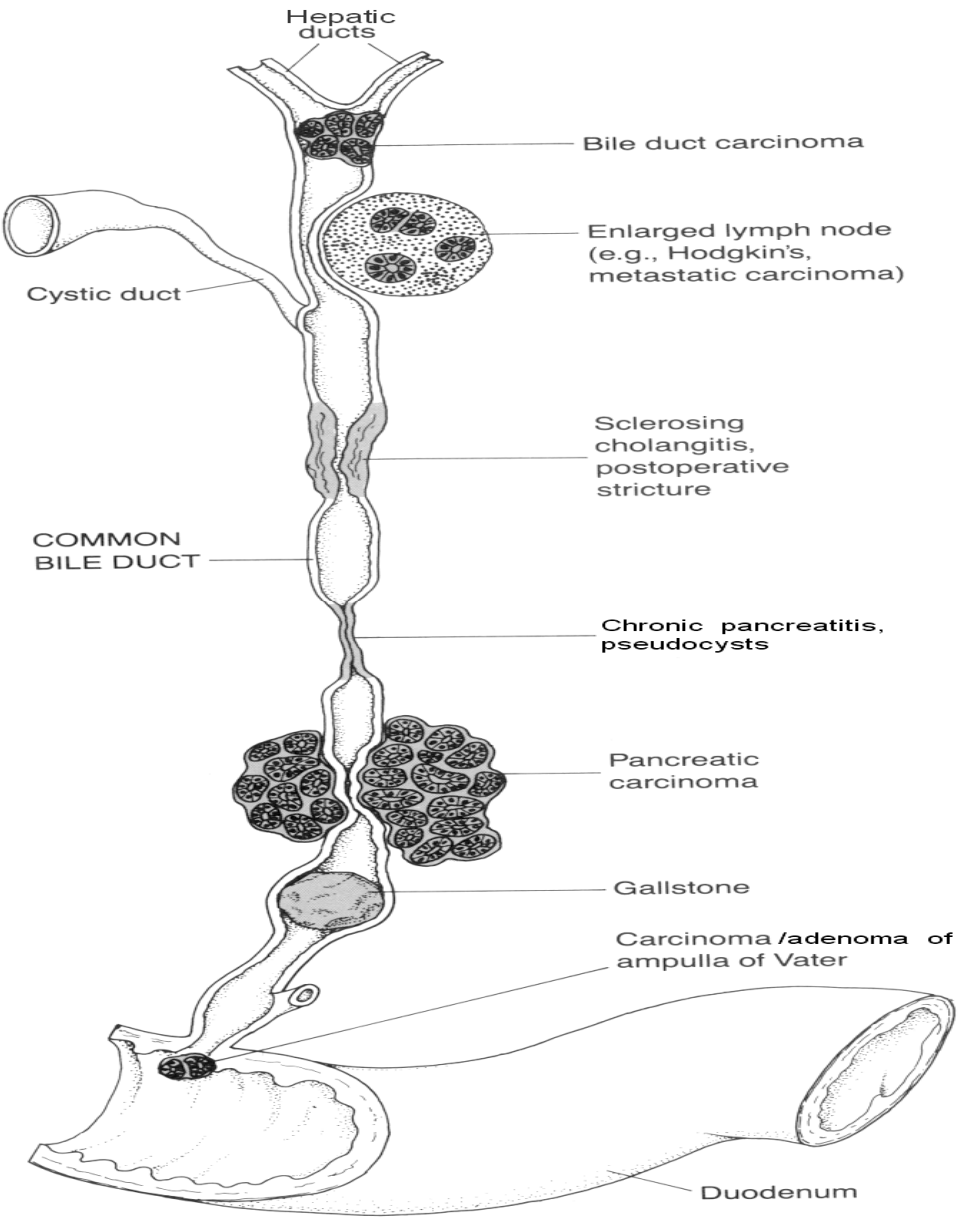

Figure 4. The most common causes of extrahepatic cholestasis. Modified from, (Rubin et al. 1990).

2.3.1. Gallstone disease

The prevalence of gallstones varies between different ethnics groups and geographical locations. In Asian and African populations, the prevalence is under 5%, whereas in western countries it varies between 10% and 20% (Aerts et al. 2003). In certain ethnic groups, such as American Indians and Maoris, the prevalence is as high as 70%. Prevalence increases with advancing age, and female gender is associated with higher prevalence, 16% compared to 9% for males (Domellof et al. 1984, Sakorafas et al. 2007)

Ten to thirty percent of the people with gallbladder stones have concomitant CBD stones, and the prevalence rises with age (Alponat et al. 1997). In western countries, most of the CBD stones are secondary, namely originating from gallbladder. Primary common bile duct stones are rare in western countries and are usually associated with biliary stasis and bacterial infections (Ko et al. 2002).

2.3.1.1. Formation of stones

There are two major categories of gallstones – cholesterol stones and pigment stones. Approximately 80%-90% of all gallstones in western countries are cholesterol stones. Formation of stones can occur when the amount of cholesterol secreted into bile exceeds the amount that can be held in a stable micellar form; supersaturation of cholesterol occurs. In supersaturated bile, cholesterol and phospholipids start to form vesicles and bile becomes lithogenic. Most of the patients who have gallstones have also defective gallbladder emptying (Donovan 1999, Beckingham 2001). Further, lithogenic bile decreases the contractibility and emptying of the gallbladder, thus leading to a vicious circle. Black pigment stones are common in patients with chronic haemolytic syndromes, biliary cirrhosis, Crohn's disease, and after prolonged parenteral nutrition (Sakorafas et al. 2007). Brown pigment stones are usually formed around bacterial nidus in the bile ducts as a result of biliary stasis and chronic infection (Beckingham 2001).

2.3.1.2. Risk factors

The pathogenesis of gallstone disease is complex, but several factors have been associated with the increased risk for formation of stones.

The female gender carries twice the risk of gallstone disease as compared to men (Beckingham 2001), it is especially prominent at a younger age, mainly because of hormonal factors. Much of the risk is related to pregnancy, as 1% to 3% of women form gallstones during pregnancy, and biliary sludge is formed in up to 30% of pregnant women, and the risk even increases with the number of pregnancies (Attili et al. 1997, Portincasa et al. 2006). Oral contraceptives and

oestrogen-replacement therapy are also linked with increased risk (Portincasa et al. 2006).

Obesity is a well known risk factor for gallstones, and if the body mass index (BMI) exceeds 30 kg/m^2, the risk is threefold compared to normal BMI (Katsika et al. 2007). Paradoxically, rapid weight loss is associated with an even greater frequency of stone formation. Over 35% of patients on a very low caloric diet and 70 % of patients after bariatric surgery develop gallstones (Wudel et al. 2002). Physical inactivity is also associated with increased risk.

With advancing age, the risk for gallstones increases in all ethnic and racial groups. Compared to the population under 40 years of age, people in their fifties and seventies run a three to six-fold risk to form gallstones, respectively (Beckingham 2001).

Genetic and environmental factors play a major role in the development of gallstones. Genetic factors are believed to account for approximately 25% of symptomatic gallstones, and the percentage for asymptomatic gallstone disease may be even higher (Katsika et al. 2005). Besides the hereditary component, the environmental factors may play an even more substantial role in formation of gallstones, as the common environmental factors (i.e. weight gain/loss, infections, childhood diet etc.) may cause 13% of the development of gallstones and unique factors as high as 62% (Katsika et al. 2005). Western (high fat, high carbohydrate, high calories, and low fibre) diet is the best single known environmental factor. The effect is seen in the East Asian countries where dietary habits have changed towards the western, more unhealthy, diets leading to a gradually rising prevalence of gallstones (Portincasa et al. 2006).

Several other factors have been associated with gallstone formation: metabolic syndrome, type 2 diabetes, hypertriglyceridaemia, decreased levels of high-density lipoprotein (HDL) cholesterol, bile salt loss (ileal Crohn's disease or after surgical resection), drugs (ceftriaxone, octreotide, and fibrates), and impaired bile flow (Donovan 1999, Beckingham 2001, Jonkers et al. 2003, Sanders et al. 2007). Neither smoking nor alcohol consumption are related to increased risk of gallstone formation (Katsika et al. 2007).

2.3.1.3. Symptoms

Gallstone disease can be divided into three categories: asymptomatic gallstones, symptomatic gallstones, and complications of gallstones. Approximately 60%-70% of the stones are asymptomatic at the time of diagnosis; 1%-4% of these become symptomatic annually. Ten and twenty percent will eventually become symptomatic within 5 and 20 years of diagnosis, respectively (Sakorafas et al. 2007). The majority of the patients become symptomatic, usually biliary colics,

before any complications develop. When symptoms arise, about 50% will recur and complications develop in 1-2% annually (Beckingham 2001).

2.3.1.4. Diagnosis and treatment

The most common presentation for gallstone disease is biliary colics. US is the definitive investigation for gallstone disease, particularly gallbladder stones, but also the liver function tests should be checked. If there are abnormalities in the liver chemistry, or the biliary tree is dilated in US, CBD stones should be suspected.
Several predictive models for CBD stones have been suggested over the years. In the era of OC, Saltzstein et al. noticed that a serum bilirubin level exceeding 30 µmol/l combined with AP levels exceeding 250 U/l indicates a 76% probability for common bile duct stones (Saltzstein et al. 1982). Hauer-Jensen et al. presented a model with following predictive factors: visible stone in preoperative imaging, serum bilirubin levels of over 25 µmol/l, diameter of cystic duct over 5 mm, and patient age up to 60 years. In patients under 60 years, the negative predictive value was 100%, if all the three factors were negative. In patients over 60 years it was 97% (Hauer-Jensen et al. 1993).
Alponat et al. noticed four factors associated with an elevated risk for having CBD stones. The combination of recent cholangitis, bile duct dilatation (over 6 mm) with visible stone in US, elevated aspartate transaminase (AST) and elevated bilirubin gives a 97% probability of common bile duct stone, whereas, if all of these were negative, the probability was 7% (Alponat et al. 1997). Prat et al. reported that in patients under 70 years, CBD dilatation combined with a seven times higher than normal elevation of GGT has a 90% probability for CBD stones, and if both are negative, 6% (Prat et al. 1999). Shiozawa et al. presented four factors: CBD dilatation (>8mm), bilirubin, AP, and serum amylase elevation with positive predictive accuracy of 79% and, if all of these were missing, the negative predictive accuracy was 98% (Shiozawa et al. 2005).

None of the single laboratory tests, symptoms or US findings is specific for CBD stones. If CBD stones are suspected, the definitive preoperative diagnosis is made with MRCP, endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography (ERCP). The diagnostic methods are discussed in more detail in chapter 2.4.

The treatment of gallbladder stones is discussed in detail in chapter 2.5. Several different options are available for management of CBD stones, but the main goal is to extract the stones with the least possible complications, cost, and number of procedures. There are three main approaches depending on local tradition, surgical expertise and availability of procedures: two-stage operation, i.e. LC with either preoperative or postoperative ERCP, LC, and laparoscopic ductal stone clearance in a single operation (= one-stage operation), and

traditional open variations for common bile duct stones. In a prospective randomized trial made by the European Association for Endoscopic Surgery two-stage operation with preoperative ERCP was compared to one-stage operation. The only difference was shorter hospital stay in one-stage operation (Cuschieri et al. 1999). Rhodes et al. reported similar results when comparing one-stage operation to two-stage operation with postoperative ERCP (Rhodes et al. 1998).

2.3.2. Neoplasms of the biliary tract

Nearly 50% of patients with extrahepatic biliary tract obstruction have other than stone-related disease, most commonly malignancy. Most of these are located in the head of pancreas, less commonly in ampulla of Vater and biliary tract. Less than 10% of pancreatic tumours are benign (Reddy et al. 2007).

Pancreatic and biliary tract cancers have very similar symptoms, signs, diagnostics and treatment. In the early phase, the symptoms and signs are usually non-specific, e.g. abdominal discomfort, or nil. In time, the obstructive signs progress and 60 – 90% of the patients are jaundiced at the time of the diagnosis (Nordback et al. 2002, Tsukada et al. 2008). As in gallstone disease, the first investigations are serum liver chemistry tests and abdominal US, which both give non-specific information. Laboratory tests usually reveal elevated bilirubin, AP and GGT levels, and US shows ductal dilatation (Cooperberg et al. 1980, Stott et al. 1991, Pasanen et al. 1993). Further diagnostics are done with CT, MRI, MRCP and EUS, depending on local resources. Most of the jaundiced patients are referred to ERCP, which allows biliary stenting and drainage for palliation of inoperable tumours, or sometimes preoperatively for resectable tumours (Miyakawa et al. 2008). For pancreatic and biliary tract cancers, the only available curative treatment is operative.

Approximately 90% of pancreatic cancers are histologically ductal adenocarcinomas and 10-15% are located in the periampullary region. The incidence of pancreatic cancer is slowly increasing and about 900 new cases are found annually in Finland (Finnish Cancer Registry 2007) and about 37000 in the USA (American Cancer Society 2008). The main causes and risk factors for pancreatic cancers are unknown but male gender has slight predisponence, smoking explains 25% and environmental factors 20% of pancreatic cancers (Ojajarvi et al. 2000). Also a 5-10% proportion of pancreatic cancers has a familial background (Jorgensen et al. 2008). At the time of diagnosis, approximately 40% of the patients have a metastatic disease and another 40% a locally advanced disease. About half of the remaining 20% patients fit for potentially curative surgery are found to have an inoperable tumour despite the findings of non-invasive imaging (Haller 2003). Pancreatic carcinoma is a lethal disease having a nearly 1:1 ratio of incidence to mortality. Most of patients pass

away within two years, five year survival rates between 10-20% have been reported (Takamori et al. 2008), but in nation-wide registers it is 3-5% (Finnish Cancer Registry 2007, American Cancer Society 2008). The most common reason for long-time survival seems to be a false initial diagnosis (Carpelan-Holmstrom et al. 2005).

Biliary tract cancers are usually tubular adenocarcinomas, more commonly cholangiocarcinomas in histology and are divided topographically into three categories: intrahepatic (10%), hilar (60-70%), and CBD tumours (20-30%) (Demols et al. 2007). As in pancreatic carcinoma, the incidence is rising and, including gallbladder carcinoma, about 250 new cases are seen annually in Finland and about 9000 in the USA. In the Finnish population, female gender seems to have a slightly higher incidence (Finnish Cancer Registry 2007). Most of the cases are sporadic but several risk factors have been detected, most of these are associated with chronic inflammation of the biliary tract. Primary sclerosing cholangitis (PSC) is one of the most common known predisposing factors, and eventually 20-30% of patients with PSC will develop biliary tract cancer (Lempinen et al. 2007). Parasitic biliary infections, gallstone disease, history of cholecystectomy, cirrhosis, and hepatitis B and C infections have also been reported as predisposing factors (Khan et al. 1999). In several articles from East Asia, pancreatobiliary maljunction (PBM), which is defined as a union of the pancreatic and biliary ducts located outside the duodenal wall, has been associated with greatly elevated risk for having biliary tract and gallbladder cancer as follows: PBM with biliary tract dilatation has a 10.6% risk and without dilatation 37.9% risk for biliary tract cancer and the incidence of gallbladder cancer is 65% and 93%, respectively (Tashiro et al. 2003, Miyazaki et al. 2008). Biliary tract cancer is a predominantly fatal disease and the five-year survival rate is usually between 10% and 40 %, but in very selected cases of cholangiocarcinoma, liver transplantation may be considered, elevating the 5-year survival rate up to 82% (Rea et al. 2005, Demols et al. 2007).

2.3.3. Benign strictures of the biliary tract

Benign biliary strictures are caused by a heterogeneous group of conditions that constitute only a small part of all strictures. The main manifestation of a stricture is scar contracture and stenosis of the duct, leading to cholestasis and eventually to secondary biliary cirrhosis (Lin et al. 2002). Despite the novel imaging modalities, the differential diagnosis between benign and malignant strictures remains challenging especially in cases without a mass lesion (Krishna et al. 2007). A definitive diagnosis can be made in about half of the patients, and the rest are treated, as they are considered to have a malignant cause until proven otherwise (Larghi et al. 2007). The most common causes of

benign strictures are iatrogenic lesions, chronic pancreatitis (CP) associated strictures, and PSC.

Postoperative strictures may occur virtually in all kinds of upper abdominal operations, although the vast majority is associated with biliary tract surgery, most notably OC and LC (McAllister et al. 1976, Roslyn et al. 1993, Nuzzo et al. 2005). Strictures may occur due to a direct injury, by misplaced clips, by cautery, or indirectly, after months or years, by interruption of vascular supply to a segment of the biliary tree, or by inflammatory conditions.

CP is a common inflammatory disease characterized by anatomical and functional alterations in pancreas and surrounding tissues, including biliary tract. Its incidence is around 6-8/100,000 and is slightly rising in western countries (Bachmann et al. 2008). Alcohol consumption is the cause in about 70-80% of CP, 20% of the cases are idiopathic, and 5-10% are of an autoimmune or hereditary form. CP induced biliary strictures are seen in 6-23% of patients and account for approximately 10% of all benign biliary strictures (Sand et al. 1995, Gupta et al. 2006). CP is associated with an increased risk of developing pancreatic cancer (Lowenfels et al. 1993). Patients with CP have also shorter life expectancy than the normal population, mainly due to non-pancreatic effects of alcohol and smoking (Tinto et al. 2002).

PSC is a progressive liver disease of unknown etiology, characterized by inflammatory destruction of both intra- and extrahepatic bile ducts leading to obliteration of the biliary tree and eventually to cirrhosis. The incidence is around 1/100,000 (Boberg et al. 1998, Bambha et al. 2003) and it is often associated with inflammatory bowel disease and has a high risk for developing cholangiocarcinoma, with a lifetime risk of up to 30% (Broome et al. 1996).

The treatment of benign biliary strictures aims to relieve symptoms of obstruction and prevent secondary biliary cirrhosis. There are several different treatment options available from endoscopic interventions to liver transplantation, and every time the best available option should be considered case by case in a multidisciplinary manner (Nordin et al. 2002). Traditionally, the operative treatment has been the method of choice but it was associated with significant morbidity and even mortality with rates between 0.6% to 11.5% (Blumgart et al. 1984, Lillemoe et al. 2000), although these figures have decrease almost to zero at present. In case of iatrogenic injuries, proper preoperative evaluation of the hepatobiliary system by means of ERCP, MRCP or percutaneous transhepatic cholangiography (PTC), or peroperatively, is of utmost importance, as 96% of repairs without it are reported to be unsuccessful (Stewart et al. 1995). In addition, the reconstructive attempts of the primary surgeon are reported to be doomed, as only 17% are successful (Stewart et al.

1995). With straightforward surgical treatment, in the tertiary center, successful results are seen in up to 98% of patients (Lillemoe et al. 2000). With advances in ERCP and its accessories in the last two decades, endoscopic therapy has become an option for even the most complicated strictures, and similar results as after operative treatment are seen with aggressive stenting (Costamagna et al. 2001). Uniform results are seen in patients with CP associated biliary strictures (Catalano et al. 2004). For PSC, short-term results with endoscopic treatment may be beneficial, but knowing its high association with cholangiocarcinoma, a possible malignancy should always be outruled before stenting. In case of PSC and suspicious biliary stricture, the aim is a liver transplantation before the development of cholangiocarcinoma (Lempinen et al. 2007).

2.4. Diagnostic methods

2.4.1. Medical history and clinical examination

Despite the extensive array of various imaging modalities and laboratory tests patient history and physical examination are the cornerstones of all patient work. On jaundiced patients, clinical examination differentiates between obstructive and non-obstructive jaundice with sensitivity of 92% and a specificity of 86% (Pasanen et al. 1992). Although a definitive diagnosis is seldom available, clinical examination is crucial to targeting of further examinations.

2.4.2. Laboratory investigations

Liver is an organ that has complex metabolic, defensive, and excretory functions. No single or simple test evaluates overall liver function and none of the “liver chemistry tests” or “liver function tests” does actually effectively assess the function of the liver, or none of them is even specific for liver disease (Green et al. 2002). Liver function tests are a selected battery of tests that usually include AST and/or ALT, GGT, AP and total bilirubin.

2.4.2.1. Transaminases

AST and ALT are the common measures of hepatocellular injury. Neither of them is liver specific, and especially AST is a very common intracellular enzyme, whose highest concentrations are found in liver, heart, lung, and skeletal muscle. ALT is also present in all of these tissues, but high concentrations are found only in liver (Reichling et al. 1988). Elevated transaminase levels are present in most hepatic diseases, but are classically associated with hepatocellular injury. The actual level and magnitude of elevation is useful in narrowing the differential diagnosis. Very high (up to 15 times normal) concentrations of transaminases are seen in all subtypes of acute hepatitis, drug-induced hepatotoxicity, ischemic conditions (hepatic artery ligation), and acute severe bile duct obstruction (Green et al. 2002, Hayat et al.

2005). Mild elevations (less than 5 times normal) are seen in most hepatobiliary diseases, but also in extrahepatic conditions, such as hemolysis, myopathy, thyroid disease, and after hard physical exercise (Reichling et al. 1988, Green et al. 2002).

2.4.2.2. Alkaline phosphatase

APs are a group of enzymes that are seen in most tissues all over the human body, especially in liver, bone and placenta. Enzyme activity fluctuates with life: during growth period and pregnancy, the level is two to three-fold compared to normal adults; also with advancing age, the activity rises in both sexes (Reichling et al. 1988). Elevations of AP activity may be associated with cholestatic disorders, although typically the levels are also elevated in bone disorders. GGT may be used to confirm the hepatic origin of the rise in AP. Mild elevations (up to three times normal) are seen in all types of hepatic disorders, levels higher than this are seen particularly in cholestatic diseases, both intrahepatic and extrahepatic. Enzyme activities have been reported to be at the same level in both entities (Reichling et al. 1988).

2.4.2.3 Gammaglutamyl transferase

GGT is found mainly in liver, but also in many other tissues including kidneys, pancreas, spleen, and heart. Elevated activities are seen in various cholestatic conditions and alcohol, and a number of drugs (e.g. anticonvulsants and barbiturates) induce serum elevations. When compared to AP, there is no variation with advancing age or in pregnancy and it is not elevated in bone disorders (Reichling et al. 1988). The greatest utility of GGT is its ability to confirm the hepatic origin of AP.

2.4.2.4. Bilirubin

Bilirubin is formed from the breakdown of erythrocytes, and their haemoglobin and serum bilirubin reflect the balance between heme formation and catabolism. Unconjugated bilirubin is water insoluble and is reversibly bound to albumin; after hepatic uptake it is conjugated by glucuronyl transferase, which converts it into a water soluble state (Green et al. 2002). After conjugation, it is secreted into the biliary tract and the small intestine. In terminal ileum and colon conjugated bilirubin is converted to urobilinogen by bacterial enzymes and eventually excreted to feces and in small amounts to urine.

Hyperbilirubinemia may result from increased production (hemolysis, blood transfusion), decreased conjugation (Gilbert's syndrome), hepatocyte injury (acute or chronic hepatitis), decreased intracellular metabolism or excretion (diffuse infiltrative disorders or drug effect), bile duct injury (primary biliary cirrhosis and sclerosing cholangitis), or obstruction of the extrahepatic biliary tract (CBD stones or malignancy). Unconjugated hyperbilirubinemia is usually

caused by hemolysis or Gilbert's syndrome (Green et al. 2002). Conjugated hyperbilirubinemias can be divided into two main categories: particularly obstructive but also non-obstructive. In both categories, there are typically elevations also in AP, GGT and transaminases.

2.4.2.5. Tumour markers

Several different tumour markers have been identified in the past few decades. For pancreato-biliary malignancies, carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) are the most commonly used ones. Neither one is specific for pancreatic or cholangiocarcinoma. Elevated levels of both markers are seen in almost all gastrointestinal cancers, but also in benign conditions such as obstructive jaundice or pancreatitis. CEA is generally used in colorectal cancer, but elevated levels are seen in 30-50% of pancreato-biliary cancers (Schlieman et al. 2003). CA 19-9 is elevated in 50-80% of pancreato-biliary malignancies and, in case of pancreatic cancer with a cut-off level of 150, 88% of the tumours were found to be unresectable despite findings of imaging studies (Schlieman et al. 2003). The limitation of CA 19-9 antigen is that patients with Lewis negative blood type (10-15% of population) are unable to synthesize it (Michl et al. 2006).

2.4.2.6. Other

There is a large quantity of other laboratory tests that may be needed in differential diagnosis. The specific tests are serological tests for different types of acute and chronic hepatitis. The most common nonspecific tests used are albumin and prealbumin levels as well as prothrombin time and international normalization ratio, which are used to evaluate hepatic function (Green et al. 2002).

2.4.3. Imaging studies

Plain films of the abdomen are the oldest imaging modality of abdominal examination. Nowadays its role is very limited, mainly in differential diagnostics on acute patients. 10-15% of the gallstones are calcified enough to be seen in plain films (Preger et al. 1989).

US is most often used as an initial study in patients with a suspected hepatobiliary disease. It has several advantages over other imaging methods: its availability is superior, it can be performed bedside, it is inexpensive and it does not involve radiation. US has also drawbacks: it is highly operator dependent, and for example obesity, fatty liver and bowel gas may attenuate the sound waves causing inadequate imaging. For evaluation of gallbladder stones, US is the gold standard with sensitivity and specificity approaching 99% (Stroszczynski et al. 2005). The detection rate for CBD stones has increased from 20% to 55-80% with improving skills and equipment (Laing et al. 1984,

Magnuson et al. 1999). US is the method of choice in early differentiation between intra- and extrahepatic cholestasis. Its sensitivity and specificity for diagnosing dilatation of bile ducts are 95% and 96%, respectively (Stott et al. 1991). Diagnostic accuracy decreases substantially after that, and the level of obstruction is identified in 71-91% and the etiology of obstruction in 57-71% of cases (Laing et al. 1986, Blackbourne et al. 1994). Approximately 15-20% of US examinations are impaired in the pancreatic region due to bowel gas and obesity (Brambs et al. 1993).

CT with contrast enhancement is another base-line examination for patients with biliary symptoms. The strength of CT is that it depicts biliary obstruction, its level and character and the surrounding parenchymal organs and vessels clearly with little variability between operators or patients. The diagnostic sensitivity for CBD stones has varied between 65 and 93%. Recent technical advances in the form of helical CT and multidetector CT have made it an equal rival to MRI (Kondo et al. 2005). For bilio-pancreatic tumours, CT has been the primary diagnostic modality for a long time and sensitivities between 90-97% for pancreatic carcinoma detection have been published. When the tumour or stones are small, less than 1 cm in diameter, or it is located periampullarily, the sensitivity drops markedly to 70-75% (Andersson et al. 2005, Kondo et al. 2005). The weaknesses of CT are the possible allergic reactions to contrast agents, and it causes relatively high exposure to radiation.

Since its introduction, MRCP has been an accurate noninvasive alternative for ERCP. As in CT cholangiography, the diagnostic sensitivity to CBD stones is 92-93% and specificity up to 100%. In case of very small stones (< 0.5 cm), sensitivity drops to 70% (Kondo et al. 2005). For periampullary lesions, the combination of MRI and MRCP seems to be the best non-invasive diagnostic method, with 92% sensitivity and 85% specificity (Andersson et al. 2005). MRCP does not involve contrast agents and gadolinium associated reactions in MRI are very rare (Dillman et al. 2007). If patients are claustrophobic or have metallic implants, such as pacemakers or aneurysmal clips, MRI or MRCP cannot be performed.

The role of EUS is problematic. Availability is still poor, it is highly operator dependent, the higher part of the biliary tract is not visible, the system is relatively expensive and it carries the same risks as standard endoscopy. For CBD stones, the sensitivity and specificity are approaching 100% in experienced hands, and especially small stones (<5mm) are usually well detected (Kondo et al. 2005). For pancreatobiliary malignancies, the accuracy of EUS in diagnosing and staging the tumours continues to be superior compared to CT and MRCP, especially for small (<2.5 cm) ampullary or pancreatic masses (Legmann et al. 1998, DeWitt et al. 2004). The diagnostic

accuracy of suspicious lesions rises with the possibility of combining fine needle aspiration samples (Agarwal et al. 2008). The detection of distant metastasis and peritoneal carcinosis is usually beyond the field of vision and thus, EUS is an examination complementary to CT and MRI/MRCP (Michl et al. 2006).

Since its introduction, ERCP has been the gold standard for visualising the biliary tree. During the last decade, several noninvasive diagnostic methods have evolved and ERCP is nowadays mainly a therapeutic tool. Due to its invasive nature, major or even fatal complications may occur in 1-7% of the procedures, mainly on the therapeutic ones (Salminen et al. 2007). The most common indications for ERCP are treatment of CBD stones and palliation for pancreatobiliary malignancies in the form of stenting. It also allows direct visualisation and biopsies of ampullary tumours (Stroszczynski et al. 2005). ERCP is usually not possible to perform after bilioenteric diversion such as Roux-en-Y hepaticojejunostomy (HJS). In these cases, PTC allows a therapeutic option although it is also associated with a slight risk of complications and even mortality (Weber et al. 2008).

2.5. Laparoscopic cholecystectomy

2.5.1. History

The history of modern laparoscopy began in 1901 when Georg Kelling, a German surgeon, performed the first endoscopic examination of the abdominal cavity to a living dog. In this first laparoscopy, air was introduced through a puncture needle and a cystoscope was used for examination (Kelling 1901). The first series of laparoscopies performed in man were performed by H.C. Jacobaeus, and by 1911 he had performed 115 laparoscopies with one complication that required exploration (Jacobaeus 1911). For most of the 20th century, the indications for laparoscopy were mainly diagnostic and the instruments developed slowly. In 1938, Hungarian Janos Veress developed a spring-loaded needle for draining ascites and evacuating fluid and air from the chest. Its main purpose was to create a therapeutic pneumothorax for treatment of tuberculosis (Veress 1938). He did not suggest it for use in laparoscopy, although its current commercial modifications make it a perfect tool for achieving pneumoperitoneum (Lau et al. 1997).

From the 1960s, the contribution of German gynaecologist Kurt Semm played a major role for the development of modern laparoscopy. He invented the automatic insufflator in 1963, developed numerous laparoscopic instruments over the years and performed a wide range of gynaecological operations. In 1982, he performed the first laparoscopic appendicectomy (Semm 1983, Semm et al. 1991).

Laparoscopic cholecystostomy with stone removal was first performed on an animal model by Frimberger in 1979 (Frimberger et al. 1987). Later, in 1983, Lukichev et al. reported a case of laparoscopic cholecystostomy for acute cholecystitis (Lukichev et al. 1983). German Eric Mühe is considered the true pioneer of LC. He performed the first LC in 1985 with single puncture technique using a modified rectoscope, which had side-viewing optics and a valved instrumentation channel (Muhe 1992, Reynolds 2001). In the early days there was a lot of scepticism against the new operating technique, but after 1986, when the first computer chip television cameras were attached to laparoscopes, the video-guided era of surgery began rapidly. In 1989, Dubois et al. reported of the multipuncture technique (Dubois et al. 1989, Dubois et al. 1990), and it was estimated that by 1992, more than 80 % of the general surgeons in the United States had adopted this new technique (Escarce et al. 1995).

2.5.2. Indications, contraindications and conversion

Cholecystectomy is the most common abdominal operation performed in western countries. In Scandinavia, the annual rate of cholecystectomies has varied between 60 and 140 per 100000 inhabitants after the introduction of LC (Mjaland et al. 1998). Soon after the adoption of laparoscopic technique, it became the gold standard for the treatment of gallstones. Nowadays, 70% to 80% of all cholecystectomies are performed laparoscopically (Rosenmuller et al. 2007). The indications for LC are the same as for open cholecystectomy (OC), i.e. symptomatic or complicated gallstone disease (biliary pain, acute cholecystitis, chronic cholecystitis). Annually about one million new patients in the United States are diagnosed with gallstones, of which 50-70% are asymptomatic at the time of diagnosis (Sakorafas et al. 2007). The prevalence of gallstone disease in Finnish males is 9% and in females 16% (Domellof et al. 1984), and rises with advancing age in both genders. At the age of 60, 30% of females have gallstones and by the age of 80, 60% of both men and women have them (Domellof et al. 1984, Misciagna et al. 1996). Each year, 1-4% of the patients with asymptomatic gallstones will develop biliary symptoms and approximately 20% within twenty years after the diagnosis (Sanders et al. 2007). Because most of these patients remain asymptomatic throughout their lives, the wait-and-see policy is suitable for their vast majority. There are certain subgroups where selected LC is indicated (Table 1).

Table 1. Indications for selective cholecystectomy for asymptomatic gallstone disease (modified from (Sakorafas et al. 2007))

Clear indications
Risk of malignancy
Large gallstones (> 3 cm)
Porcelain gallbladder
Gallstones and large gallbladder polyps (> 1 cm)
Certain ethnic groups or areas with high prevalence of gallbladder cancer
Any polypoid lesion of gallbladder in patients with PSC
Gallbladder stones with simultaneous CBD stones
Immunosuppressive patients (transplant patients)
Prolonged total parenteral nutrition
Chronic haemolytic conditions
Relative indications
Increased risk of conversion to symptomatic disease
Gallstones > 2 cm
Gallstones detected by age 50
Small gallstones (< 3 mm)
Non-functioning gallbladder
Diabetes mellitus
Non-specific upper abdominal pain with presence of gallstones
Questionable indications
Gallbladder stones detected during another abdominal operation

The most common contraindications to LC are the same patient dependent factors that are usually contraindications to any operation requiring general anaesthesia: severe cardiopulmonary disease or other comorbid disease which excludes operation (Stuttmann et al. 1995). Patients who are usually not eligible for LC include those with generalized peritonitis, septic shock, severe acute pancreatitis, hemodynamic instability, end-stage liver cirrhosis, severe coagulopathy unresponsive to treatment, known cancer of gallbladder, and cholecystoenteric fistulas (Bowers et al. 2006). In addition, patients in the first or third trimester of pregnancy should not undergo LC.

Originally, there was a long list of contraindications to LC, including morbid obesity, acute cholecystitis, previous upper abdominal operations, biliary pancreatitis, advanced age, and CBD stones. With increasing surgical

experience, most of these have changed from absolute contraindication to risk factor for conversion to OC. The risk factors for conversion can be divided in three categories: patient-related, disease-related, and surgeon-related.

Patient-related factors

Male gender has been associated with higher conversion rates in several studies (Livingston et al. 2004, Simopoulos et al. 2005, Pavlidis et al. 2007, Shamiyeh et al. 2007), probably because men tend to have a more severe disease (Lein et al. 2002). Two to four-fold conversion rates are reported in male patients (9.1% to 12.9%) as compared to female patients (3.9% to 5.3%). With advancing age, there is also a tendency towards severe acute or gangrenous cholecystitis, higher incidence of CBD stones, as well as comorbid diseases, and many patients have had previous abdominal operations (Brunt et al. 2001). Conversion rates ranging from 9% to 35% have been reported in patients aged over 80 years (Brunt et al. 2001, Bingener et al. 2003). For obese patients, LC has the same advantages as for non-obese patients, but morbidity and the risk for conversion are higher (Li et al. 2007). Highly varying conversion rates are reported, between 0% and 50% (Sperlongano et al. 2002, Pavlidis et al. 2007), although, in larger series, no significant difference is seen between obese and non-obese patients (Gatsoulis et al. 1999, Hawn et al. 2005, Simopoulos et al. 2005). Previous abdominal surgery is a clear risk factor for conversion from LC to open operation mainly because of adhesion formation, although the extent of adhesions cannot be predicted with certainty preoperatively. Karayiannakis et al. reported that over two-thirds of the patients who had previously undergone upper abdominal operation had adhesions, and over 50% of these required adhesiolysis. In lower abdominal operations, the rates are 59% and 18%, respectively (Karayiannakis et al. 2004). The risk for conversion after upper abdominal operations is nearly 20% (Schirmer et al. 1995, Karayiannakis et al. 2004) and after lower abdominal operations 2%-9% (Schirmer et al. 1995, Alponat et al. 1997, Karayiannakis et al. 2004, Akyurek et al. 2005). In emergency setting, the risk for conversion from LC to OC is nearly tenfold when compared to elective LC. In addition, morbidity rises up to fivefold (Rosen et al. 2002, Johansson et al. 2003).

Disease-related factors

Several disease-related factors have been associated with higher conversion rates. Thickened gallbladder wall (> 3.5 mm) at preoperative ultrasound has up to sixfold increase in the rate of conversion (Hutchinson et al. 1994, Rosen et al. 2002). For acute cholecystitis, the timing of operation is crucial, and LC should be performed within 48 hours of admission. After that, the conversion rate rises considerably, up to 25%, and in case of gangrenous cholecystitis, up

to 35% (Merriam et al. 1999, Habib et al. 2001, Kanaan et al. 2002, Peng et al. 2005). If the acute cholecystitis is treated conservatively and delayed LC is performed, typically 6-8 weeks after the original admission, the conversion rate to OC is at the same level or even higher than in the acute phase (Johansson et al. 2003, Yamashita et al. 2007). Even if delayed LC is chosen, about 25% of the patients require an emergency operation because of progressive disease (Johansson et al. 2003).

An estimated 8% of the cholecystectomies are performed because of gallstone pancreatitis (Taylor et al. 2004). These patients have an increased risk for conversion, ranging from 0 to 18% (Tang et al. 1995, Ammori et al. 2003, Taylor et al. 2004). As in acute cholecystitis, the timing of operation has been discussed extensively in the literature in case of gallstone pancreatitis. Especially in case of mild disease, when abdominal tenderness is improving and serum amylase and bilirubin levels have a downward trend, LC should be considered during the same hospital stay (Tang et al. 1995, Taylor et al. 2004). The Mirizzi syndrome is generally considered a contraindication to laparoscopic approach, conversion rates ranging from 74% to 100% are reported, depending of the type of disease (Lai et al. 2006) (Table 2). Incidental gallbladder carcinoma is found in up to 2% of the patients undergoing LC for symptomatic gallstone disease; especially in elderly patients with acute cholecystitis, the incidence is higher. If carcinoma is suspected, the conversion to OC should be performed without hesitation (Liu et al. 1997, Lam et al. 2005).

Table 2. Conversion rates for specific risk factors

Patient-related		Disease-related	
Gender		Thickened gallbladder wall	6 x
male	9-13%	Acute cholecystitis	8-36%
female	4-5%	early	11-24%
Advanced age	9-35%	delayed	24-36%
Obesity	8-50%	Biliary pancreatitis	0-18%
Previous abdominal surgery		Mirizzi syndrome	74-100%
Upper	19 %		
Lower	2-9%		

Surgeon-related factors

The complication and conversion rate has been shown to decrease with the surgeon's experience. In the early reports, the learning curve varied from 10 to 30 operations (The Southern Surgeons Club 1991, Moore et al. 1995); also an

institute-specific learning curve was noted to be around 100 LCs (Liu et al. 1996). In more recent studies, the learning curve appears to be remarkably longer and a steady improvement persists for about the first 200 LCs, resulting in fewer conversions and reduction in operating time (Voitk et al. 2001), although there is a considerable individual-specific variation in this: some surgeons are naturally gifted and gain skills very rapidly, and some will never reach the required skills necessary for performing LC proficiently. The vast majority of surgeons, however, reach proficiency with good training (Sir Alfred 2003).

It has been stated that in case of technical difficulties, the conversion to OC is wisdom rather than complication and even a single avoided BDI during the career of the surgeon supersedes the transient disappointment of conversion (Ishizaki et al. 2006).

2.5.3. Complications

LC carries many of the same risks as OC, and the overall complication rate is 3%-5% (Lee et al. 1993, Ovaska et al. 1996, Shea et al. 1996), although a rate as high as 12% has been reported (Veen et al. 2008). There are certain specific complications associated with laparoscopy. These can be divided into four different categories: abdominal wall complications, visceral or vascular complications, retained foreign bodies, and pneumoperitoneum-related complications. The most common complications are associated with the creation of pneumoperitoneum and trocar insertion, namely trocar site bleeding, visceral or vascular puncture and solid organ injuries (Ponsky 1991). Other abdominal wall complications include trocar site infection, hernia and fistula. Foreign bodies may remain after LC, the inorganic bodies are usually lost clips and the organic ones lost gallstones (Zehetner et al. 2007). Pneumoperitoneum-related complications include cardiopulmonary complications, venous thrombosis and various minor complications, such as subcutaneous emphysema (Soper et al. 1994, Cullen 2006).

Besides these general complications, there are certain complications highly specific to cholecystectomy, namely BDIs. In the era of OC, the incidence of BDIs remained at 0.1% - 0.2% (Roslyn et al. 1993), but after the introduction of LC, the rate has at least doubled (Flum et al. 2003, Nuzzo et al. 2005).

2.5.3.1. Mechanisms and incidence of the biliary tract injuries

The incidence of BDIs depends on the classification system used. If leakages from the cystic duct and the gallbladder bed are included, the reported incidence has varied between 0.8% and 2.8% (Wherry et al. 1996, Adamsen et al. 1997, Fletcher et al. 1999) and even in a steady state, the rate of injuries is between 0.4% and 1.0% (Nuzzo et al. 2005, Veen et al. 2008).

The usual mechanism behind cystic duct leakage is the spontaneous slippage or malposition of the clip (Regoly-Merei et al. 1998). Most major bile duct injuries (97%) are caused by misinterpretation of perceived anatomy, and only in 3%, there are clear faults in technical skills (Way et al. 2003). Strictures following LC can occur either acutely or late in the postoperative phase and are usually caused by blindly applied clips, misplaced clips, and diathermy-associated thermal injury (Way et al. 2003). Several different factors are associated with increased risk of BDI (Table 3).

Table 3. Risk factors associated with bile duct injuries

Surgeon
Learning phase
Operation time >120 min
Institutional learning curve
Misperception
Amount of voltage used in diathermy
Circumstances
Acute / chronic cholecystitis
Adhesions (Mirizzi syndrome)
Bleeding
Obesity
Anatomy
Anatomical variations
Short cystic duct
Instruments
0° laparoscope
Inadequate image quality
General condition of instruments and diathermy

2.5.3.2. Classification of the biliary tract injuries

Several different classification systems have been proposed in the last 25 years but none of them has proved to be superior compared to any other. All of them have certain advantages and disadvantages over each other. In the early 1980s, Bismuth et al. presented a classification system based on the level of healthy biliary mucosa available for biliary anastomosis (Bismuth et al. 2001). It is mainly used for classification of biliary strictures. In 1994, Siewert et al. introduced their classification, which includes also the possible arterial injuries

but does not tell the level of injury (Siewert et al. 1994). In 1995, Strasberg et al. presented their classification that describes also the level of injury but does not take into account the possible additional vascular injuries (Strasberg et al. 1995). The Amsterdam classification was introduced in 1996 (Bergman et al. 1996). It is the simplest of these classifications but does not describe the level of the injury or additional injuries. In 2000, Neuhaus et al. presented their classification (Neuhaus et al. 2000) that describes all the possible BDIs, but not the level of injury or vascular lesions. The Stewart-Way classification of 2004 ignores all the injuries associated to cystic duct and peripheral radicals (Stewart et al. 2004). The Hannover classification is the most recent one and was introduced in 2007 (Bektas et al. 2007). It describes almost every possible variants including the type and level of the BDI and all the different vascular injuries. Although this system is comprehensive, it may be too detailed to be easily mastered. In general, classification of injuries aids in comparison and reporting of them.

2.5.3.3. Diagnosis of the biliary tract injuries

BDIs are detected intraoperatively with a highly variable rate, and rates between 21% and 81% have been reported (Krahenbuhl et al. 2001, Seeliger et al. 2002), although, in the majority of reports, about one-third of the BDIs are noticed during operation (Regoly-Merei et al. 1998, Way et al. 2003, Sicklick et al. 2005). If BDI is suspected, an intraoperative cholangiography (IOC) should be performed without hesitation. IOC naturally gives a good roadmap but its routine use is still under debate. Five small randomized trials have been reported in the literature comparing routine IOC with selective or no use in cholecystectomy (both OC and LC) (Hauer-Jensen et al. 1986, Soper et al. 1992, Murison et al. 1993, Nies et al. 1997, Tusek et al. 1997). Hauer-Jensen et al. noticed almost three-fold morbidity in the IOC group, otherwise no major differences were identified between the groups. The current practice favours selective use of IOC, although there is a lot of surgeon, area, and country-dependent variability in normal practice. The downsize aspect of IOC is that BDIs may occur afterwards and that BDI may even originate at IOC by catheter manipulation (Thomson et al. 2003, Massarweh et al. 2007).

In the majority of the cases, the diagnosis is delayed and there is no single standard approach to the diagnosis. Symptoms may appear weeks or months, or even years later (Chapman et al. 2003). Any patient who fails to recover within 48 hours after LC should be suspected to have BDI. The early symptoms are non-specific: mild abdominal pain, mild fever, nausea, vomiting, and possibly a slight elevation in liver chemistry. The non-specificity of the early symptoms may further delay the diagnosis, and usually only when jaundice or sepsis becomes manifest, the actual diagnosis is suspected (Gouma et al. 2002). Abdominal US or CT should be done promptly for detection of fluid

collections, and subsequent percutaneous drainage of any collections performed to confirm the diagnosis (Wudel et al. 2001). In the next phase, the extent of BDI should be determined by means of ERCP; if a total blockage of the biliary tree is detected, PTC or MRCP is required. In case of major BDI, concomitant vascular lesions are present in one-third of cases (Stewart et al. 2004) and therefore CT angiography is recommended for exclusion of additional vascular lesions (Chapman et al. 2003). If late stricture is suspected, cholangiography, nowadays in form of MRCP, is the gold standard for screening methods (Baron et al. 2002). If the diagnosis of BDI is delayed, laparotomy is not recommended prior to a proper classification of the injury (Gouma et al. 2002).

2.5.3.4. Treatment of the biliary tract injuries

The treatment of BDIs is complex and demanding and requires an experienced team including radiologist, endoscopist and a hepatobiliary surgeon. The definitive treatment should not be tied to local habits or standards, but rather to what is best for the single patient, and all the possible options from endoscopic treatment to liver transplantation should be considered. Prompt decision making is essential as delay increases morbidity and mortality and early definitive therapy is crucial for the patient's outcome (Boerma et al. 2001, Nordin et al. 2002).

If BDI is suspected and the surgeon is inexperienced, biliary drainage without exploration is recommended and the patient should be transferred to a tertiary center (Gouma et al. 2002) or if available, an outreach service of a "moving" surgeon should be utilized (Silva et al. 2008). With adequate expertise in biliary surgery, conversion to laparotomy and making of IOC is advisable. If the leakage is from the cystic duct or hepatic radicals, reclipping or suturing of the defect is usually sufficient therapy. When only a small choledochotomy without extensive damage is found, reconstruction over T-tube may be attempted, although there is a tendency for late biliary strictures (Gouma et al. 2002). In case of extensive injury, reconstruction with Roux-en-Y hepaticojejunostomy is generally considered the operation of choice (Boerma et al. 2001, Sicklick et al. 2005).

When the diagnosis of BDI is delayed, the therapy after proper classification includes drainage of intra-abdominal fluid collections and biliary decompression either by ERCP or PTC. In case of minor injuries ERCP usually provides sufficient therapy. There is one randomized study comparing biliary stenting with combination of biliary stenting and sphincterotomy after biliary leak (Mavrogiannis et al. 2006). In both groups, the intervention was 100% successful and no further interventions or surgery were needed. Complications related to endoscopic sphincterotomy are reported in nearly ten percent of patients (Freeman et al. 1996, Prat et al. 1996). In low-grade leaks either

endoscopic sphincterotomy or stenting alone is usually sufficient treatment for biliary leaks (Sandha et al. 2004).

In delayed setting the chance for immediate repair is usually lost, but if the patient is stable and no evidence of biliary peritonitis or sepsis is present, the reconstruction of the biliary tree can often be made immediately after the preoperative imaging (Chapman et al. 2003), although some authors recommend delayed reconstruction also for these patients (Gouma et al. 2002). If BDI is complicated by biliary peritonitis, the definitive reconstruction should be done after the infection and inflammation have completely subsided, usually 2-3 months after the initial incident (Lillemoe et al. 2000, Gouma et al. 2002).

There are two main treatment options for biliary strictures. Lillemoe et al. suggested Roux-en-Y HJS for every patient and reported excellent outcomes in the majority (98%) of patients (Lillemoe et al. 2000). On the other hand, Bergman et al. reported successful outcome in 80 % of patients after endoscopic dilatation and stenting, and suggested it as an initial treatment for strictures (Bergman et al. 2001). If stenting fails, i.e. a stricture recurs after a period of twelve months' stenting, a surgical reconstruction should be considered (Bergman et al. 2001).

2.5.3.5. Results of the treatment

Iatrogenic BDIs are associated with increased morbidity and mortality, and the treatment is time-consuming and expensive. When compared to uneventful LC, the cost is up to 26-fold and the average time of postoperative period is 378 days (Savader et al. 1997). Mortality rates between 0% and 7% have been reported (Savassi-Rocha et al. 2003, de Santibanes et al. 2006).

In severe lesions, Stewart et al. noticed four factors associated with either the success or failure of treatment: correct preoperative diagnosis, choice of surgical repair, surgical technique, and experience of the surgeon (Stewart et al. 1995). Only 4% of HJSs performed without cholangiography were successful, and when cholangiography was completed, 84% of the repairs were successful. In case of complete transection, 63% of the primary HJSs were successful whereas none of the end-to-end repairs succeeded. All the successful anastomoses were done in a single layer. Repair attempts done by a primary surgeon were successful in 17% of cases as compared to a 94% success rate of an experienced biliary surgeon.

In selected cases of biliary leaks, overall success rates between 90% - 100% are reached with therapeutic endoscopy (Boerma et al. 2001, Mavrogiannis et al. 2006). Successful recovery rates between 84% and 98% after surgical therapy

at a tertiary referral centers have been reported (Lillemoe et al. 2000, Gouma et al. 2002, Savassi-Rocha et al. 2003). Despite the excellent objective and functional outcomes, Boerma et al. noticed impaired quality of life after BDI. The severity of the injury or its type were not associated with worse outcome but rather with the length of treatment (Boerma et al. 2001, de Reuver et al. 2008).

3. AIMS OF THE STUDY

The purpose of the present work was to study the early diagnosis and treatment of the common CBD disorders, i.e. stones, malignant strictures and iatrogenic lesions. In more detail, the specific aims were:

1) To analyze the value of common liver function tests in separating patients with malignant CBD strictures from those with stones.

2) To clarify whether the degree of CBD dilatation assists in separating patients with malignant strictures from those with stones.

3) To analyze the occurrence of BDIs during LC in and around Turku University Central Hospital, with special attention paid to the early diagnosis of the lesion and the sex distribution of the patients in different severity classes.

4) To analyze the treatment of BDIs at Turku University Central Hospital and long-term results of the treatment.

4. PATIENTS AND METHODS

All the patients were treated at the Department of Surgery, Turku University Central Hospital (TUCH) between January 1995 and November 2003.

4.1. Extrahepatic cholestasis (Studies II and IV)

Studies II and IV were retrospective studies evaluating the value of liver function tests (Study II) and the degree of CBD dilatation (Study IV) in differential diagnosis of extrahepatic cholestasis. Consecutive patients undergoing ERCP between August 2000 and November 2003, for whom the cause of extrahepatic cholestasis proved to be either a malignant stricture or a CBD stone, were included. Patients with repeated ERCP procedures, benign strictures or with postoperative complications were excluded. After these criteria, there were 244 patients, but there were ten patients with missing ERCP films and 22 patients with missing laboratory values. 212 patients were included in the final analysis. The patients were divided into two groups according to the ERCP findings: stricture group and stone group.

In the malignant stricture group, there were 103 patients, of whom 42 were males and 61 females, with the mean age of 70 (range 22-89) years. The stricture was distal or ampullar in 73 patients, in the medial part of CBD in 21 patients, and in the proximal part in nine patients. Ampullary tumours were identified in six patients, pancreatic carcinoma in 52 patients, cholangiocarcinoma in 34 patients and the remaining eleven cases were various metastatic tumours. Four patients had liver metastases at the initial imaging studies, four patients had symptomatic acute pancreatitis, and four patients had been initially treated because of CP. Seven patients with either acute or chronic pancreatitis were eventually diagnosed with pancreatic carcinoma and one patient had distal cholangiocarcinoma. Three patients with malignant bile duct stricture had simultaneously common bile duct stones

In the stone group, there were 109 patients, of whom 34 were males and 75 females, with the mean age of 68 (range 22-98) years. Eight patients had acute pancreatitis and three patients had acute cholangitis. 61 patients had had their gallbladders operated earlier; of the 48 patients with their gallbladder in situ, 36 had gallbladder stones. The CBD stones were less than one centimeter in diameter in 50 patients and between one and two centimeters in 53 patients, only six patients had stones with a diameter of more than two centimeters. Seventy patients had a single stone, twenty patients had two to five stones and the rest had more than five stones.

Blood samples (plasma ALT, AP, GGT, and bilirubin) were obtained from patients in the morning before ERCP and after an overnight fast (study II).

The ALT activity in plasma was determined in Hitachi 917 analyzer by using the ECCLS recommended assay (Klauke et al. 1993) with reagents supplied by Roche (Roche Diagnostics, Mannheim, Germany). The between-run coefficient of variation (CV) was 4.8% at 48 U/l. The upper limit of reference interval is 45 U/l for females and 60 U/l for males.

The AP activity in plasma was determined in Hitachi 917 analyzer by using the Scandinavian recommended assay (Jarvisalo et al. 1989) with reagents supplied by Roche (Roche Diagnostics, Mannheim, Germany). The between-run CV was 2.6% at 253 U/l. The upper limit of reference interval is 270 U/l.

The GGT activity in plasma was determined in Hitachi 917 analyzer by using the ECCLS recommended assay (Klauke et al. 1993) with reagents supplied by Roche (Roche Diagnostics, Mannheim, Germany). The between-run CV was 2.6% at 49 U/l. The upper limit of reference interval is 75 U/l for females and 90 U/l for males (Jarvisalo et al. 1989).

The bilirubin concentration in plasma was measured in Hitachi 917 analyzer by using the Roche acidic diazo method with reagents supplied by Roche (Roche Diagnostics, Mannheim, Germany). The between-run CV was 2.6% at 27 μmol/l. The upper limit of reference interval is 20 μmol/l.

In Study IV after the complete opacification of the extra- and intrahepatic bile ducts had been achieved in ERCP, the CBD diameters were manually measured at the widest point on the films. All measurements were corrected for magnification with the aid of the diameter of the endoscope in the duodenum.

4.2. Iatrogenic bile duct injury (Studies I and III)

Between January 1995 and April 2002, a total of 3736 LCs (2627 female patients and 1109 male patients) were performed in and around TUCH. In these operations 34 patients sustained BDIs, of whom two patients with gallbladder and biliary tract carcinomas, respectively, were excluded. TUCH is the only hospital in the area with MRCP and ERCP facilities and, therefore, almost all the patients with suspected BDI in this area are treated in TUCH.

In the final analysis, there were 32 patients with BDI, of whom 25 (78%) were females and 7 (22%) males. The median age of the patients at the time of LC was 44 (range 17-79) years. Four (12%) patients were treated because of acute cholecystitis, one (3%) patient was waiting for renal transplant and was operated for asymptomatic gallstones, and most of the patients (85%) were

operated for symptomatic gallstones. Eleven (34%) operations were performed by residents of surgery with or without a senior surgeon and 21 (66%) by an experienced laparoscopic senior surgeon. Eleven (34%) patients underwent operation at TUCH, one (3%) patient was operated on the private sector, and twenty (63%) patients were operated at one of the six district hospitals. The patients were divided into subgroups by the type and severity of BDI according to Amsterdam classification (Bergman et al. 1996) (Figure 5).

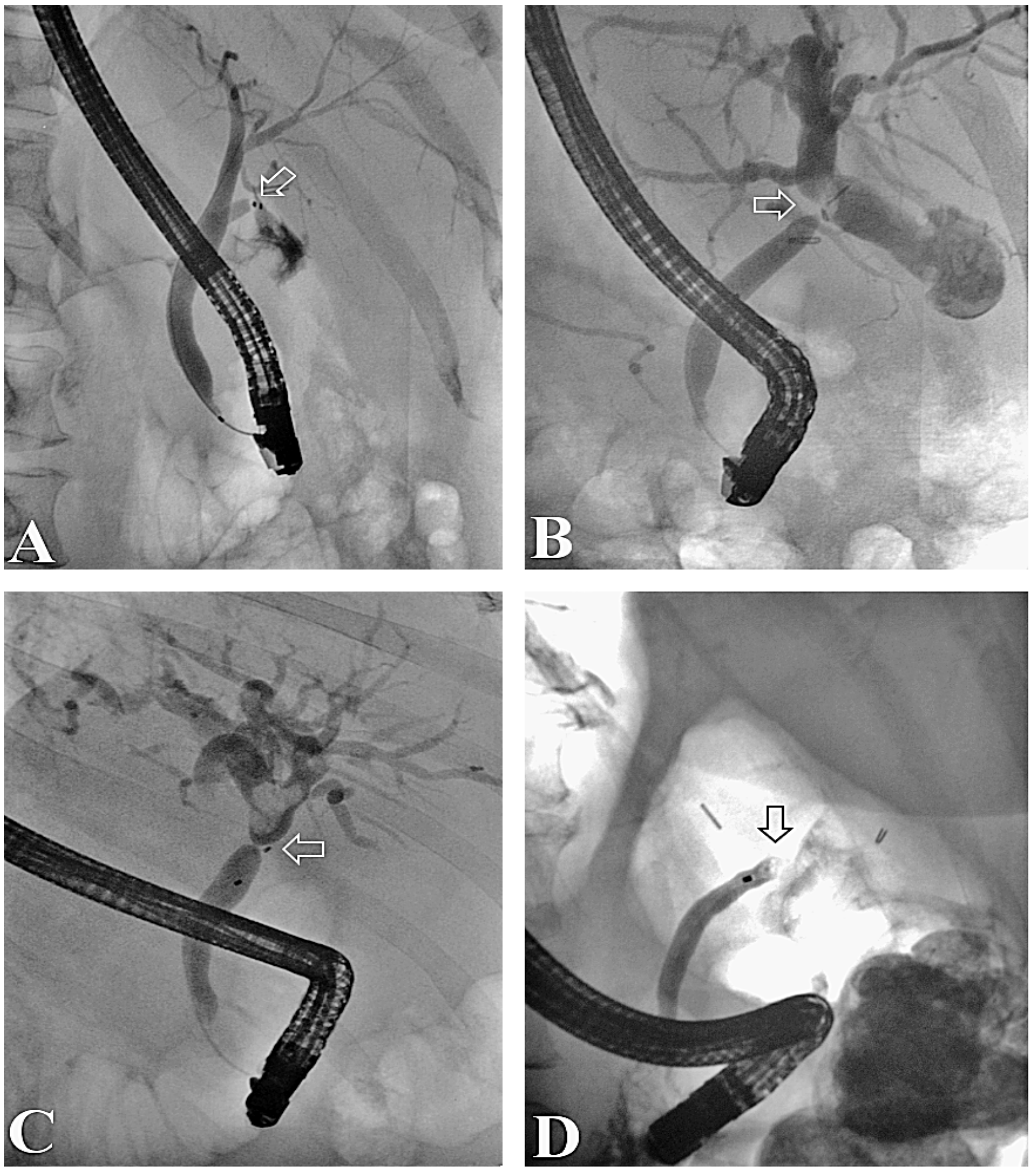

Figure 5. Amsterdam classification. A, leakage from cystic duct or hepatic radical. B, Major BDI with leakage. C, Bile duct stricture without leakage. D, complete transection or excision of CBD.

Patient, preoperative, intraoperative, postoperative, and cumulative follow-up data were collected retrospectively from the hospital records and electronic archives of the hospital district of southwestern Finland. All the patients were also interviewed by phone in May 2006 when the median follow-up time was 7.5 (range 4-11) years (Study III).

4.3. Statistics

In Study I, the comparison between genders was done using Fisher's exact tests and Chi-square tests.

In Study II, the differences between the stricture and the stone groups as well as the gender-specific differences in ALT, AP, GGT, bilirubin and age variables were compared by Mann-Whitney U-test and Wilcoxon two-sample test. The association of age with the stone group was examined by Chi-square statistic. In Study IV, the differences between the stricture and the stone groups were compared by Wilcoxon two-sample test. The association of age, sex, common bile duct diameter and bilirubin with the stricture group was examined by multiple regression analysis. P-values below 0.05 were considered statistically significant. Receiver Operating Characteristics (ROC) analyses were carried out to compare the ability of the ALT, AP, GGT, and bilirubin tests as well as CBD diameter to classify correctly patients into the stricture and stone groups at all possible cut-off limits. Sensitivity-specificity plots were used to evaluate the optimal limit of clinical decision making. Statistical analyses were performed with SAS for Windows software, ver. 8.02 (SAS Institute, Cary, NC) and GraphROC for Windows software, ver. 2.0 (Kairisto et al. 1995)

5. RESULTS

5.1. Laboratory values and degree of common bile duct dilatation (II, IV)

The median (range) values for common plasma liver function tests are shown in Table 4. Patient age did not show any association with the probability of having a malignant stricture. Male gender was significantly associated with higher bilirubin (p=0.045) values. No gender specific effects were seen for ALT, AP, GGT, and CBD diameter. Plasma bilirubin (p<0.001), AP (p<0.001), ALT (p=0.040), and CBD diameter (p=0.004) levels were significantly higher in patients with malignant strictures than in those with stones. GGT values also seemed to be higher, although the difference did not reach statistical significance (p=0.053).

Table 4. The median (range) values for the plasma liver function tests and CBD diameter for the patients with malignant bile duct strictures (n=103) and for those with CBD stones (n=109) on ERCP. Where marked, stricture-group is significantly different (*p<0.05, **p<0.01 or ***p<0.001) from stone-group, when the two sided probabilities of the two groups are compared by the Mann Whitney U test.

	ALT, U/l	AP, U/l	GGT, U/l	bilirubin, µmol/l	CBD, mm
Stricture	141 (13-946)*	905(202-5722)***	511 (19-2350)	188(11-861)***	16(5-33)**
Stone	109(7-990)	564 (97-3093)	426 (16-3941)	33 (4-241)	15 (6-29)

5.2. ROC analysis (II, IV)

The ROC curves for laboratory values are shown in Figure 6 and CBD diameter in comparison to bilirubin in Figure 7. As all values originated from the same individuals, with no missing values, the areas under the curves (AUC) could be compared by the paired method of Hanley & McNeil (Table 5) (Hanley et al. 1983). Bilirubin had the highest area under the curve, and the AUC for bilirubin was significantly (p=0.0001) higher than that for AP, which was the second best discriminating test. A completely random test would have a ROC curve approaching the function y=x. To include a sampling error comparable to that of the included laboratory tests, a "random" ROC curve was produced by generating a random number for each patient. The AUCs for ALT and GGT were not significantly different from the AUC of these random values. When combining the bilirubin test with AP, ALT, GGT, and/or CBD diameter test(s),

the diagnostic accuracy did not improve when compared to bilirubin test alone (results not shown).

Table 5. AUC in the ROC-analysis. The given p-values are for pairwise comparison of AUC of each test when compared to plasma bilirubin and to random values.

	Areas under the ROC-curves	Pairwise comparison of AUC to bilirubin (p-value)	Pairwise comparison of AUC to random value (p-value)
ALT	0.582	< 0.0001	0.1722
AP	0.716	0.0001	0.0001
GGT	0.577	< 0.0001	0.2018
CBD	0.617	< 0.0001	0.0399
bilirubin	0.867	-	< 0.0001

Sensitivity-specificity plots were generated to evaluate the clinical sensitivities and specificities of plasma bilirubin (Figure 8), AP, and CBD diameter at all cut-off limits. The cut-off values for plasma bilirubin and AP in diagnosing malignant biliary strictures with the highest clinical accuracy were 145 µmol/l and 651 U/l, respectively. Plasma bilirubin had a superior diagnostic efficiency compared to plasma AP ($p=0.0001$) and CBD diameter ($p<0.0001$). At a cut-off value of 145 µmol/l, plasma bilirubin distinguished malignant bile duct strictures from stones with a sensitivity of 66% and specificity of 91% (Table 6), whereas AP at the cut-off value of 651 U/l had a sensitivity of 73% and specificity of 63% (data not shown). With plasma bilirubin cut-off value of 145 µmol/l, four out of five patients were categorized correctly. Although the diameter of CBD reached statistical significance in Mann-Whitney U-test ($p=0.0038$) and in ROC analysis when comparing to random-value ($p=0.0399$), the difference in median values on cholangiograms was only one millimeter.

Table 6. Predictive values, clinical sensitivities, clinical specificities and accuracy values for selected cut-off limits of plasma bilirubin in the differential diagnosis of the malignant bile duct stricture from CBD stone.

Plasma bilirubin (μmol/l)	Probability of stricture, % (= predictive value)	sensitivity, %	specificity, %	accuracy, % (proportion of correctly classified patients)
≥ 24	60.1	95.1	46.8	68.9
≥ 60	65.8	90.3	60.6	74.1
≥ 100	73.2	80.6	75.2	77.7
≥ 145	85.8	66.0	90.8	79.5

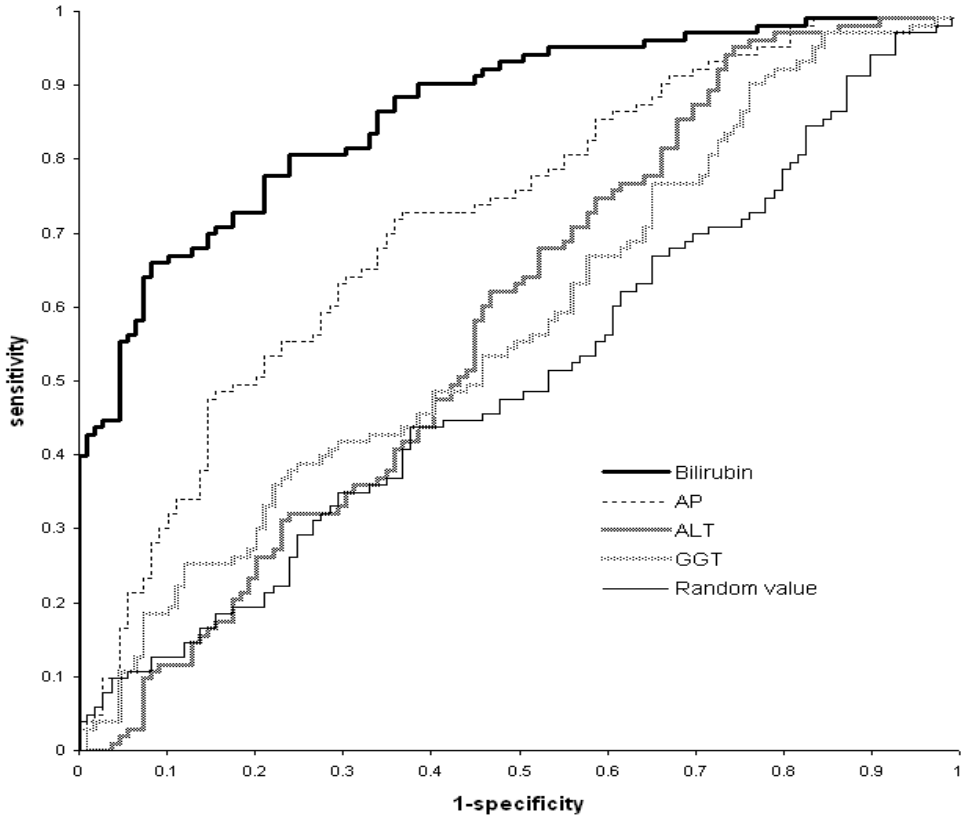

Figure 6. ROC-curves for bilirubin, AP, ALT, GGT and random value in the differential diagnosis of the malignant biliary stricture from CBD stone.

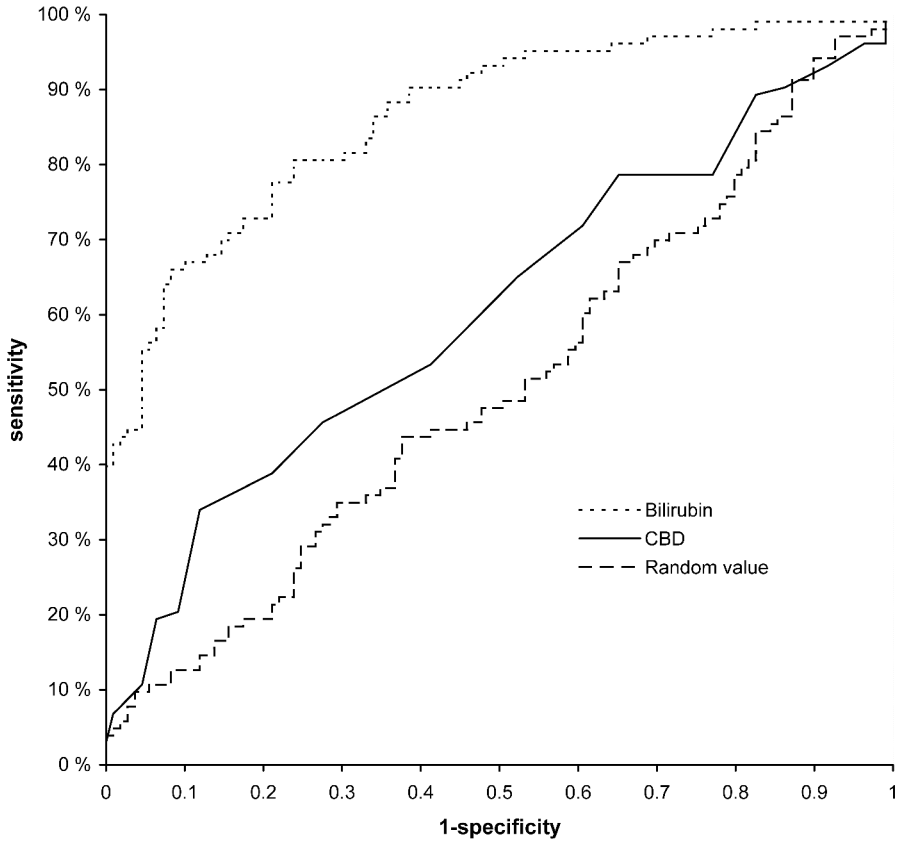

Figure 7. ROC curves for bilirubin, CBD diameter (CBD) and random value in the differential diagnosis of the malignant biliary stricture from CBD stone. AUC for bilirubin and CBD are 0.867 and 0.615, respectively.
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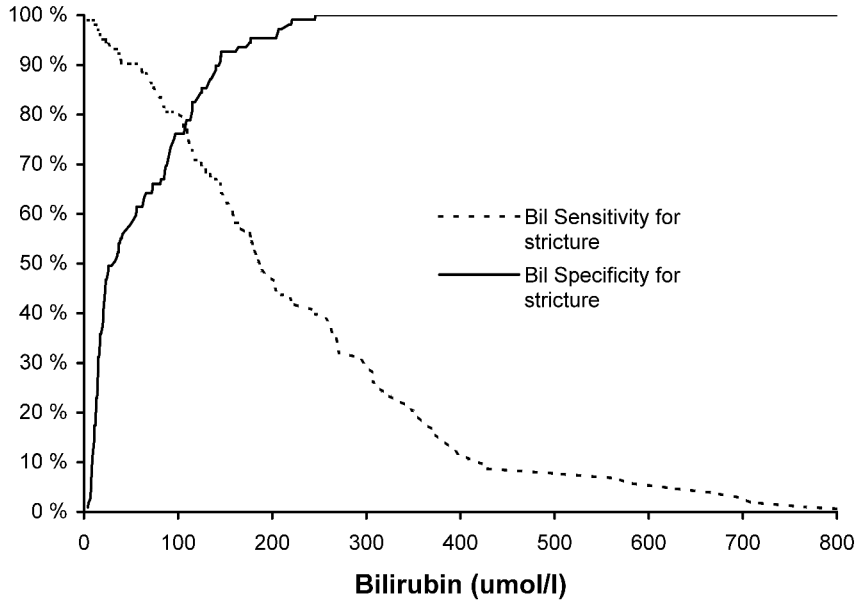

Figure 8. Clinical sensitivities and specificities for plasma bilirubin in differential diagnosis of the malignant bile duct stricture from CBD stone. *Reproduced with permission of the copyright holder.*

5.3. Iatrogenic bile duct injuries (I, III)

The total risk of BDI in the whole population was 0.86%, 0.95% for females and 0.63% for males (p=0.33). In severe injuries (Amsterdam type B, C, and D) 19 out of 22 patients (86%) were females. The risk of severe injuries for females was 0.72% and for males 0.27% (p=0.10). 88% of patients who underwent laparotomy were females. For Amsterdam type A injuries, the risk was relatively similar for both genders, females 0.23% and males 0.36% (p=0.50).

Only 19% of the BDIs were detected intraoperatively. The median diagnostic delay was 10 days (range 0-181 days). Certain technical problems were encountered in 69% of the operations (Table 7). One (3%) patient was treated percutaneously, 18 (56%) endoscopically, and 13 (41%) were operated. The overall mortality was 3% (one patient).

Table 7. Technical problems during laparoscopic cholecystectomy were reported in 22 out of 32 patients with bile duct injuries. Some patients had multiple problems.

Technical problem	Number encountered
Chronic cholecystitis	9
Obesity	5
Acute cholecystitis	4
Bleeding	4
Short cystic duct	4
Adhesions	3
Rupture of cystic duct	2

The gender and type of treatment in the different severity groups are described in Table 8. All the Amsterdam type A injuries were treated endoscopically with a 90% success rate, one patient died from sepsis. One type B lesion was treated percutaneously, the other four patients required laparotomy. Although, in one patient the definitive therapy of the leakage was endoscopic stenting. Endoscopic treatment was sufficient in seven out of eight patients (87%) with type C lesion, one patient required HJS. All the patients with type D lesions were operated and HJS was the operation of choice.

Table 8. Division of patients with bile duct injury (by gender and treatment modality) according to severity.

	N (total=32)	Female	Male	Endoscopic*	Laparotomy
A	10	6	4	10	-
B	5	4	1	2	3
C	8	8	-	7	1
D	9	7	2	-	9

* endoscopically and percutaneously treated patients

The median follow-up time was 7.5 years (range 4-11 years). One patient has had chronic cholangitis (3%) and three patients (9%) have had one to six episodes of acute cholangitis. One of these patients is on disability pension. Six patients (19%) required repeated endoscopic dilatations, one patient developed CBD stones 5 years after the initial operation, and one patient required operative correction of ventral hernia. Despite repeated procedures, 94% of all

the endoscopically or percutaneously treated patients and 84% of the whole study population have recovered without complications.

6. DISCUSSION

Jaundice, roughly divided into intrahepatic and extrahepatic form, is a clinical challenge. Extrahepatic cholestasis is caused by either a CBD stone or a stricture; of these, stricture most often refers to malignancy. In the early phase of differential diagnosis, when novel imaging studies, such as MRCP or ERCP, giving a definitive diagnosis are seldom available, the clinical workup has to be done with means of readily available tests, e.g. common liver function tests and US.

6.1. Laboratory values in extrahepatic cholestasis

Liver function tests are a selected battery of clinical laboratory tests which usually include ALT, AP, GGT and bilirubin. Although these tests are extremely widely used in clinical practice, their role in clinical decision-making is relatively poorly studied and, usually, there are only the reference limits available to aid physicians in the interpretation of the results of these tests. Normal liver function tests may vary according to the patient's age, sex, medication, comorbid diseases and postprandial state or even in a normal physiological state as in case of pregnancy; thus any abnormalities in these tests must be interpreted within the whole clinical context of the patient (Green et al. 2002).

The predictive value of the common liver function tests in the diagnosis of bile duct stones is widely studied and well documented (Saltzstein et al. 1982, Onken et al. 1996, Prat et al. 1999, Gronroos et al. 2001, Peng et al. 2005). However, increased values of liver function tests are seen also in patients with bile duct strictures (Reichling et al. 1988, Green et al. 2002). As for the role of common liver function tests in differential diagnosis between benign and malignant causes of extrahepatic cholestasis, earlier literature is lacking such kind of scientific efforts. Common knowledge is mainly based on textbooks describing that common liver function tests do not have a place in differential diagnosis of extrahepatic cholestasis, or that these tests have only limited value in this respect.

One earlier study on the value of common liver function tests in differential diagnosis of extrahepatic cholestasis was found (Pasanen et al. 1993). The authors conclude that serum bilirubin and AP are potential tests in differential diagnosis and that high values are suggestive of a malignant disease, which is in accordance with the results of the current study. In addition, in the present study, the ROC analysis was utilized to determine the predictive value of the common liver function tests in extrahepatic cholestasis, and it was found that the bilirubin test is superior when compared to the other liver function tests in

differentiating between malignant strictures and CBD stones, and, further, that even when combining the bilirubin test with AP, ALT and/or GGT test(s), the diagnostic accuracy in extrahepatic cholestasis does not improve any more, when compared to the diagnostic accuracy of the bilirubin test alone. Even if it has been stated that the bilirubin level reflects the severity but not the cause of cholestasis (Rosalki et al. 1999), the present study gave a cut-off value that can be used to discriminate patients with malignant strictures from CBD stones. With a bilirubin cut-off value of 145 µmol/l four out of five patients could be classified correctly.

6.2. Common bile duct dilatation in extrahepatic cholestasis

Earlier studies on the CBD diameter have focused mainly on discussion about the normal width of the CBD (Niederau et al. 1983, Niederau et al. 1984, Bowie 2000), or on factors affecting it. Aging, overweight and previous cholecystectomy are associated with the dilatation (Laks 2002, Daradkeh et al. 2005). In patients planned for elective cholecystectomy (Prat et al. 1999, Shiozawa et al. 2005) or thereafter (Gronroos et al. 2001), dilatation of the common bile duct is associated with increased risk of bile duct stones. There is a certain time lag after the onset of obstruction until the dilatation of the biliary tree. Experimental animal studies have shown that it takes two to three days for the extrahepatic ducts and about one week for intrahepatic ducts to dilate (Shawker et al. 1981, Zeman et al. 1981).

In earlier literature, there are no studies on the role of the degree of bile duct dilatation in predicting the diagnosis in extrahepatic cholestasis. In the current study, the difference in the diameter of CBD between CBD stones and malignant strictures was statistically significant. When compared to the value of plasma bilirubin in differential diagnosis, the degree of dilatation of the CBD seems to be clinically worthless. The only clinical value of CBD dilatation seems to be its ability to demonstrate the presence of extrahepatic cholestasis and direct further examinations.

6.3. Incidence of iatrogenic bile duct injuries and the role of gender

After the introduction of laparoscopic cholecystectomy in the late 1980s, it rapidly replaced open cholecystectomy as the golden standard operation for symptomatic gallstones. Laparoscopic operation has several benefits over open procedures, including shorter hospital stay and sick leave, better cosmetic results, earlier return to normal activity and diminished postoperative pain. Prior to the introduction of LC, the rate of BDIs was around 0.1-0.2% (Roslyn et al. 1993), but shortly thereafter the incidence rose to 0.8-1.4% (Wherry et al. 1996, Adamsen et al. 1997, Fletcher et al. 1999). After the learning curve, the rate is still double as compared to OC, being around 0.5% (Flum et al. 2003, Nuzzo et al. 2005). The classic severe BDI occurs during LC when the cystic

duct and CBD are aligned by traction on the gallbladder, and the CBD, which is mistaken for a cystic duct, is isolated, clipped and divided

Male gender has been reported to be associated with over two-fold risk of iatrogenic BDIs compared to females (Fletcher et al. 1999). In the studies after the introduction of LC, female gender is present in 67-89% of the BDIs (Stewart et al. 1995, Lillemoe et al. 1997, Mirza et al. 1997, Savader et al. 1997, Carroll et al. 1998, Boerma et al. 2001). All of these figures are well in accordance with the present study (78%), but the information on the severity distribution between genders is lacking in all the above-mentioned reports, as was the case in a large nationwide series from USA (MacFadyen et al. 1998), Switzerland (Krahenbuhl et al. 2001), Denmark (Adamsen et al. 1997), Hungary (Regoly-Merei et al. 1998), and Australia (Fletcher et al. 1999). In the current study, the proportion of female patients (86%) seems to be higher in severe lesions (Amsterdam type B, C, and D), and 76% of females had a severe lesion, while the corresponding percentage in male patients was only 43%.

By contrast, there was no difference between female and male patients in the occurrence of cystic duct leaks during LC in the present study. However, this is not surprising, since leakages from cystic ducts are simply due to poor clip placement or slippage of clips.

6.4. Avoiding and treatment of bile duct injuries

Several different conditions have been associated with increased risk of BDI, including acute cholecystitis, acute pancreatitis, cholangitis, scarring of the Calot's triangle, intraoperative bleeding, anatomical variations, misperception and lacking surgical skills (Way et al. 2003, Schmidt et al. 2005, Soderlund et al. 2005). Other factors included are uncontrolled clip placement and liberal use of diathermy. In the current series, only 12% of the BDIs occurred in acute cases. The most common problem encountered was scarring of the Calot's triangle due to chronic cholecystitis in one-third of the cases. Altogether, technical problems were encountered in over two-thirds of the cases. The results of the present study support earlier views in this respect. The surgical technique is the most important aspect in preventing BDIs. Most problems can be avoided by following Hunter's principles (i.e. use of 30º laparoscope, use of combination retraction involving meticulous dissection close to gallbladder-cystic duct junction) and critical view technique, both emphasizing the need to see all the structures before dividing any ductal structures (Hunter 1991, Strasberg et al. 1995, Traverso 1999, Strasberg 2008). Also the role of IOC has been debated since its introduction in 1937 (Mirizzi 1937). Although the role of IOC in preventing BDIs remains unclear, it is an important tool in cases involving anatomic uncertainty and should be used liberally in these cases (Strasberg et al. 1995).

The definitive therapy for BDI depends on the type of the lesion, the timing of its recognition and possible concomitant vascular injury. In the present study, the rate for intraoperative detection of BDI was only 19%, which is well in line with earlier reports (Bergman et al. 1996, Regoly-Merei et al. 1998). If Amsterdam B or D lesion is detected during primary operation and the surgeon has enough experience on biliary surgery, HJS or primary repair over T-tube should be performed. In case of limited surgical competence, only drainage tubes should be placed and the patient should be referred to a tertiary center and reoperated by experienced hepatobiliary surgeons. If the lesion is not detected during primary operation, explorative laparotomy should be avoided before further classification and possible therapy at ERCP (Gouma et al. 2002). In case of total transection, PTC or MRCP give additional information on the proximal part of the biliary tree.

In most Amsterdam type A and C lesions, ERCP and endoscopic measures are not only diagnostic but also therapeutic. Particularly in type A lesions, endoscopic treatment has proved to be very effective and success rates between 89-100% have been published (Bergman et al. 1996, Boerma et al. 2001, Sandha et al. 2004, Mavrogiannis et al. 2006). Our findings are consistent with previous findings in this respect. In biliary strictures (type C lesions), the results of endoscopic treatment have been somewhat disappointing with a success rate of 38% (Bergman et al. 1996). Contrary to earlier studies, in the present study seven of eight strictures (87%) were treated successfully with endoscopic measures only, and only one patient (12%) required HJS. To reach a high success rate for endoscopic therapy in type C lesions, the use of multiple plastic stents as well as rendezvous procedures in difficult cases is of utmost importance (Gronroos 2009). Similarly, the use of removable self-expanding metallic stents may prove essential in endoscopic treatment of type C lesions in the future (Gronroos 2009). In type B and D lesions, Roux-en-Y HJS is generally considered the operation of choice (Boerma et al. 2001, Sicklick et al. 2005). The role of primary repair over a T-tube has been debated, because the anastomosis tends to stricture over the time. However, in the current study, all the strictures encountered were treatable by endoscopic dilatations, and if endoscopic measures fail to overcome the problem, HJS can be performed afterwards. The main goal is prompt treatment within 6-12 months. If the stricture does not resolve within this time HJS should be performed without hesitation.

6.5. Long-term results

In case of BDI, the optimal treatment requires a multidisciplinary team including an interventional radiologist, ERCP and MRCP facilities and an experienced endoscopist as well as a hepatobiliary surgeon. In the most

complicated cases, early referral to a tertiary center is crucial. At tertiary referral centers, specialized in hepato-biliary surgery, the successful outcome after surgical therapy of BDI is around 95% and even over (Gouma et al. 2002, Savassi-Rocha et al. 2003, Schmidt et al. 2005) In earlier studies, the recovery rates have varied between 76% and 87% (Regoly-Merei et al. 1998, Lillemoe et al. 2000). Our findings are in line with previous studies as 84% of the whole study population, 79% of the operated patients, and 94% of the endoscopically treated patients recovered well and are asymptomatic within a median follow-up of 7.5 years. Especially in young patients, possible endoscopic therapy should be utilized as bilio-enteric anastomosis with possible chronic inflammation has been reported to be associated for late development of biliary tract malignancies (Tocchi et al. 2001).

6.6. The clinical implications of the present study

In primary healthcare the first available diagnostic methods in clinical workup of jaundiced patients are usually liver function tests and abdominal ultrasound. The availability of CT and MRI/MRCP is still poor outside of university clinics and waiting times vary from few weeks to few months. The sensitivity and specificity of abdominal US for showing the ductal dilatation is very good and due to its availability US is a perfect method for diagnosing extrahepatic cholestasis. However, the degree of dilatation does not aid in differential diagnosis. The ability of bilirubin to distinguish the patients with CBD stones from malignant strictures usually confirms the clinical suspicion as deeply icteric patients most often have a malignant cause of cholestasis. These findings serve best the physicians working in primary care and in small hospitals as an aid for determining the urgency of the referral for further investigations.

Limitation of the study II is that the laboratory values were determined only once, as dynamic changes may also suggest the possible cause of extrahepatic cholestasis. Limitation of the study IV was that the diameters of CBD were measured by cholangiograms, which may overestimate the CBD diameter. On the other hand, cholangiography allows visualisation of the biliary tract virtually without patient or operator dependent variability, on contrary to US.

The optimal treatment of BDIs requires an experienced multidisciplinary team including a hepatobiliary surgeon, an endoscopist with ERCP experience and an interventional radiologist with MRCP facilities. All of these are usually available only in a university hospital setting emphasizing the centralization of the treatment of BDIs. The current hospital district -system in Finland makes the patient catchment area for every university hospital very rigid, thus diseases needing special attention, as BDIs in the current study, are usually treated in the

only university hospital of each hospital district. Other strengths of the study were that all the patients were available for long-term follow-up allowing long-term quality control for the treatment BDIs as well as for LC. The treatment results for postoperative CBD strictures were very positive compared to most of the previous reports and nowadays more complex strictures are treated endoscopically. Also the attitude to resident training has changed positively and nowadays they are assisted by specialists even after the learning phase of LC. The low number of patients in different subgroups presents a limitation in studies I and III.

7. CONCLUSIONS

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

1. Plasma bilirubin is the best liver function test for distinguishing patients with malignant CBD strictures from those with stones. With a plasma bilirubin cut-off value of 145 μmol/l, four out of five patients are categorized correctly.

2. The degree of CBD dilatation does not play a clinical role in differential diagnosis of extrahepatic cholestasis.

3. The overall incidence of BDIs during LC was 0.86% at the area of responsibility of TUCH. Only one out of five BDIs was detected intraoperatively. Female gender was associated with higher number of BDIs.

4. More than half of the patients with BDI could be treated endoscopically, while the remaining patients had to be operated. In the long-term follow-up of a median 7.5 years, 84% of the patients were asymptomatic.

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