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ASPECTS OF INTERVENTIONAL ENDOSCOPIC TREATMENT OF COMMON BILE DUCT STONES

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Institutet**

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Frontispiece illustrations

Front cover: **Thomas Coe**, (d. 1761). A Treatise on Biliary Concretions: Or, Stones in the Gall-bladder and Ducts. London, D. Wilson and T. Durham, 1757.

Back cover: **Herman Lebert**, (1813-1878). Traité d'Anatomie Pathologie Général et Spéciale ou description et iconographie pathologique des altérations morbides tant liquides que solides observées dans le corps humain. Paris, J.-B. Baillière et Fils, 1857-1861.

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To Heidi

One thing about trains: It doesn't matter where they're going, what matters is, deciding to get on.

Chris Van Allsburg, The Polar Express

ABSTRACT

Background: During the last 30 years, important changes have been introduced in the management of common bile duct stones (CBDS) which can be detected in about 10% of patients undergoing cholecystectomy because of symptomatic gallstone disease. Established minimally-invasive treatment options for CBDS include endoscopic retrograde cholangiopancreatography (ERCP) and laparoscopic common bile duct exploration. A complex and demanding situation occurs if conventional ERCP extraction methods fail because of the large size and/or the location of the CBDS.

Objectives: The hypothesis of the thesis were: 1). The peroperative combination of laparoscopy and endoscopy, with so-called rendezvous ERCP (RV-ERCP) is by comparison with conventional ERCP, a safe and efficient treatment method regarding feasibility in clinical practice, complete stone clearance and ERCP associated complications. 2). Extremely large or so-called difficult CBDS can safely and efficiently be managed with ERCP assisted peroral cholangioscopy in conjunction with laser lithotripsy (LL) or by electrohydraulic lithotripsy (EHL), in order to obtain complete stone clearance.

Methods: Study I and II are descriptive case series. Study I included patients from 2000 through 2001 at the Karolinska University Hospital that was treated with RV-ERCP because of CBDS. Study II included patients from 1995 through 2006 recruited from the Karolinska and Östersunds Hospitals, treated with peroral cholangioscopy assisted EHL or LL due to difficult CBDS. In study III, patients with symptomatic gallstone disease were prospectively enrolled in a comparative case-control study. Patients who underwent laparoscopic cholecystectomy were, depending on the peroperative cholangiography results, either treated for CBDS using RV-ERCP or assigned to the control group if their cholangiograms were negative. Pancreatic proenzymes were analyzed at 0, 4, 8 and 24 hours. Study IV was a nationwide population-based nested case-control study within a cohort of 12,718 ERCP investigations selected from the Swedish Registry for Gallstone Surgery and ERCP (GallRiks) from 2007 through 2009. The outcome of post-ERCP pancreatitis (PEP) was analysed for a number of possible risk factors.

Results: In study I, 34 patients had a RV-ERCP that was successful in terms of biliary cannulation (100%), duct clearance (94%) and no ERCP related complications such as PEP. The operation time was quite long (mean 82 min), but the hospital stay was equal to those who were operated with LC alone. In study II, 44 patients were treated with EHL or LL and overall ductal clearance was achieved in 34 (74%) cases, of which 13 (30%) patients needed repeated sessions. Large stones (>20 mm) were associated with failure. Old age (≥ 80 years) and poor physical condition did not affect clinical outcomes, and a majority of the patients remained free from biliary symptoms for many years at follow-up. In study III, the patients treated with RV-ERCP and the control group without ERCP, had significantly less pancreatic enzyme leakage, 4 hours after the intervention and at later time points, compared with the conventional ERCP group. Inadvertent pancreatic duct cannulation and contrast injection into it, were positively associated with higher levels of pancreatic enzymes. Among 17,787 patients registered in GallRiks and observed in study IV, 12,718 patients with no previous ERCP, were eligible for further analysis. The overall rate of PEP was 3.6%. A 50% reduction in the risk of PEP was noted in patients treated with RV-ERCP compared with those who were cannulated by conventional means (OR 0.5, 95% confidence interval 0.2-0.9, $p = 0.02$). Other factors associated with an increased risk of PEP were young age, prolonged procedure time and elective ERCP.

Conclusion: Taken together evidence is hereby provided that RV-ERCP reduces pancreatic damage and decreases the frequency of PEP. CBDS identified during LC can safely and effectively be managed by RV-ERCP in a routine clinical setting. These findings challenge the current management concept of two-step ERCP for treatment of CBDS. In addition, ERCP is an efficient and safe first line method in the management of difficult CBDS and should be recommended even for old and/or frail patients.

Keywords: ERCP, common bile duct stones, rendezvous, post-ERCP pancreatitis, electrohydraulic lithotripsy, laser lithotripsy.

LIST OF PUBLICATIONS

- I. ***Intraoperative endoscopic retrograde cholangiopancreatography (ERCP) to remove common bile duct stones during routine laparoscopic cholecystectomy does not prolong hospitalization: a 2-year experience.***
Enochsson L, Lindberg B, **Swahn F**, Arnelo U.
Surg Endosc 2004;18:367-371.
- II. ***Ten years of Swedish experience with intraductal electrohydraulic lithotripsy and laser lithotripsy for treatment of difficult common bile duct stones. An effective and safe option for octogenarians.***
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- III. ***Intraoperative ERCP with rendezvous cannulation; a laparo-endoscopic way to avoid post ERCP pancreatitis.***
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Swahn F, Nilsson M, Arnelo U, Persson G, Löhr M, Enochsson L.
Submitted to The American Journal of Gastroenterology 2012.

Additional publications (papers) during my PhD studies, which are not included in this thesis:

Nationwide, population-based data from 11,074 ERCP procedures from the Swedish Registry for Gallstone Surgery and ERCP.

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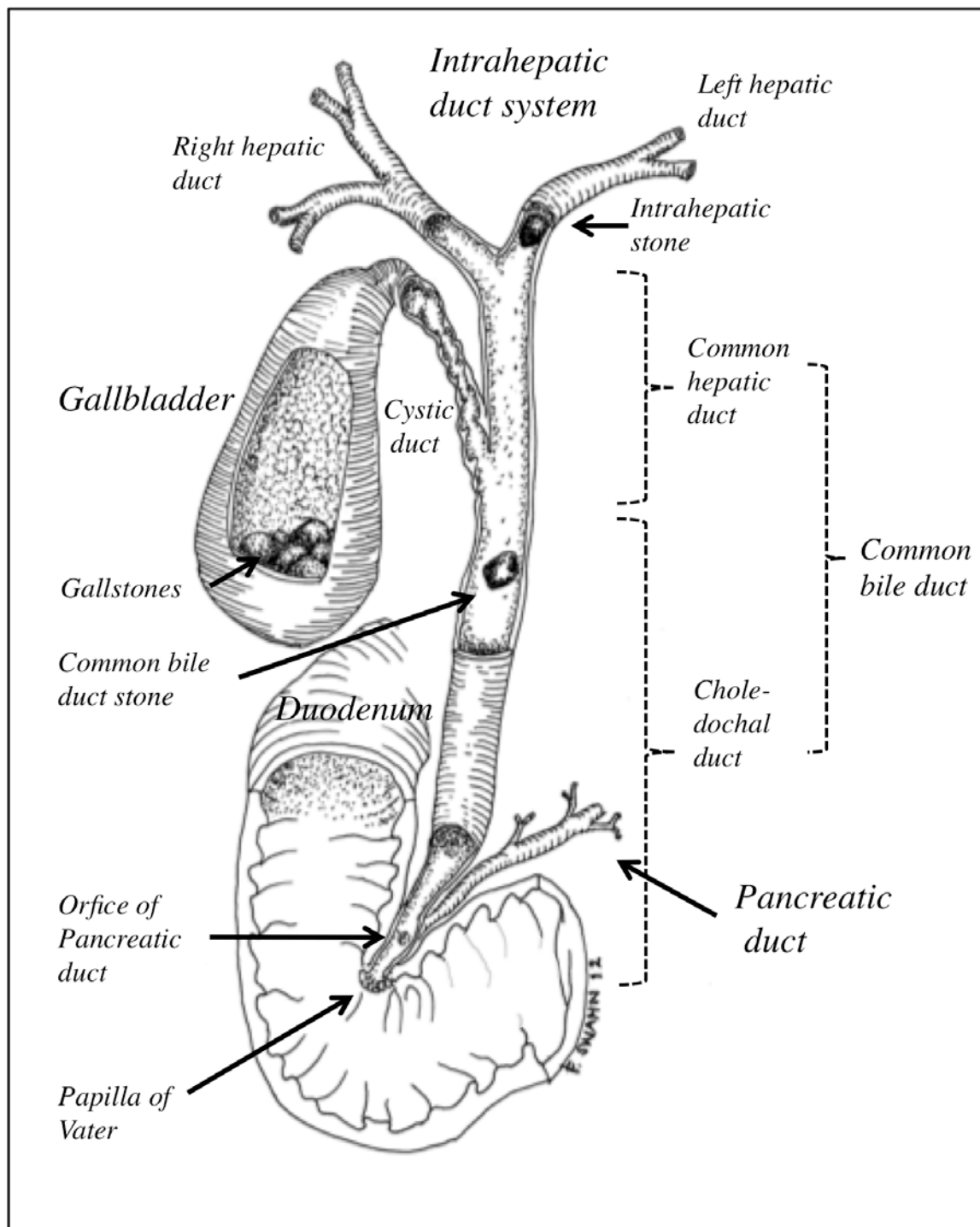


Figure 1. *Anatomy of the biliary system*

*Grades of evidence**

| Grade | therapy/prevention |
|--|--|
| 1a | Systemic review with homogeneity of RCTs |
| 1b | Individual RCT (with narrow CI) |
| 1c | All or none* case-series |
| 2a | Systemic review (with homogeneity**) of cohort studies |
| 2b | Individual cohort study (including low quality RCT; e.g., <80% follow-up) |
| 2c | Outcomes research |
| 3a | Systemic review with homogeneity of case-control studies |
| 3b | Individual Case-Control Study |
| 4 | Case-series (poor quality cohort studies, poor quality case-control studies) |
| 5 | Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" |
| <p>*) When all patients died before the therapy became available, but now some survive on it, or when some patients died before the therapy became available, but none now die on it</p> <p>**) By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies.</p> | |

*Grades of recommendation**

| Grade | Grades of recommendation |
|----------|---|
| A | Consistent level 1 studies. Directly applicable to the target population |
| B | Consistent level 2 or 3 studies or extrapolations from level 1 studies. A body of evidence, directly applicable to the target population |
| C | Level 4 studies or extrapolations from level 2 or 3 studies. |
| D | level 5 evidence or troublingly inconsistent or inconclusive studies of any level. For interventions analyzed in a single study, no recommendation was made |

*) According to the North of England evidence-based guidelines development project.

LIST OF ABBREVIATIONS

| | |
|----------|--|
| ASA | American Society of Anesthesiology |
| BMI | Body mass index |
| CBD | Common bile duct |
| CBDS | Common bile duct stone |
| CGC | Contrast guided cannulation |
| CI | Confidence interval |
| CRP | C-reactive protein |
| CT | Computer tomography |
| EG | Evidence grade |
| EHL | Electrohydraulic lithotripsy |
| ELISA | Enzyme-linked immunosorbent assay |
| ERCP | Endoscopic retrograde cholangio-pancreatography |
| EST | Endoscopic sphincterotomy |
| ESWL | Extra-corporal shock-wave lithotripsy |
| EUS | Endoscopic ultrasonography |
| GallRiks | Swedish National Quality Registry for Cholecystectomy and ERCP |
| IOC | Intra operative cholangiography |
| LC | Laparoscopic cholecystectomy |
| LL | Laser lithotripsy |
| MR | Magnetic resonance |
| MRCP | Magnetic resonance cholangio-pancreatography |
| OR | Odds ratio |
| PEP | Post-ERCP pancreatitis |
| ProCAPB | Procarboxypeptidase B |
| RCT | Randomised controlled trial |
| RG | Recommendation grade |
| SOD | Sphincter of Oddi dysfunction |
| SD | Standard deviation |
| SIRS | Systemic inflammatory response syndrome |
| US | Ultrasonography |
| VAS | Visual analogue scale |
| WGC | Wire guided cannulation |

1 HISTORY OF BILIARY STONE DISEASE AND TREATMENT

1.1 HISTORY

It seems that gallstone disease has virtually followed and plagued mankind since the very beginning of human history. The earliest evidence of gallstones that we have is from a 4000 year old Stone Age tomb in Gotland, Sweden [Mörner 1936], and gallstones were also found in a female Egyptian mummy dating from more than 3500 years ago [Smith 1906]. Despite the fact that throughout history many physicians, including Hippocrates of Cos (460-370 B.C.), Galen of Pergamon (129-216), Alexander of Tralles (525-605), Gentilis Da Foligno (died in 1348), Antonio Benivieni (1443-1502), Andreas Vesalius (1536-1564), and Jean Fernel (1497-1558), had recognized the presence of the gallbladder, the bile ducts, and gallstones, it was not until 300 years ago that scientists started to elucidate the true underlying function and pathology of the gallbladder [Glenn 1971]. In the early history of medicine, the state-of-the-art treatment was diet, purgatives, phlebotomy, and emetics according to the ancient humoral theory of pathology, with opiates being used against biliary pain. The overall prognosis for curing symptomatic biliary stone disease remained poor, and many times the condition was fatal. The English anatomist Francis Glisson (1597-1677) summarized his own painful crisis secondary to gallstones with the words "only death was the solution for a biliary colic", and his own remedy was to eat fresh grass since he observed that cattle after their winter diet of hay and straw had stones in the gallbladder, but these ceased to appear after a summer diet of fresh grass [Haeger 1988].

It was not until the second half of the nineteenth century that the first true surgical interventions began to appear. The prerequisites for successful surgical procedures were notably improved by several major anaesthetic breakthroughs, including the use of ether in 1846 by Thomas Green Morton (1819-1868) and the use of chloroform in 1847 by James Young Simpson (1811-1870). In 1859, Johann Thudichum (1829-1901) presented a theoretical description of a two-stage procedural approach with transabdominal cholecystostomy followed by lithotripsy through the resulting fistula [Thudichum 1859]. It is noteworthy that Thudichum did not perform any cholecystostomies himself, but his idea was later adopted by several other surgeons, such as Marion Sims (1813-1883) from the U.S.A. [Sims 1878], Theodor Kocher (1841-1917) from Switzerland [Kocher 1878] and Robert Lawson Tait (1845-1899) from Great Britain [Shepard 1986]; all three performed their first two-step cholecystostomies during 1878. An American surgeon from Indianapolis, John Bobbs (1809-1870), became the first to perform a successful elective cholecystotomy in 1867 [Bobbs 1868]. The achievement was perhaps more the result of a coincidence since he was operating on a patient for a suspected ovarian cyst, but instead found a hydropic gallbladder. Bobbs opened the gallbladder, removed the stones, and left the gallbladder *in situ* after closing the defect.

At a time when surgeons endeavored to construct the perfect gallbladder fistula, the German surgeon Carl Langenbuch (1846-1901) stated that his colleagues were busy with the product of the disease, not the cause of it. He performed the first cholecystectomy at the Lazarus Hospital in Berlin in 1882 [Langenbuch 1882]. Obviously Langenbuch was ahead of his time since many of his contemporary colleagues continued to perform cholecystostomies, but the Langenbuch procedure gradually won popularity both in Europe and the United States. The first cholecystectomy in Sweden was conducted by Hugo von Unge (1849-1935) in 1889 [Bolling 1891]. However, it was many years before surgical removal of the gallbladder became the "gold standard" for treatment of symptomatic gallbladder disease. There had been several attempts to explore the CBD, all of which resulted in the death of the patients, before the first successful CBD exploration was done by Knowsley Thornton (1845-1904) in 1889.

This was followed shortly by the work of Robert Abbé (1851-1928) in the U.S.A., Ludwig Courvoisier (1843-1918) in Switzerland, and Hans Kehr (1862-1916) in Germany. Kehr also invented the rubber T-tube (the Kehr tube) for post-operative decompression of the CBD [Morgenstern 1993].

Before the 1930's, only about 1/4 of all patients with symptomatic gallstone disease underwent surgery and the procedure was strictly reserved for individuals suffering from severe biliary complications. At this time and even much later, most physicians considered the mortality risk to be too high to justify the routine use of surgery. Nowadays, with the advent of modern medical care including new surgical techniques, anaesthesia, radiology, antiseptics and perioperative care, cholecystectomies can be carried out on routinely basis with low morbidity and mortality rates.

The first laparoscopic cholecystectomies were conducted in 1985 by the German surgeon Erich Mühe [Mühe 1986], followed by Phillipe Mouret in 1987 in France [Spaner and Warnock 1997]. Laparoscopic cholecystectomy spread extremely rapidly throughout the world and gained wide acceptance by surgeons in a remarkably short period of time. In 1990, Dag Arvidsson performed the first laparoscopic cholecystectomy in Sweden [Arvidsson et al. 1992]. Laparoscopic cholecystectomy has become the gold standard in the treatment of biliary disease. In the early 1990's Petelin described both transcystic and transductal explorations [Petelin 1991]. The first laparoscopic common bile duct explorations in Sweden were performed in 1992 [Arvidsson et al. 1998].

A recent development in laparoscopic procedures was the introduction of robotic surgery, including the cholecystectomy performed in 2001 by the French surgeon Jacques Marescaux that demonstrated the possibilities of this technique. Although Marescaux, as the performing surgeon, was physically in New York, he removed a gallbladder from a patient in Strasbourg, France, and thereby carried out the first transatlantic tele-surgery [Marescaux et al. 2001].

1.2 THE ADVENT OF ERCP

Transpapillary infusion of radiopaque contrast media into the bilio-pancreatic duct during open operation was described by Henry Doubilet and John Mulholland in 1955 [Doubilet and Poppel 1955]. However, the first true diagnostic ERCP, which used a long flexible lateral-viewing fiber bundle duodenoscope, was performed in 1968 by William McCune (1909-1998) from the U.S.A. [McCune et al. 1968]; he was followed in 1969 by Itaru Oi from Japan [Oi 1970]. The first diagnostic ERCP in Sweden was done in 1972 by Lennart Wehlin (1922-1983) [Cronstedt 1985]. In 1974, Meinhard Classen and Ludwig Demling (1921-1995) from Germany [Classen and Demling 1974] and Keiichi Kawai et al. from Japan [Kawai et al. 1974] independently presented their first therapeutic ERCP procedures with sphincterotomy and transpapillary common bile duct stone extraction. In Sweden, the first ERCP with sphincterotomy and stone extraction was reported in 1978 by Gustav Liedberg [Liedberg 1979] and Carl-Erik Nordgren [Nordgren 1979]. A major global change in the treatment of CBDS then occurred during the 1990's when ERCP became the preferred treatment option together with laparoscopic cholecystectomy, a combination that allowed the patient the benefits of minimally-invasive surgery. The two-stage procedure involving pre- or postoperative ERCP together with laparoscopic cholecystectomy became the most widespread treatment of CBDS, as it still is today. Simultaneously, ERCP lost much of its diagnostic importance during the 1990s when MRCP could produce more information without exposing the patient to the risks associated with an ERCP investigation.

As an extension of ERCP, the first orally performed choledochopancreatoscopies, which used the mother-baby technique, were done by Classen and Demling in 1972 [Classen 1972]. Even though first-generation intraductal endoscopes were received with scepticism, since the instruments were extremely fragile and

expensive and provided pictures of poor quality, they served as an important step in the development of intra-ductal endoscopy. The latest generation of intra-ductal endoscopy is represented by the SpyGlass System that was launched in USA 2006 and in Europe 2007 [Chen and Pleskow 2007, Arnelo et al. 2007, Fishman et al. 2009, Chen et al. 2011].

In summary, we can recognize the legacy of many pioneers in the field who, during the course of the 20th century, advanced the knowledge of biliary stone disease. Inventions like laparoscopy, flexible endoscopy and modern radiology, became landmarks that changed the practice of biliary tract surgery. These inventions were not just different methods of access; they also represented a different mindset concerning how to approach a surgical problem. There have also been great expectations, in part patient driven, which have been greatly supported by the medical industry that produced the optical instruments and endoscopic devices that made it possible to fulfill these expectations.

1.3 GALLSTONE DISEASE

1.3.1 Formation of gallstones

The formation of biliary stones is a complex process, and not yet fully understood. In principle, there are three types of biliary stones: cholesterol, black pigment, and brown pigment stones. In Western society, about 75% of biliary stones are cholesterol, 20% are black pigment and 5% are brown pigment stones [Carey 1993].

Cholesterol stones

Cholesterol stones are largely composed of cholesterol monohydrate crystals and are formed in the gallbladder from supersaturated bile. The common theme is an unbalance between excessive amounts of biliary cholesterol and the secreted amounts of solubilizing bile salts or phospholipids (lecithin). There are four major groups of pathophysiological factors that contribute in the formation of cholesterol stones: (1) those that lead to supersaturation of the bile, such as genetic expression and dysregulation of hepatic transport proteins [Marschall et al. 2010], (2) those that stimulate cholesterol precipitation and chrySTALLIZATION (mucin formation) [Portincasa et al. 2006], (3) those that result in functional impairment of the gallbladder, due to heavy weight loss [Dittrick et al. 2005], diabetes mellitus [Ruhl and Everhart 2000], total parental nutrition [Guglielmi et al. 2006] or medication [Attanasio et al. 2008], and (4) those factors that lead to a dysfunction of the enterohepatic circulation of bile acids, such as gastric bypass surgery [Reshetnyak 2012].

Black pigment stones

Black pigment stones are formed in the gallbladder by acid salts of calcium bilirubinate, calcium carbonate, and calcium phosphate in polymer-like complexes together with mucin glucoproteins [Bar Dayan et al. 2004]. Bilirubin, a breakdown end product of haemoglobin, is conjugated in the liver in different steps and secreted into the bile as water-soluble bilirubin diglucuronide. However, unconjugated bilirubin is poorly water-soluble and in situations of excessive haemolysis, biliary excretion of unconjugated bilirubin may increase the risk calcium bilirubinate precipitation. Formation of black stone pigment stone is, for example, associated with chronic haemolytic diseases like sickle cell anaemia, hereditary spherocytosis, Gilbert syndrome, and cirrhosis. Another example of excessive bilirubin in bile can be observed among patients with increased recycling of bilirubin in the bowel, such as patients suffering from Crohn's disease with an affected or resected distal part of the ileum.

Brown pigment stones

Unlike the others, brown pigment stones are formed in the bile ducts as a consequence of a chronic bacterial or parasite infection. Bacteria such as *Escherichia coli*, *Bacteroides*, and *Clostridium* species, promote enzyme activity through hydrolysis of bile salts, resulting in unconjugated bilirubin, palmitic and stearic acids, and unconjugated bile acids, which can form complexes with calcium and lead to subsequent stone formation [Vitek and Carey 2012]. Intraductal infestation of parasites such as *Ascaris lumbricoides*, *Clonorchis sinensis*, *Opisthorchis*, and *Fasciola* species can produce a calcified overcoat of the parasite egg that serves as a nidus for the precipitation of calcium bilirubinate.

Biliary sludge and microliths

Hypersecretion of gallbladder mucin promotes nucleation of cholesterol crystals or bilirubinate salts in the gallbladder. This mud or gel-like suspension, called biliary sludge, reduces the buffering capacity of bile acids and is believed to be an essential stage in the formation of both cholesterol and black pigment stones. Biliary sludge contains comparatively large particles (1-3 mm) called microliths. Microlithiasis and sludge may cause biliary pain and cholecystitis cholangitis [Jüngst et al. 2006], but if it is a causative etiology for acute pancreatitis remains controversial. Several studies have shown the presence of biliary sludge in as many as 75% of patients with unexplained acute pancreatitis.

Impaired motility in the gallbladder

Normally, one or two hours after meal ingestion, the gallbladder has emptied up to 70% or 80% of its contents as a response to the hormone CCK, which is released from the upper intestine. However, it is during the state of fasting that gallstone formation is likely to occur, especially during the night when biliary cholesterol saturation and secretion is high and bile salt secretion is low. Excessive amounts of cholesterol are incorporated in the sarcolemma plasma membranes of the gallbladder muscle cells, resulting in relaxation and decreased contractility. Impaired gallbladder emptying prolongs the residence of bile in the gallbladder, allowing more time for nucleation of cholesterol crystals from supersaturated bile. Microscopic crystals that might have been ejected to the common bile duct if the gallbladder had functioned normally are instead retained and grow in size. Although impaired gallbladder motility is secondary to cholesterol supersaturation, it may secondarily promote the process of gallstone formation [Dittrick et al. 2005].

1.3.2 Epidemiology of gallstone disease

The prevalence of gallstone disease varies globally among different ethnic populations, ages and genders. In Western society, biliary stone disease is present in approximately 5% - 25% of adults [Halldestam et al. 2004, Bates et al. 1992]. Epidemiological data derived from Scandinavian population sources have shown an overall prevalence ranging from 11% - 55% in females and 4% - 25% in men (the higher rates were found in autopsy investigations [Wenkert and Robertson 1966, Torvik and Hoivik 1960] and the lower rates were obtained from ultrasonography screening [Janzon et al. 1985, Mellström et al. 1988, Muhrbeck and Ahlberg 1995]). Populations with an overall low prevalence of gallstone disease are found in Asia and in Africa (<5%) [Walker et al. 1989, Kratzer et al. 1999]. In contrast, an extremely high prevalence can be found in Native American Indian population such as the Pima Indians in Arizona, who have an overall prevalence of 46% [Sampliner et al. 1970].

The prevalence of gallbladder disease correlates positively with age and female gender. Gallstones seldom occur in childhood; they begin to appear more frequently in adolescence (age < 30 years; male 2% to 4%: female 5% to 6%). Prevalence increases markedly between the ages of 40 to 60 years (60 years; male 13% to 37% : female 20% to 40%) and continues to rise gradually in higher ages (70 years; male 19% : female 30%) [Jørgensen 1987, Glambek et al. 1987]. In females in their 80's, up to 50% have gallstones or have previous undergone cholecystectomy [Mellström et al. 1988]. Females with previous multiple full-term pregnancies [Jørgensen 1987, Ko et al. 2005] and those who have received exogenous estrogen therapy [Cirillo et al. 2005] seem to have a higher prevalence of gallstone disease.

1.3.3 Natural history of biliary stone disease

The vast majority of individuals with gallstones are completely asymptomatic and will continue to be so throughout their lives. In previous studies, nearly two-thirds of patients with biliary stones were referred to as asymptomatic [Janzon et al. 1985, Jørgensen 1989] and in other epidemiological reports up to 80% - 90% of the stone carriers were characterized as asymptomatic [Angelico et al. 1997, Barbara et al. 1987, Berger et al. 2000]. The reason why gallstones give rise to symptoms in one patient and not in another remains obscure; there is no evidence that silent stones differ in number, size, or composition from symptomatic stones [Bouchier et al. 1968]. The increasing use of radiology in clinical practice has produced incidental detection of gallstones. Many of these patients can experience various forms of indigestion and abdominal discomfort that are not normally associated with biliary disease. Dyspeptic symptoms like belching, flatulence, nausea, intolerance to fatty food, bloating of the abdomen, epigastric discomfort and acid regurgitation, have been shown to be as common in individuals without gallstones as in individuals with biliary stones [Muhrbeck and Ahlberg 1995, Borch et al. 1998]. Studies of the natural history of asymptomatic gallstones suggest that the cumulative probability of developing biliary colic after ten years ranges from 10% - 30% and symptoms requiring surgical treatment occurred in 1.3% -3.0% annually [Gracie and Ransohoff 1983, McSherry et al. 1985]. For patients with asymptomatic gallstones, the natural history is so benign that cholecystectomy is not recommended (RG: B). This recommendation includes patients at risk such as diabetic patients [Del Favero et al. 1994], patients submitted for obesity surgery [Plecka Östlund et al. 2012], children in general, and children with sickle cell disease [Gummiero et al. 2008]. Studies have suggested that complications are less likely the longer the stones have remained asymptomatic [Attili et al. 1995].

1.3.4 Symptoms of gallbladder stones and aspects of management

Symptomatic gallstones without complications

Biliary colic is defined as a steady right upper quadrant abdominal pain lasting for more than half an hour, which may be associated radiation to the back and nausea and may force patients to stop their activities [Berger et al. 2000]. The distinction between symptomatic and asymptomatic gallstones and the timing of when to perform cholecystectomy are controversial subjects. Several reports suggest wait-and-see management after the first day of illness until further symptoms or more severe complications are present [Ransohoff and Gracie 1993, Friedman et al. 1989, Vetrhus et al. 2002], while others recommend early cholecystectomy once symptoms have started, based on several longitudinal studies demonstrating a reduction of medical costs and morbidity for patients with early surgical intervention [Rutledge et al. 2000, Somasekar et al. 2002, Sobolev et al. 2003] (EG: III, RG: B).

Manifestations of cholecystitis

If a gallstone obstructs the outlet of bile from the gallbladder, pressure gradually increases within the gallbladder and an inflammatory process is established [Jivegård *et al.* 1987]. Typically it begins with a biliary colic type of pain with tenderness under the right subcostal margin, but it does not settle down until one or more days. Laboratory examinations are not specific for the diagnosis, but C-reactive protein (CRP) and the white blood cell count (WBC) are usually elevated. Occasionally, a mild jaundice can be noticed with elevation of liver transaminase and bilirubin, probably due to peribiliary edema surrounding the gallbladder. However, CBDS may be present in approximately 20% of the cases and even more frequently among elderly patients [Claesson *et al.* 1984]. Bacterial infection of the bile is relatively less important in the early phase of acute cholecystitis [Järvinen 1980]. Older age [Glenn and Dillon 1980], diabetes mellitus [Hickman *et al.* 1988], CBDS, and previous biliary surgery [Wells *et al.* 1989] are known to be risk factors that are associated with positive bacterial cultures. Most surgeons recommend cholecystectomy after a first bout of cholecystitis (RG: B) [Rutledge *et al.* 2000, Somasekar *et al.* 2002, Sobolev *et al.* 2003, Friedman *et al.* 1989, Johansson *et al.* 2003], even for elderly patients [Edlund and Ljungdahl 1990], since that is associated with a shorter hospital stay and cost savings (RG: A) [Gurusamy and Samray, Wilson *et al.* 2006]. In severely ill or fragile patients, ultrasonically-guided percutaneous catheter drainage of the gallbladder (cholecystostomy) with broad-spectrum antibiotics may be an alternative choice for treatment for those who are not suited for abdominal surgery (RG: A) [Gurusamy and Davidson 2010a].

Acute gangrenous cholecystitis and emphysematous cholecystitis are serious variants of acute cholecystitis with rapid formation of gas-forming organisms penetrating the gallbladder wall into the surrounding area, which severely increases the risk of serious outcome and mortality [Nikfarjam *et al.* 2011]. Gallbladder perforation or empyemas are other critical features that call for emergency cholecystectomy or percutaneous/transhepatic cholecystostomy [Al-Jundi *et al.* 2012].

Chronic inflammation with bilio-enteric fistula formation is a rare condition that is associated with elderly patients who have large gallstones that erode into the adjacent duodenum and, if large enough, cause a mechanical obstruction in the intestinal lumen [Reisner and Cohen 1994] that calls for an emergency laparotomy with enterolithotomy. Even though controversy remains, cholecystectomy and repair of cholecysto-enteric fistula are recommended to be done later only if there are continuing or recurrent symptoms [Shenoy and Cassim 2010].

The Mirizzi syndrome is a rare, chronic inflammatory condition that can be classified in subtypes [Mirizzi 1948, Csendes *et al.* 1989]. Type I is limited to an impacted large gallstone in the cystic duct or in the neck of the gallbladder that mechanically compresses the adjacent CBD running parallel to the cystic duct, gradually resulting in complete or partial obstruction of the CBD. Type II involves the formation of a bilio-biliary fistulation into the CBD by the impacted stone.

1.3.5 Common bile duct stones (CBDS)

Etiology

In Western countries, the majority of CBDS are secondary since they are originally formed in the gallbladder by cholesterol or more seldom by bilirubin and migrate through the cystic duct. The diameter of the cystic duct (>4mm) seems to play a critical part in the migration of stones [Taylor and Armstrong 1987]. Primary

CBDS are more common in South Asia and are associated with parasitic infection or superimposed bacterial infections. Primary CBDS formation of infectious origin can also be seen in patients with duodenal diverticula, bile duct strictures from various causes, and foreign bodies such as stents and suture remnants.

1.3.6 Symptomatology and aspects of management

Asymptomatic common bile duct stones

The natural history of CBDS is not as fully understood as that of stones in the gallbladder. It is a well-recognized fact that approximately 25% of patients with CBDS are more or less asymptomatic and a substantial number of these (30% to 50%) will eventually pass their CBDS spontaneously and silently. Furthermore, it is unclear what stone size will actually permit passage or why some stones leave silently into the duodenum whereas others do not. In addition, one must also consider the critical functional role of the sphincter of Oddi in passing or retaining CBDS [Vracko and Wiechel 1999]. This somewhat haphazard circumstance is reflected in several important clinical situations, for example, during elective cholecystectomy, where the prevalence of unexpected CBDS can be as high as 4% to 10%. Another example is the disappearance of CBDS during the time between radiological detection and the following intervention, e.g. ERCP or a cholecystectomy. The prevalence of existing CBDS at the time of intervention may be as low as 10% - 20% [Neuhaus et al. 1992, Saltzstein et al. 1982, Houdart et al. 1995]. In an increasingly litigious society, most physicians would recommend removal of a detected asymptomatic CBDS for the fear of subsequent complications that may ensue, especially since asymptomatic stones tend to develop complications rather than symptoms [Caddy and Tham 2006]. What is clear, however, is that once a stone has revealed itself with symptoms, it will always represent a potential danger for the patient and consequently needs to be taken care of [Besselink et al. 2009] (EG: III, RG: B).

Obstructive jaundice

Partial or complete obstructive jaundice can develop as a consequence of CBDS. Obstructive jaundice may lead to secondary fatal consequences such as cholangitis, renal dysfunction, cardiovascular dysfunction and coagulopathy. Indissoluble obstruction of the biliary outflow will eventually lead to secondary biliary cirrhosis and portal hypertension [Williams et al. 2008].

Acute cholangitis

Acute cholangitis is a severe suppurative infection that affects the bile ducts, usually from bacteria ascending from the duodenum, and it is often associated with biliary outflow obstruction. Clinical signs are jaundice, fever, and upper right abdominal pain. If the condition fails to respond to antibiotic therapy or deteriorates into septic shock, it should be considered as an emergency situation that could pose an immediate threat to the patient if not treated with biliary decompression by either ERCP or PTC (EG: Ib, RG: A) [Lai et al. 1992].

Acute biliary pancreatitis

Common bile duct stones are by far the most common cause of acute pancreatitis in Western society and account for about 30% - 60% of all cases [Lowenfels et al. 2009]. Small stones, which are prone to be trapped in the narrow ampulla, or stones that occur in high numbers that might allow repetitive obstructions are typical risk factors associated with acute biliary pancreatitis [Taylor and Armstrong 1987, Dihel et al. 1997]. The severity of acute pancreatitis seems to be proportional to the duration of the pancreatic duct obstruction, and persistent bilio-pancreatic occlusion is associated with a more severe outcome [Senninger et al. 1986, Rünzi et al. 1993, Lerch and Aghdassi 2010]. These observations may provide a rationale for early attempts to

decompress the intraductal pressure by removing an obstructive stone in the early stage of the disease and removing the threat of additional remaining CBDS. Nevertheless, the current opinion is that early (<48 hours) ERCP with sphincterotomy may be useless. Because several clinical studies have shown a 71–88% rate of spontaneous disobstruction within 48 hours after the onset of acute biliary pancreatitis, only a relatively small subgroup of patients might, in fact, have a theoretical justification for undergoing early ERCP with sphincterotomy [Petrov 2009] (EG: Ib, RG: A). Only patients with co-existing acute cholangitis or sepsis and those with a persistent CBD obstruction (<72 hours) may benefit from early ERCP intervention [Forsmark and Baillie 2007] (EG: Ib, RG: B). ERCP intervention beyond 72 hours of the onset of illness, does not produce any benefit, thus raising a concept of a therapeutic window [Acosta et al. 2006].

There are different opinions of how to prevent patients from subsequent relapses of biliary pancreatitis. No treatment at all or a wait-and-see policy is associated with a potential risk of having a relapse that is estimated to be up to 50% to 90% [Kelly and Swaney 1982, Uomo et al. 1997, Trust et al. 2011]. Consequently, conservative management is not to be regarded as an acceptable treatment.

If the gallbladder is removed, the risk of having another relapse of biliary pancreatitis should be very low [Frakes 1999]. A prospective study with a follow-up time of 34 months has found recurrence rate of 2.4% after surgery [Kaw et al. 2002]. The current recommended policy is to perform a cholecystectomy as soon as possible after an attack of biliary pancreatitis, preferably within the same hospital stay or at least within 2 to 4 weeks after discharge to prevent relapses of acute pancreatitis (EG: Ib, RG: A).

Endoscopic sphincterotomy is an effective therapeutic approach for reducing the risk of relapsing biliary pancreatitis close to 2%-4%, but not from late gallbladder-related complications [Hammarström et al. 1998, Vázquez-Lglesias et al. 2004]. A prospective randomized Dutch multicenter trial reported that a wait-and-see policy after endoscopic sphincterotomy could not be recommended as a standard treatment since 47% of the expectantly-managed patients developed recurrent biliary events within the 2-year follow-up period, compared with 2% in the prophylactic cholecystectomy group, and up to 37% in the deferral group needed cholecystectomy on demand [Boerma et al. 2002]. Therefore, cholecystectomy is strongly recommended after an attack of gallstone pancreatitis (RG: A) [Gurusamy et al. 2010b].

However, in patients who are considered to be unfit for surgery for any reason, sphincterotomy can provide acceptable protection from future attacks of biliary pancreatitis. The same applies to patients who need an extended recovery time after a severe attack of pancreatitis, in whom a cholecystectomy can be performed safely when their general condition improves.

1.3.7 Diagnosis of common bile duct stones

Choledocholithiasis is often suspected in patients who have elevated liver function test results, jaundice, pancreatitis, radiologic signs of dilated intra- or extra-hepatic ducts, or evidence of common bile duct stones either by transabdominal ultrasound (US), computed tomography (CT), magnetic resonance (MR), endoscopic ultrasonography (EUS), or cholangiography. ERCP can also be perceived as a diagnostic tool for confirming the presence of CBDS, but given the risk of complications, these other diagnostic modalities should be utilized instead of ERCP (EG: IIb, RG: B) [Williams et al. 2008].

Biochemical tests

Various clinical indicators and combinations of biochemical tests such as serum bilirubin, alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT) have been suggested as valuable cholestatic liver function parameters for predicting CBDS in clinical practice [Anciaux *et al.* 1986, Yang *et al.* 2008]. Data from prospective studies are inconsistent, and it appears that no single biochemical marker or combination of markers can currently provide a reliable test for predicting CBDS. Several promising attempts have been made to compensate for this lack of prediction by making sophisticated risk assessment nomograms or scoring system analyses based on various preoperative data [Menezes *et al.* 2000, Taylor 1988, Trondsen *et al.* 1998]. However, these have never really gained acceptance in clinical practice since they tend to be too complicated to use or unreliable. A previous consecutive study of 1390 cholecystectomies by Rieger *et al.* [Rieger and Wayand 1995], showed a 60% accuracy of concomitant CBDS when the assessment was based on altered liver chemistries alone, 69% when liver chemistries were combined with radiological abnormalities, and 42% when radiologic criteria of CBDS were used alone. Another study by Videhult *et al.* [Videhult *et al.* 2011], which included 1171 cholecystectomies in a prospective population-based trial, found CBDS in 42% of patients with elevated liver function values, in 20% with a history of acute pancreatitis and in 9% with acute cholecystitis. The association between elevated liver function values and CBDS was somewhat stronger in patients scheduled for elective cholecystectomy compared with emergency cases. Nevertheless, the risk for CBDS was only 6% when liver function test was normal for ALP and bilirubin [Cohen *et al.* 2001].

Transabdominal Ultrasonography

Transabdominal ultrasound is generally used as a screening test in the diagnosis of gallbladder stones; however, it is not extremely sensitive in the detection of CBDS (sensitivity 36%, specificity 98%) [Stott *et al.* 1991]. Nevertheless, ultrasonography in combination with clinical symptoms and laboratory abnormalities is a safe and convenient first line of investigation for selecting patients who may need further imaging (EG: III, RG: B).

Endoscopic Ultrasonography (EUS)

Endoscopic ultrasonography (EUS) is an accurate test for detection of CBDS, with a sensitivity and specificity of greater than 90% [Garrow *et al.* 2007]. EUS can also be valuable diagnostic modality in detecting cholecystolithiasis, sludge or microlithiasis and in identifying the presence of lodged stones in papillary region in the early phase of acute biliary pancreatitis [Tandon and Topazian 2001, De Lisi *et al.* 2011]. EUS is a safe investigation and should be considered a low-risk alternative to ERCP, especially in cases with low to moderate likelihood of CBDS (EG: IIb, RG: B). However, EUS is a user-dependent technique and cannot clearly identify stones above the common hepatic duct [Gupta *et al.* 2008].

Intraoperative Laparoscopic Ultrasonography (ILUS)

Intraoperative laparoscopic ultrasonography has been used increasingly instead of IOC over the last years as screening methods of choice to identify the presence of CBDS during ongoing cholecystectomy. Results are promising and ILUS seems to be a reliable method in experienced hands with a success rate close to 95% together with a high sensitivity and specificity comparable with IOC [Nasu *et al.* 2012]. Compared with IOC, however, there is a considerable learning curve to overcome and ILUS is considered to be inferior to delineate bile duct anatomy and duct anomalies.

Computed tomography (CT)

Trials with conventional computed tomography (CT) [Mitchell and Clark 1984] or unenhanced CT [Neitlich et al. 1997] have reported an approximate sensitivity of 80% and specificity around 90% in the detection of CBDS [Lee et al. 2006]. Oral enhanced CT cholangiography has shown a higher sensitivity of 92% [Soto et al. 2000]. CT scans are commonplace and are useful in the management of patients with obscure abdominal symptoms. However, CT is not justified as a routine method for the diagnosis of CBDS prior to cholecystectomy, due to its low positive predictive value and the exposure to radiation that is involved.

Magnetic Resonance Cholangiopancreatography (MRCP)

Magnetic resonance cholangiopancreatography (MRCP) has become an accepted substitute for diagnostic ERCP. MRCP has a high sensitivity (85%-95%) and specificity (90%-100%) for CBDS down to the size of 3 mm [Lendro-Cano 2006]. MRCP is not operator-dependent, and all liver segments and the complete extra hepatic duct system and the pancreatic duct can be visualized. Despite good results, MRCP cannot be recommended as a routine investigation for CBDS detection in unselected patients owing to its high cost and limitations of resources. However, MRCP should always be prioritized over ERCP in cases with low probability of CBDS or in cases where one would expect technical endoscopic difficulty in performing endoscopy [Holzknecht et al. 1998].

Intravenous cholangiography (IVC)

The purpose of using preoperative intravenous cholangiography (IVC) is to select patients with CBDS who should undergo preoperative ERCP or intraoperative cholangiography and thereby reduce operating time in the following LC [Dorenbusch et al. 1995]. However, reported experiences have yielded contradictory results, demonstrating that the use of routine IVC exposes the patient population to a large radiation burden and that the cost is high for the relatively small number of patients who may benefit, since the sensitivity is too poor. Moreover, it does not seem to be helpful in reducing the incidence of operative bile duct injuries during LC [Järhult 2005].

Intraoperative cholangiography (IOC)

Intraoperative cholangiography (IOC) is the gold standard for detecting CBDS during laparoscopic or open cholecystectomy. The sensitivity, specificity, and positive and negative predictive values of IOC in detecting common bile duct stones are higher than 95% [Videhult et al. 2009]. The procedure is safe and can be performed routinely on 97% to 99% of patients, without any preoperative preparation [Sackier et al. 1991]. IOC offers an immediate “real-time” CBDS imaging that allows treatment to be performed as a single operative procedure. Large population-based studies have shown that IOC not only detects stones but also permits delineation of the operative bile duct anatomy, thereby decreasing the incidence of inadvertent bile duct injuries by 34% [Waage and Nilsson 2006] to 70% [Flum et al. 2003]. Nevertheless, there are those who are questioning whether IOC is worth the effort, operation time, and cost to detect asymptomatic CBDS, particularly in patients in whom the suspicion of CBDS is low, and are therefore reluctant to perform IOC routinely in all patients [Clair et al. 1993]. Some people refer to the natural history of asymptomatic stones, which shows that the majority of stones leave spontaneously and suggest that it is acceptable to use subsequent ERCP to treat the few percentage of stones that may lead to symptoms [Gerber and Apt 1982].

However, the frequency of referred patients with post-laparoscopic cholecystectomy complications from retained stones may be more common than some other investigators have suggested [Cuschieri et al. 1994]. The controversy is complicated by the fact that no study has yet been completed to determine the true outcome of stones intentionally left in the CBD.

1.3.8 Surgical treatment of common bile duct stones

If CBDS are detected during the course of a LC, there are basically three different modalities of procedures: 1) complete laparoscopic management (transcystic or choledochotomy) (EG: Ib, RG: A), 2) conversion to open surgery with common bile exploration (EG: III, RG: B), or 3) endoscopy, either by intra-, pre- or post-operative ERCP (EG: Ib, RG: A) [Williams et al. 2008].

1.3.9 Laparoscopic or open common bile duct exploration

Laparoscopic transcystic common bile duct exploration (LTCE)

LTCE is a method in widespread use because it can be conducted quickly, it is relatively easy to learn, and it can be performed at a low expense [Lyass and Phillips 2006]. Results based on one-center case series show that LTCE is applicable in about 58% to 92% of the cases. Quoted rates of stone clearance after LTCE are reported between 65% to 95% and rates of retained CBDS are reported in approximately 5% [Petelin 2003, Paganini et al. 2007, Strömberg et al. 2008a]. If there is doubt whether complete stone clearance has been obtained, transcystic drainage is usually inserted and checked postoperatively with secondary cholangiography.

Laparoscopic common bile duct exploration (LCBDE)

Laparoscopic choledochotomy has a high success rate, from 85% to 92% and is not limited by the size of stones [Petelin 2003]. However, laparoscopic choledochotomy has its own share of complications; morbidity rates around 10% and mortality less than 1% have been reported. Some of the morbidity can be attributed to the placement of a T-tube. There are people who advocate alternative techniques with primary suture of the incision without using a T-tube or who use a transcystic duct tube or biliary endoprosthesis instead. Mean hospital stay is approximately 2 to 9 days. LCBDE adds approximately 60 to 100 minutes or more to the cholecystectomy operation time, depending on the complexity of the case [Costi et al. 2010, Elgeidie et al. 2011b].

Open common bile duct exploration, choledochotomy

Although open common bile duct exploration is performed very seldom today because of the success of stone removal by ERCP or laparoscopic techniques, there are still several indications for open exploration. The most obvious example is patients who are undergoing another open abdominal procedure or when a laparoscopic procedure is converted to an open one. Other indications for an open approach are large or multiple CBDS that may be difficult to remove by ERCP or the suspicion of Mirizzi syndrome. In these and other cases, the decision should be based on the estimated risk of alternative strategies. After removal of CBDS, the closure of the opening can be done with a protective T-tube or without a tube (primary repair). A T-tube offers decompression of the biliary outflow obstruction due to residual stones or edema and to obtain postoperative (secondary) cholangiography before removal of the T-tube. If there is a need for subsequent biliary treatment, the T-tube can act as a connection to the common bile duct. However, the T-tube cannot

usually be removed before 10-14 days after surgery, and there is a risk of intraabdominal infection, bile leakage and peritonitis after tube removal. Exploring the CBD during open cholecystectomy seems to add little to the risk of mortality in patients with low risk from surgery (< 1% for patients under 60 years), but it does, however, increase mortality in patients aged over 60 years (1.8%-4.7%) [Morgenstern *et al.* 1992, McSherry 1989].

1.3.10 Endoscopic treatment of common bile duct stones

Endoscopic retrograde cholangiopancreatography (ERCP)

In Western society today, ERCP is the dominating therapy in the management of CBDS. Principally the procedure consists of cannulation of the papilla, followed by cutting of the sphincter of Oddi and then stone removal.

Cannulation

Cannulation is usually a straight-forward, swift procedure in the hands of an experienced endoscopist. Deep cannulation is a prerequisite for any therapy during ERCP, and failure to achieve ductal access leaves the disease untreated. When the duodenoscope is positioned into a short loop facing the papilla, cannulation is conducted using various accessories and techniques; however, the safest and most effective approach has yet to be determined. The wire-guided cannulation technique (WGC), **figures 2 and 3**, which uses a standard triple-lumen sphincterotome together with a hydrophilic guidewire, appears to be gaining acceptance as an efficient device for biliary access (RG: A) [Freeman and Guda 2005, Karamanolis *et al.* 2005, Zhou *et al.* 2006, Bailey *et al.* 2008].

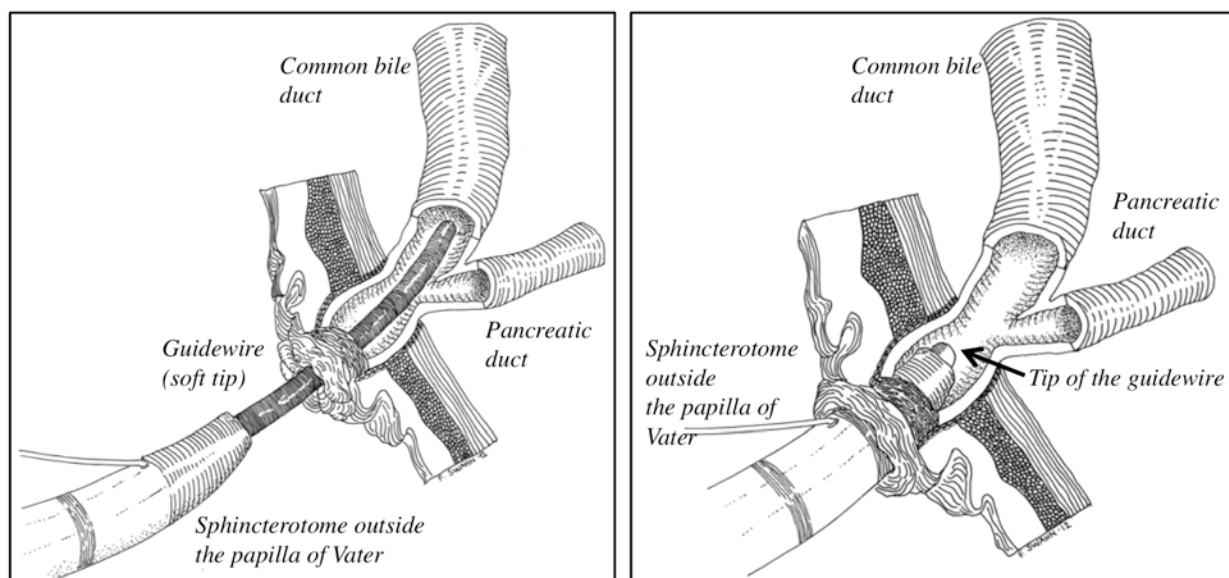


Figure 2 and 3. Wire guided cannulation (WGC): Figure 1: The sphincterotome can be bowed into variable upward angulation and allow rotation of the tip in order to address the correct direction of the advancing guidewire. The success rate may be further increased by using a hydrophilic coated guidewire, that becomes slippery in contact with liquid, which facilitates the passage in a narrow or tortuous duct. WGC can be performed with the sphinctero-tome just in front of or, as seen in figure 2, just inside the papilla of Vater. The guidewire is gently advanced and if the guidewire is located in the common bile duct, as seen on fluoroscopy, the sphincterotome is advanced over the guidewire and contrast is injected for confirmation.

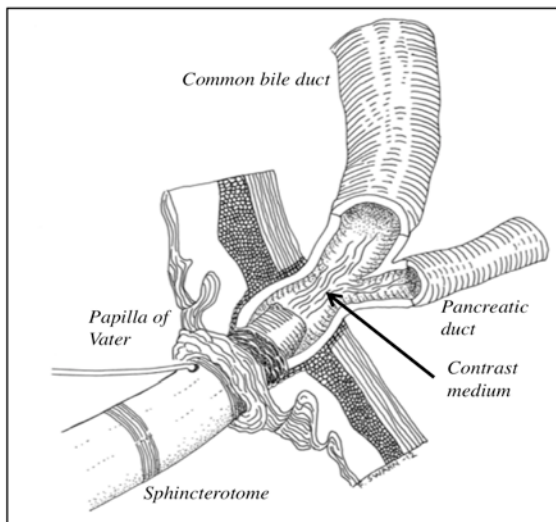


Figure 4. Contrast guide cannulation (CGC): The sphinctero-tome is inserted just inside the papilla of Vater and addressed in a 11 o'clock position for attempted biliary cannulation. A small amount of contrast is injected under simultaneous fluoroscopy in order delineate the correct direction of the sphincterotome into the bile duct.

The traditional contrast guided (CGC) technique has the potential disadvantage that contrast medium may end up in the main pancreatic duct, an event that could promote development of PEP, **figure 4**. On the other hand, WGC may traumatize the papilla or the pancreatic duct by direct injury from the tip against the ductal epithelium, especially in the case of repeated contact. Inadvertent pancreatic opacification may be possible if the guidewire is introduced unintentionally into the pancreatic duct, which was mistaken for the CBD.

RCT trials have found that biliary cannulation with or without WGC technique can be performed with equivalent results for successful cannulation, but it is not entirely clear whether WGC technique reduces the risk of PEP. However, a meta-analysis by Cennamo et al [Cennamo et al. 2009] concluded that the WGC technique increased the primary cannulation rate by 10 % (85 % versus 75 %) compared with CGC. WGC also reduced both the number of difficult cannulations and the use of the pre-cut

technique. These findings may also explain why the investigators could show a significant reduction in PEP (OR 0.23, 95% CI 0.13 – 0.41).

Nevertheless, in daily practice, both cannulation techniques may be used as crossover methods if the other has failed, thereby producing a cumulative increase in risk as a result of excessive papillary trauma and pancreatic duct injections. A circumstance that also prevails in the prospective randomized "cross over" trials that did not demonstrate a reduced risk of pancreatitis [Mariani et al. 2012, Bailey et al. 2008].

Endoscopic sphincterotomy (EST)

Cleavage of the papilla and the sphincter of Oddi is done in order to obtain biliary access and space for stone extraction and to prevent further stone obstruction, **figure 5**. One of the early controversies concerning the use of ERCP was the need to perform endoscopic biliary sphincterotomy. As a precautionary measure, sphincterotomy was only advocated for elderly or frail patients with other co-morbid illness that excluded them for surgical treatment or for patients with a history of previous cholecystectomy. In such patients, the relatively low rate of serious complications was clearly a major advantage compared with surgery. However, increased use of sphincterotomy in younger patients led to a serious concern about long-term sequelae of the chronic enteric-biliary reflux that occurred following permanent disruption of the barrier between the duodenum and the duct system. The potential problems discussed included cholangitis, cholecystitis, infectious stone recurrence, biliary strictures, biliary pain [Bergman et al. 1996, Costamagna et al. 2002,

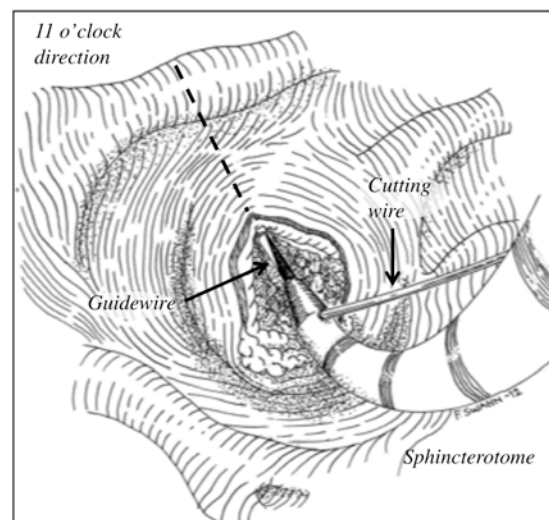


Figure 5. Endoscopic sphincterotomy (EST): With the guidewire secured into the common bile duct, a 5-10 mm long incision is performed by the cutting wire in a 11 o'clock upward direction. It is important for safety reasons that the guidewire is leading the sphincterotome along the correct course and that the cleavage is restricted to the intra-duodenal portion of the sphincter of Oddi.

Hawes et al. 1990], and ultimate development of cholangiocarcinoma [*Tanaka 2002*]. However, data from almost 40 years of experience with sphincterotomy have not supported many of the worst apprehensions mentioned above [*Karlson et al. 1997, Schreurs et al. 2002, Strömberg et al. 2008b*] and patients suffering from benign recurrent biliary complications can be managed endoscopically [*Costamagna et al. 2010*]. Instead, the indications for endoscopic sphincterotomy have been broadened, and sphincterotomy is now offered to most patients, regardless of age [*Sugiyama and Atomi 1998, Tham et al. 1997*]. Other procedure-related complications like bleeding, perforation, cholangitis, and pancreatitis, are all discussed separately later. Most published data suggest that significant complications occur in about 4% to 15% of patients after sphincterotomy, with an overall mortality of about 0% to 1.5% [*Cotton et al. 2009, Christensen et al. 2004, Cheng et al. 2006*].

Endoscopic papillary balloon dilatation (EPBD)

A compelling reason for not using sphincterotomy is that sphincter function is permanently damaged by endoscopic biliary sphincterotomy, whereas the choledocho-duodenal pressure gradient is restored immediately after EPBD [*Isayama et al. 2003*]. A number of prospective trials have compared EPBD with sphincterotomy, and overall complication rate was about the same between the two methods [*Ochi et al. 1999, Vlavianos et al. 2003*], with the important exception that some trials reported a significant higher incidence of severe PEP after EPBD and subsequent death due to pancreatitis [*Bergman et al. 1997, Arnold et al. 2001, Fujita et al. 2003*]. Since endoscopic sphincterotomy is associated with a relatively low complication rate, there is almost no margin for improvement for EPBD, and EPBD is not recommended in routine ERCP practice (EG: Ia, RG: A).

Difficult cannulation

Difficult cannulation refers to the situation where there are major difficulties in entering the bile duct with regular cannulation methods. Some studies have aimed to provide specific criteria for defining a difficult cannulation. These include repeated cannulation attempts (5 or 10 attempts) [*Lee et al. 2009*], extension of cannulation time (10 or 30 minutes) [*Lee et al. 2009, Zhou et al. 2006, Katsinelos et al. 2008, Laasch et al. 2003, Maeda et al. 2003, Kaffes et al. 2005*], repeated guidewire passages or contrast injections into the pancreatic duct (3 or 5 times) [*Zhou et al. 2006, Kaffes et al. 2005*], the necessity of resorting to pre-cut cannulation methods, or complete failure. However, despite attempts to standardize these values, there are no established thresholds to determine at what point a cannulation is termed difficult [*Löhr et al. 2012*]. Even with experienced endoscopists and effective primary cannulation techniques, the rate of difficult cannulations remains approximately around 10% to 30% among unselected cases of non-sphincterotomized patients, depending on how the difficult cannulation is defined [*Udd et al. 2010*]. Irrespective of the technique used, primary cannulation failure rates in most studies are up to 10%, declining to less than 1% at a second or third ERCP attempt [*Kim et al. 2012, Kumar et al. 1995*]. The reason for the great interest in trying to define difficult cannulation is that difficult cannulation probably represents the single most important risk factor that may cause ERCP-related complications such as PEP [*Freeman et al. 1996*]. The risk of PEP after difficult cannulation is approximately 11% to 15%, compared with a rate of 3% to 4% for a standard non-difficult cannulation. [*Freeman et al. 2001, Vandervoort et al. 2002*]. Possible reasons for the increased risk may be prolonged ampullary manipulation, resulting in tissue oedema of the pancreatic sphincter and repeated traumatization or opacification of the pancreatic ductal system [*Masci et al. 2001, Vandervoort et al. 2002, Bailey et al. 2008*].

Pre-cut sphincterotomy

Pre-cut biliary sphincterotomy with the use of a needle-knife sphincterotome is perhaps the most commonly used approach for overcoming a difficult cannulation [Siegel 1980]. It can be performed by two basic approaches: needle-knife papillotomy or supra-papillary fistulotomy, **figure 6 and 7**.

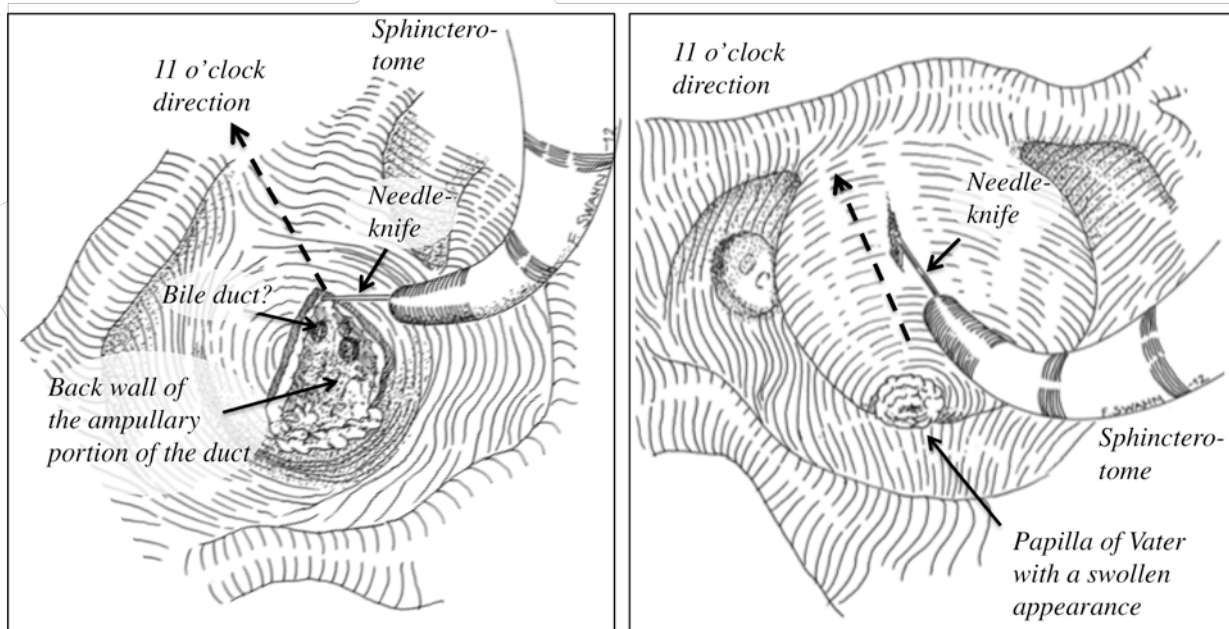


Figure 6 and 7. Figure 6: Pre-cut or needle knife sphincterotomy starts from the papillary orifice and the incision divides the anterior duodenal wall of the ampulla, including the anterior part of the sphincter of Oddi, in a 11 o'clock direction. When opening of the bile duct is identified, cannulation can be completed with the guidewire.

Figure 7: Supra-papillary fistulotomy could be a viable alternative when the papilla is enlarged, for example due to a lodged CBDS. A transmural incision is performed, just a short distance above the orifice, through the anterior wall of the ampulla.

Both methods provide equivalent results for successful cannulation (90% to 96%) and for complication rates of about 2% to 13% [Gullichsen *et al.* 2005, Abu-Hamda *et al.* 2005]. The question of whether the pre-cut technique has a higher risk of PEP than conventional cannulation has long been debated. Some studies report that pre-cut sphincterotomy is associated with a 10%-20% increase in the risk of acute pancreatitis and is, therefore, a dangerous procedure [Suissa *et al.* 2005, Masci *et al.* 2001]. However, there are studies reporting equivalent rates of PEP in patients undergoing pre-cut and conventional cannulation [Freeman *et al.* 2001, Vandervoort *et al.* 2002]. Prolonged cannulation attempts using standard cannulation techniques before a pre-cut probably represent a more significant risk factor for PEP than the pre-cut itself [de Weerth *et al.* 2006, Parlak *et al.* 2007]. Nevertheless, a prospective randomized controlled trial in Toronto [Tang *et al.* 2005] suggested that needle-knife papillotomy after 12 minutes of cannulation attempts is not safer than persistence in the standard cannulation strategy and that both approaches are equally effective in terms of cannulation success (>99%). A meta-analysis of six prospective randomized studies has shown that early application of pre-cut has about the same cannulation frequency as prolonged cannulation attempts, but that early conversion to pre-cut sphincterotomy reduces the risk of PEP, although it does not reduce the overall risk of other procedure-related complications [Cennamo *et al.* 2010]. Pre-cutting with a needle-knife requires substantial endoscopic therapeutic experience and is one of the predictive factors of ERCP-related complications [Shakoor *et al.* 1992]. Furthermore, performing a pre-cut should be considered only when there is a strong indication for bile duct cannulation (EG: III, RG: B) [Cotton 2010].

Pre-cut with an Erlangen papillotome is an unusual alternative method, **figure 8**. The instrument resembles a sphincterotome but there is no tip in front of the cautery wire. The two small single-center case series that are available report excellent cannulation success (98%) and complication rates (8.3%) for the Erlangen papillotome; these are equivalent to needle-knife cannulation [Binmoeller et al. 1996, Palm et al. 2007].

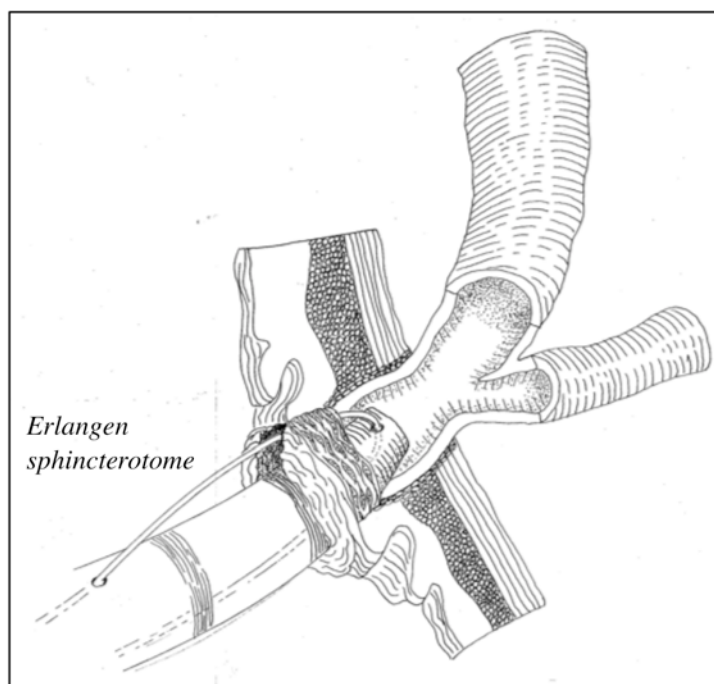


Figure 8. Precut performed by a Erlangen sphincterotome: The cutting wire is placed very close to the tip and the prerequisite to achieve a precut with the Erlangen sphincterotome is to get inside the orifice and then divide the roof of the ampulla.

Pancreatic duct assisted cannulation techniques

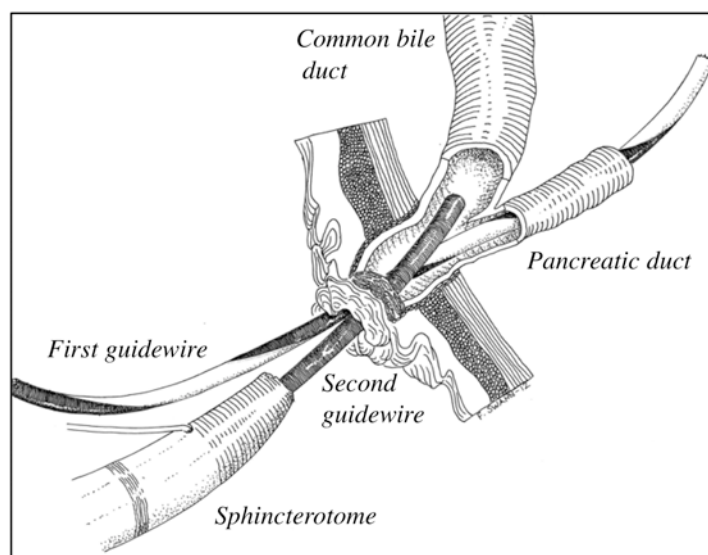


Figure 9. Pancreatic guidewire-assisted or double-wire technique: The first guidewire is placed and left in the pancreatic main duct. With the guidewire fixed in this position, the papillary anatomy is somewhat straighten out and stabilized. A sphincterotome is then advanced through the same instrumental channel alongside the first guidewire and biliary cannulation attempts can be performed with a second guidewire.

There are different two-step procedures for obtaining biliary cannulation by taking advantage of the situation in which cannulation persistently enters the pancreatic duct unintentionally. One of these is the pancreatic guidewire-assisted or double-wire technique, **figure 9**, and the other is trans-pancreatic sphincterotomy, **figures 10 and 11**.

Pancreatic guidewire-assisted or double-wire technique: Few data are available concerning the success and PEP rates for these techniques, and the existing data are inconsistent. In four small case series, the success rate for biliary cannulation ranged from 47%-83%, and the rate of PEP ranged from 2%-12% [Draganov et al. 2005, Ito et al. 2008, Grönroos et al. 2011]. In another trial containing 97 patients in the double-wire group, de Tejada et al. [Herreros de Tejada et al. 2009] concluded that the success rate was not significantly different between the two methods (double-wire 47%

versus standard cannulation 56%) but the percentage of PEP was slightly higher in the double-wire group (17% versus 8%). The discrepancy in results probably reflects the different settings of the studies, with the results favoring the double-wire technique coming from high-volume centres. Nevertheless, the cannulation method itself may be appropriate to try, and if it is not successful, it can always serve as a first step in a trans-pancreatic sphincterotomy.

Some experts advocate the placement of a pancreatic stent before removing the guidewire from the pancreatic duct as a protective measure for avoiding PEP. Pancreatic stent can also be used as a guide for biliary cannulation in combination with or without needle-knife sphincterotomy [Slivka 1996]. Small case series report an overall cannulation success rate close to 90% and a PEP rate around 5% to 20% [Goldberg et al. 2005, Fogel et al. 1998].

Trans-pancreatic sphincterotomy: Data from case series show a successful cannulation rate of 85% after initial trans-pancreatic sphincterotomy and a successful cannulation rate greater than 95% after an additional needle-knife incision [Weber et al. 2008, Halttunen et al. 2009].

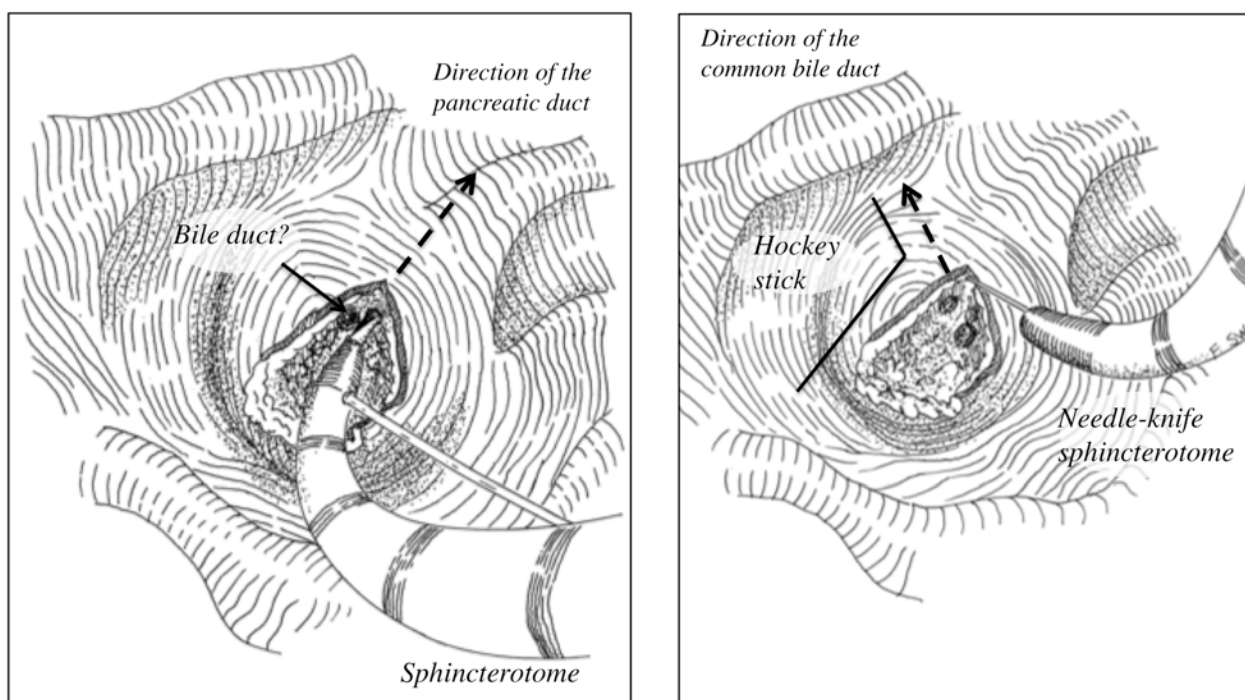


Figure 10 and 11. Transpancreatic sphincterotomy: Figure 10: With the guidewire placed in the pancreatic main duct, a pancreatic sphincterotomy helps to open up and expose the inner side of the ampulla. In about half of the case, the lumen of the bile duct can be visible and cannulated selectively. Figure 11: If the biliary duct does not reveal itself, an additional oblique needle-knife incision is made, from the top of the first pancreatic incision towards the assumed intraduodenal direction of the bile duct (The incision resembles a hockey stick).

It might be assumed that the risk of causing PEP would be increased by these procedures. However, in comparative studies between trans-pancreatic sphincterotomy and conventional pre-cut technique, it appears that the risk of PEP is comparable [Kahaleh et al. 2004, Halttunen et al. 2009]. The rationale for using a prophylactic pancreatic stent would appear to be closest to redundant after the sphincter has disrupted the outlet resistance. The lifetime risk for a young individual undergoing pancreatic sphincterotomy remains unknown. The risk of developing papillary stenosis is currently unclear, and whether it is of any significant clinical importance remains to be seen in future follow-up studies [Udd et al. 2010].

1.3.11 Combined endoscopic treatment of common bile duct stones

Various invasive or surgical approaches are available for entering the supra-papillary portion of the biliary system by insertion of an antegrade guidewire that crosses the papilla of Vater. When the tip of the guidewire is positioned in the duodenum, a so-called rendezvous cannulation can take place in order to get an instant biliary access, **figures 12 and 13**. **Figures 14-17** describes alternative two-step solutions for RV-ERCP.

Combined laparoendoscopic ERCP with rendezvous cannulation (RV-ERCP)

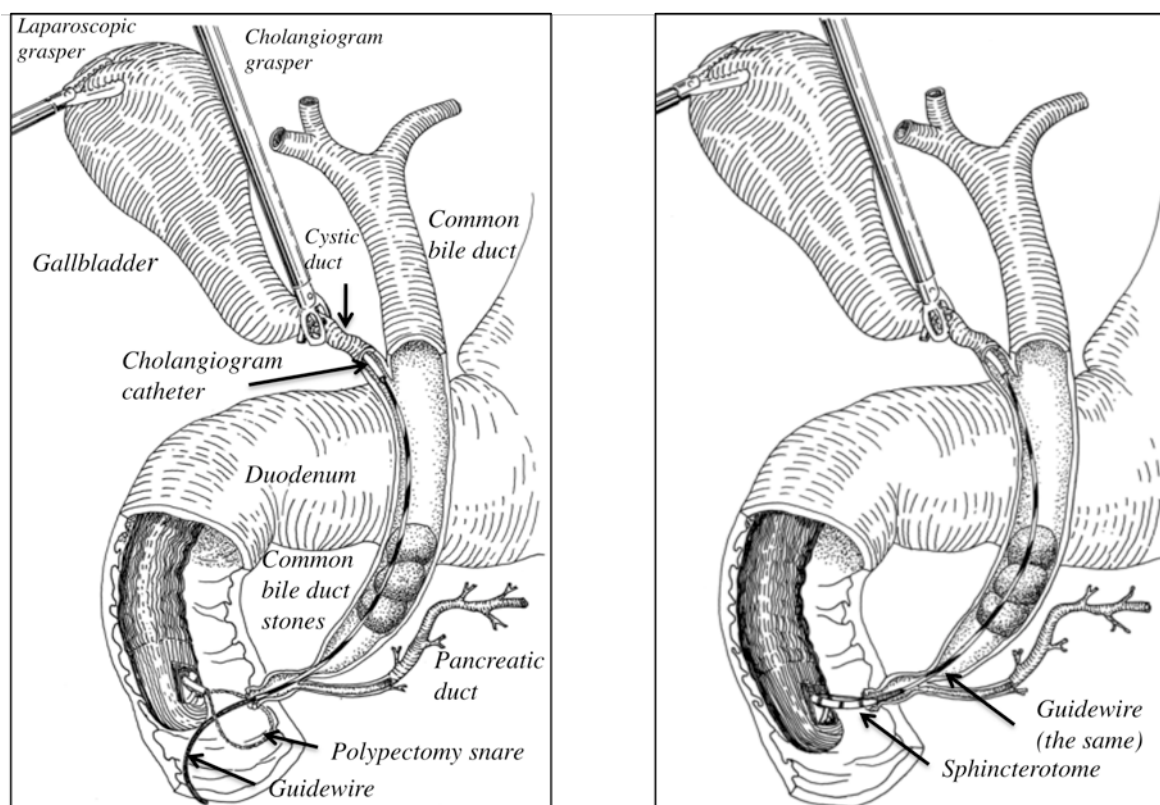


Figure 12 and 13. Figure 12: A guidewire is inserted by the surgeon through the cholangiogram catheter and advanced, under the supervision of fluoroscopy, into the duodenum. The visible end of the guidewire is caught by the endoscopist with the help of a polypectomy snare and pulled through the instrumental channel of the duodenoscope. Figure 13: The sphincterotome is mounted on the same guidewire and advanced down to the duodenum to complete the cannulation.

The first case report concerning laparoendoscopic ERCP with rendezvous was presented by Deslandres *et al.* in 1992 at an international meeting [Gagner 1992]. Later a case series of four patients was published in 1993 [Deslandres *et al.* 1993]. The procedure used can more accurately be described as a needle-knife pre-cut sphincterotomy supported by a biliary-placed catheter in the papilla that was introduced trans-cystically by the surgeon. In 1992-1994 Mayrhofer *et al.* [Mayrhofer *et al.* 1992] and Feretis *et al.* [Feretis *et al.* 1994] independently described a technique in which the surgeon inserted a sphincterotome, rather than a catheter, through the cystic duct and performed a sphincterotomy under simultaneous endoscopic surveillance by a duodenoscope. In 1996, Nakajima *et al.* [Nakajima *et al.* 1996] presented a case in which they carried out the rendezvous procedure by using a front-viewing endoscope and snared the transcystic-placed guidewire with a basket catheter and pulled the guidewire, together with the endoscope, back to the mouth. The duodenoscope was then introduced the entire way down to the duodenum with the guidewire stretched gently at both ends, and cannulation was completed with the sphincterotome running along the transcystic guidewire. Judging by the description, this was probably the first complete laparoendoscopic guidewire-assisted rendezvous

procedure. In 1997, Huntington et al. [Huntington and Bohlman 1979] presented a case series of 14 patients who underwent two-step laparoendoscopic rendezvous with a transcystic guidewire that was left *in situ* with the distal end curled in the duodenum. However, after the first five cases, they had to change the method because the guidewire had escaped out of reach when ERCP was done the next day. Instead, they successfully employed the Nakajima approach. However, this somewhat cumbersome two-step method did not gain any immediate interest. At the end of the millennium, rendezvous technique was still evolving, and Miscusi et al. [Miscusi et al. 1997] and Cavina et al. [Cavina et al. 1998] presented small case series of different ways of performing rendezvous-like procedures by using retrieving baskets or inserting a sphincterotome through the cystic duct and assisting the cannulation by opening the papilla by opening the basket or by capturing the sphincterotome and pulling it into the bile duct. Notably, the study by Cavina et al. [Cavina et al. 1998] seems to present a single case of guidewire-assisted rendezvous as we know it today. At the same time, interest was expressed in implementing peroperative ERCP without using rendezvous techniques. A plurality of case series [Basso et al. 1999, Cemachovic et al. 2000, Kalimi et al. 2000, Meyer et al. 2002, Williams and Vellacot 2002, Wright et al. 2002] and a recent randomized trial [ElGeidie et al. 2011] showed that peroperative ERCP without rendezvous assistance could be as effective and safe as conventional pre- or post-operative ERCP, in terms of stone clearance and ERCP-associated complications. However, an important and unanimous conclusion of these studies was that single-stage management of CBDS offers a stricter indication for ERCP, provided peroperative cholangiography is done at the same time, which in turn minimizes the risk of unnecessary (negative) ERCP investigations. Moreover, if endoscopic treatment fails, the surgeon may take immediate action to convert the procedure for surgical treatment options.

Another controversy was whether common bile duct stones detected at the time of laparoscopic cholecystectomy should be managed by laparoscopic technique or with peroperative ERCP. A comparative study by Wei et al [Wei et al 2003], two randomized trials by Hong et al [Hong et al 2006], and two studies by ElGeidie et al [ElGeidie et al 2011a, 2011b] could not find any overall statistically significant differences between laparoscopic stone extraction and non-rendezvous ERCP treatment in terms of success rate (88% to 92% versus 89% to 97.2%) or post-operative complications (5% to 12% versus 7% to 9.3%).

An extension of the previous issue was whether peroperative ERCP performed with rendezvous and assisted by the transcystic approach was an improvement over standard ERCP techniques. Five Italian case series [Tatulli et al. 2000, Filauro et al. 2000, Iodice et al. 2001, Saccomani et al. 2005, Borzellino et al. 2010], one Swedish study [Enochsson et al. 2004], and one Egyptian [Ghazal et al. 2009] case series included a total of 345 patients with CBDS treated with laparoendoscopic techniques with consistent use of guidewire-assisted rendezvous. The overall stone clearance rates ranged from 86% to 98% with mean and median values close to 94%. Furthermore, compared with the expected situation, PEP was markedly absent. The latter observation became a target issue in two RCT between preoperative ERCP and RV-ERCP. A study by Rabago et al. [Rábago et al. 2006] and another by Lella et al. [Lella et al. 2006] suggested that preoperative ERCP followed by LC was equally effective as RV-ERCP in terms of stone clearance but that PEP was significantly lower in the RV-ERCP group. A comparative study by La Greca et al. [La Greca et al. 2007] found that pathological high levels of pancreatic amylase, which are indications of iatrogenic pancreatic injury, were significantly greater in patients who were treated with conventional ERCP than in patients undergoing laparoendoscopic rendezvous ERCP.

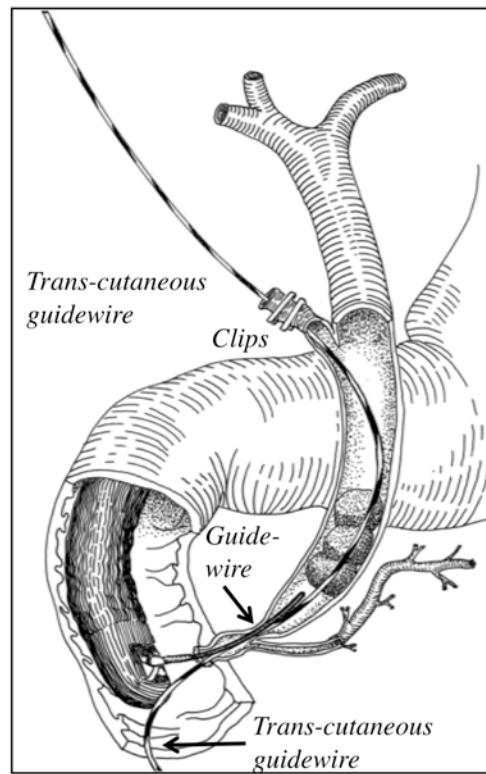
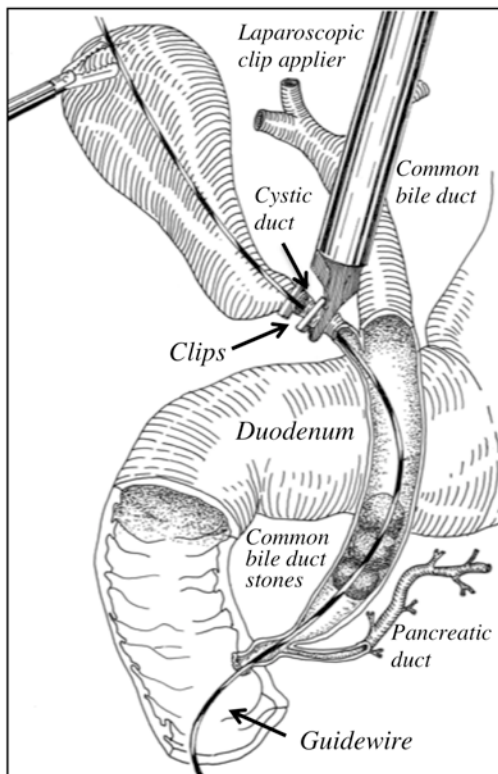


Figure 14 and 15. The rendezvous procedure can also be performed in a two-step version.

Figure 14: During cholecystectomy a guidewire is placed and left in the duodenum and the cystic duct is closed with clips around the guidewire. The cholecystectomy is completed and the following ERCP will take place within the following 48 hours to avoid accidental dislodgement of the guidewire.

Figure 15: At postoperative ERCP the endoscopist will find the guidewire in the duodenum and in order to cannulate one may slide alongside the existing guidewire or try to insert the sphincterotome directly over the tip. The trans-cutaneous guidewire can then be removed when the cannulation and sphincterotomy is completed.

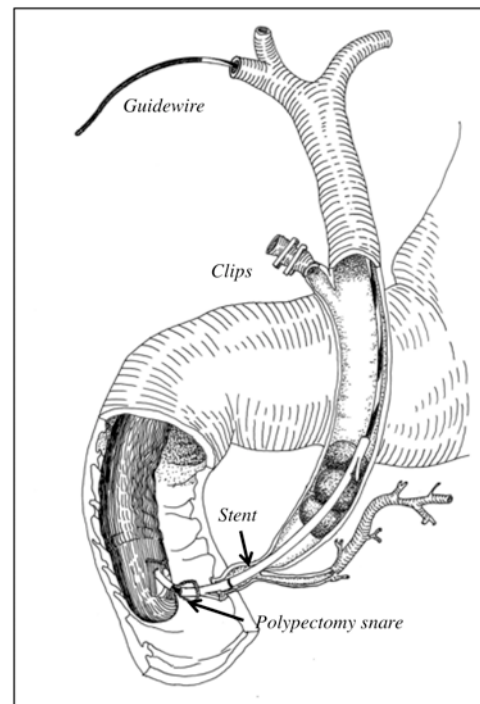
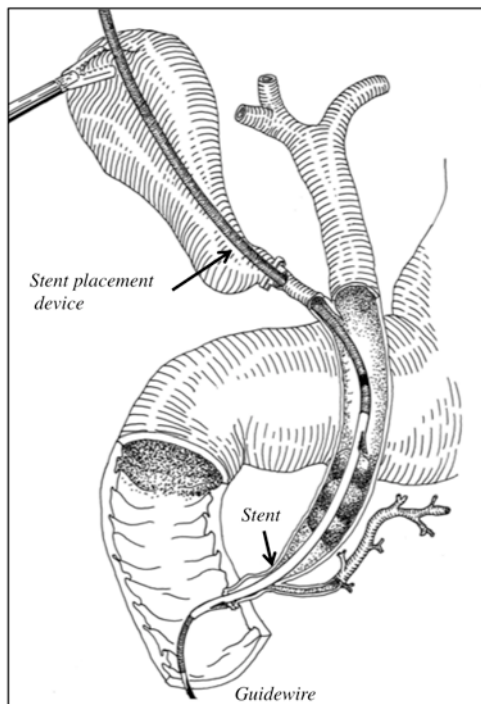


Figure 16 and 17. Figure 16: An alternative rendezvous procedure is to insert, under the guidance of fluoroscopy, a plastic stent which is placed across the papilla for downstream control. The guidewire is then removed and the cholecystectomy is completed. Figure 17: At the following post-operative ERCP, guidewire cannulation can be performed through the stent and then removed over the guidewire with the help of a polypectomy snare.

1.3.12 Alternative methods for obtaining biliary access

Failure to achieve deep biliary cannulation occurs in less than 10% of patients [Enochsson et al. 2010]. Alternative management includes a percutaneous approach by PTC or a transmural approach by means of EUS.

Percutaneous transhepatic cholangiography (PTC)

Percutaneous transhepatic cholangiography was originally a radiologic imaging technique for the purpose of visualizing biliary anatomy and pathology [Carter and Saypol 1952]. PTC requires the insertion of a needle through the abdominal wall and into the liver to reach an intrahepatic bile duct. PTC is no longer used for routine diagnostic purposes, but it may be used as an alternative option when ERCP or surgery is not feasible [Ozcan et al. 2012]. With PTC technique, CBDS can be removed [Dotter et al. 1979] and fragmented [Burhenne et al. 1989]. A percutaneous transhepatic choledochoscope can provide support and improve the therapeutic results. Reported success rates for extra-hepatic stones are over 95% [Ozcan et al. 2012]; success rates for intrahepatic stones are somewhat lower, ranging between 60% and 90% [Cheon et al. 2009]. However, it is generally accepted that percutaneous biliary procedures have higher complication rates than ERCP; these include cholangitis, subphrenic abscess, bleeding, haemobilia and intra-abdominal bile leakage [Sirinek and Levine 1989]. PTC was used in the original method of a rendezvous cannulation that was described in the mid 1980's [Long et al. 1984, Shorvon et al. 1985, Scapa et al. 1994] and was quite similar to the RV-ERCP that Nakajima et al. described [Nakajima et al. 1996] (see 1.3.11).

Endoscopic ultrasonography guided rendezvous (EUS RV)

With the recent advent of linear-array echo endoscopes, EUS has emerged as a salvage procedure for failed biliary cannulation. Dilatated intrahepatic bile ducts can be needle-punctured under EUS guidance from the stomach into the liver (hepaticogastrostomy) [Burmester et al. 2003] and extra-hepatic ducts can be reached through supra-papillary puncture of the duodenum (choledochoduodenostomy) [Artifon et al. 2007] followed by cholangiography and antegrade insertion of a guidewire into the CBD and transpapillary advancement. Although the literature is sparse, the available data concerning choledochoduodenostomy appear promising, with a cannulation success rate exceeding 90% and a procedural complication rate around 3% to 4%, which seems to be on par with pre-cut sphincterotomy [Dhir et al. 2012]. However, hepaticogastrostomy seems to have a considerably higher rate of complications (20%) [Artifon et al. 2012].

1.3.13 Endoscopic extraction of common bile duct stones

Balloon and basket

With an adequate endoscopic sphincterotomy, sometimes combined with papillary balloon dilatation, stones measuring up to 15 mm can be removed with retrieval balloons or baskets, and it is suggested that more than 80% of all common bile duct stones should be managed when these standard procedures are used (EG: IV, RG: C) [Bergman et al. 1997]. Stones that cannot be extracted using this first-line treatment are referred to as difficult common bile duct stones.

Dilatation-assisted stone extraction (DASE)

In the cases in which standard techniques fail due to large stone diameter, endoscopic papillary large balloon dilatation following sphincterotomy could be an appropriate second-line alternative for difficult stones, **figure 18**. Previous prospective studies [Maydeo and Bhadari 2007, Ersoz et al. 2003] have reported successful and safe removal in approximately 95% of the cases when using an esophageal/pyloric balloon ranging from 15 mm to 20 mm. Complications, mostly transient bleeding, occurred in 15%. The risk for developing PEP seems to be surprisingly low, considering the similarity with EPBD technique. The DASE technique, however, is preceded by sphincterotomy; therefore mechanical compression is less towards the pancreatic duct [Attam and Freeman 2009]. However, experience is still limited in this area. There are concerns about whether this technique is applicable to young patients, and the dilatation limit for patients with a slender bile duct has not yet been determined [Attasaranya and Sherman 2007].

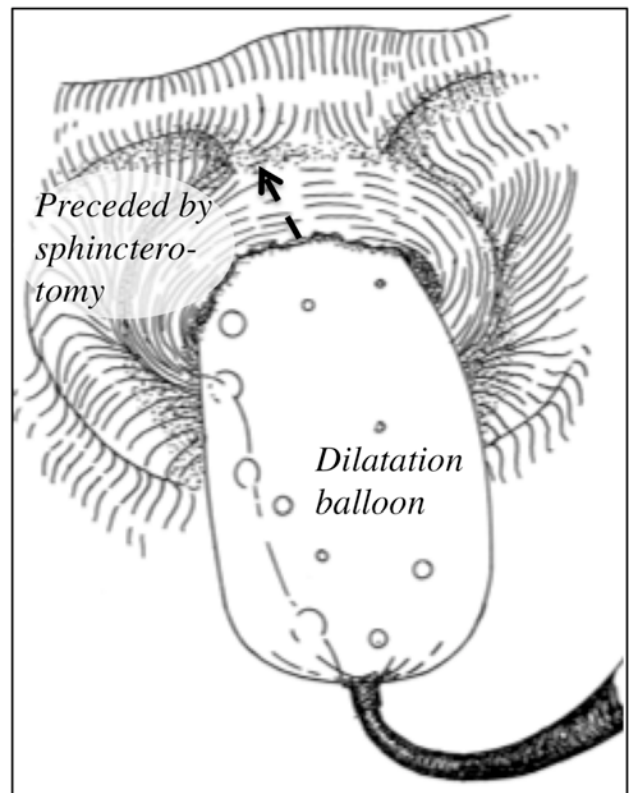


Figure 18. Dilatation-assisted stone extraction (DASE): After conventional biliary cannulation and sphincterotomy, a large balloon dilatation ranging from 15-20 mm is performed. Large stones can then be extracted by various means.

Mechanical lithotripsy

Mechanical lithotripsy involves the use of a lithotripter that fragments the stone by sheer compressing or crushing force against the metal sheet of the lithotripsy device after the stone has been captured within a wire basket. Bile duct clearance using a mechanical lithotripter is successful 80% to 90% of the time, even when stones from 15 mm to 35 mm in size are included in the analysis. Complications are seen in about 10% of cases [Cipolletta et al. 1997].

Intraductal endoscopy with electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL)

As a third-line treatment for difficult stones, for use when the previously-mentioned methods have failed or are not feasible, electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL) can be applied as an alternative, **figure 19**. Although EHL and LL do not share the same physical principles, both methods lead to electrical energy that, when discharged in liquids, forms an explosive plasma channel or bubble by vaporization, which in turn will cause a high-energy shock wave that is delivered as brief pulses that will finally shatter the stone into pieces [Binmoeller et al. 1993]. Both EHL and LL have about the same efficacy, with fragmentation rates >95% and stone clearance rates ranging from 80% to 90%, and minimum numbers of adverse events [Jakobs et al. 1997, Arya et al. 2004] (EG: III, RG: B).

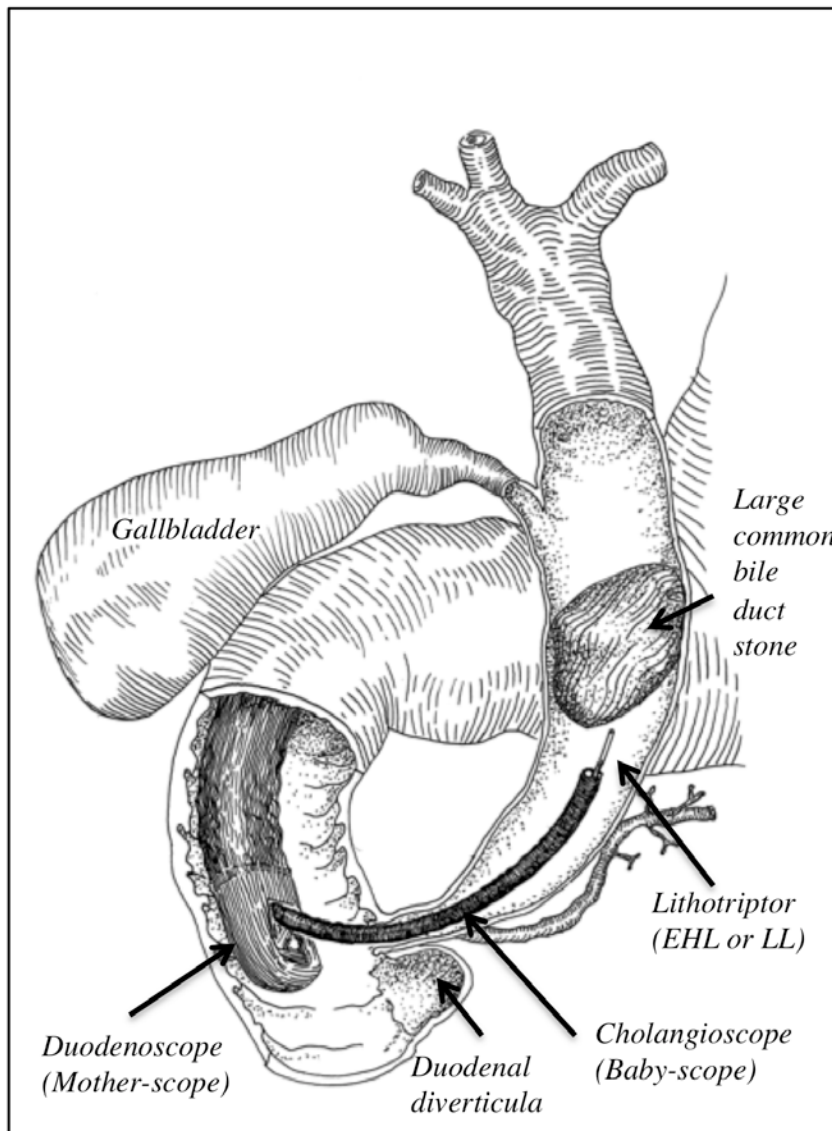


Figure 19. Intraductal endoscopy with electrohydraulic lithotripsy with so called mother-baby endoscopy. To target the stone, the lithotripter probe must be placed close to the stone, which is accomplished under direct visual cholangioscopic control in order to prevent ductal trauma or perforation.

1.3.14 Permanent endoprosthesis of common bile duct stones

Biliary stenting has been suggested as an alternative to curative therapy in elderly or frail patients who are unlikely to tolerate surgery or prolonged endoscopic procedures [Bergman *et al.* 1995, De Palma *et al.* 2000]. In addition, some authors support long-term stenting (3 to 6 months) because there are numerous examples showing that 60% of stones can eventually decrease in size, split into pieces, or even disappear under the influence of an indwelling plastic endoprosthesis, preferably multiple pigtail ones [Horiuchi *et al.* 2010, Lee *et al.* 2011]. Nevertheless, the greatest draw-back to long-term indwelling stenting is the increased risk of recurrent cholangitis and mortality, especially for patients with a gallbladder *in situ* [Chopra *et al.* 1996, Hui *et al.* 2003, Pisello *et al.* 2008]. In view of the long-term risk of biliary-associated morbidity and death, bile duct clearance should always be prioritized as first-line treatment if possible (EG: Ib, RG: A).

1.3.15 Alternatives to surgical and endoscopic treatment

Extracorporeal shockwave lithotripsy (ESWL)

ESWL can be a safe and effective alternative for the treatment of difficult common bile duct or cystic duct (Mirizzi) stones in patients who are at high risk for surgery and in whom all conventional methods, including EHL and LL, have failed [Lindström *et al.* 1992]. Bile duct stone clearance following ESWL ranges from 80%-90%. However, the procedure is rather difficult and time-consuming to perform. Most patients will require ERCP with nasobiliary tube placement prior to the first ESWL session to enable stone identification. Following the ESWL session, a second ERCP is performed to remove the CBDS and/or fragments. In general, ESWL has to be repeated and followed by subsequent ERCP.

Dissolution agents

During the late 1970s and early 1980s, alternatives to cholecystectomy for the treatment of biliary stone disease became available. Pharmacological dissolution of common bile duct stones by different solubilizing agents such as mono-octanoin, methyl tert-butyl ether (MTBE) [Diaz *et al.* 1992] and EDTA/bile acid solution, administered with an ERCP-installed nasobiliary tube, has been proposed. Unfortunately, the overall efficacy of these agents is disappointingly low. In addition, they have serious side-effects and are, therefore, not recommended under any circumstances in clinical practice (EG: III, RG: B).

Bile acid dissolution therapy with chenodeoxycholic [Schoenfield and Lachin 1981] and ursodeoxycholic acid [Bachrach and Hofmann 1982] has been tested together with extracorporeal lithotripsy methods (ESWL) for use against gallstones (cholesterol stones). However, interest waned when it became apparent that recurrence of symptomatic biliary stones was seen in over 50% of the patients [Lanzini and Northfield 1994].

1.3.16 ERCP-associated complications

Acute pancreatitis or post-ERCP pancreatitis (PEP)

Acute pancreatitis is the most frequent and important complication associated with ERCP and has an approximate incidence around 3.5% among unselected patients [Andriulli *et al.* 2007b, Enochsson *et al.* 2010]. In 90% of cases, the disease occurs as a mild (45%) to moderate (46%) inflammation that is harmless in its nature when it is limited to the pancreatic gland. Usually the patient recovers within days after treatment with conservative measures. In case of severe PEP, a serious and seemingly uncontrolled inflammation develops that, in a worst case scenario, can lead to systemic inflammatory response syndrome (SIRS) and necrosis of pancreatic tissue with severe consequences in the form of secondary infection, abscess development, sepsis and multiple organ dysfunctional syndrome (MODS). The overall reported mortality rate for unselected patients with pancreatitis is around 3% (CI, 1.65% - 4.51%) and patients diagnosed with severe necrotizing pancreatitis have a mortality rate around 40% to 60%, despite intensive care treatment [McKay *et al.* 1999].

Definition of post-ERCP pancreatitis: The consensus definition of PEP and the classification of severity were proposed by Cotton *et al.* [Cotton *et al.* 1991]: a clinical pancreatitis with amylase at least three times normal more than 24 hours after the procedure that requires hospital admission or prolongation of planned admission. There are, however, some variations across studies in the definition of clinical pancreatitis, such as new or worsened abdominal pain that take into account patients having a temporary outburst of already-established

pancreatitis [Freeman et al. 1996]. There are also examples of authors who have different pathological thresholds for amylase - two-fold [Acosta et al. 2006] or even five-fold [Lella et al. 2006] increased values. However, high levels of amylase (hyperamylasemia) are also frequently observed shortly after ERCP without concomitant clinical signs of pancreatitis, and sometimes the opposite is observed [Testoni and Bagnolo 2001, Bretthauer et al. 2007]. The grading system for severity proposed by Cotton et al. [Cotton et al. 1991] is based mainly on the length of hospitalization: mild is less than three days, moderate is more than four and shorter than ten days and severe is more than ten days or hemorrhagic pancreatitis, phlegmon, pseudocysts or the need for interventional procedures.

The mechanism responsible for PEP is not fully known. A number of large prospective multicenter studies [Loperfido et al. 1998, Williams et al. 2007] and a large meta-analysis [Masci et al. 2003] suggest that there are a number of procedure-related and patient-related causes that should be considered as independent risk factors. The independent risk factors used in multivariate analysis may also have a cumulative effect when they are combined [Freeman et al. 2001, Cheng et al. 2006].

Procedure-related risk factors: A number of events have been associated with PEP, including biliary balloon dilatation, a high number of cannulation attempts, ampullectomy, and mechanical damage to the papilla and pancreatic sphincter by, for example, pre-cut sphincterotomy with resulting development of papillary edema. Contrast medium in the main pancreatic duct causing intracellular disruption of acinar cells due to high hydrostatic injection pressure is also a well-known cause.

High-risk patients: Certain categories of patients seem to be at greater risk than others. Suspected sphincter of Oddi dysfunction (SOD) is probably the strongest solitary risk factor, with an incidence of post-ERCP pancreatitis between 10% to 30%. Female gender, a previous history of acute pancreatitis, young age, is also categories associated with a higher risk. Chronic pancreatitis appears to decrease the risk.

Hemorrhage

Bleeding is a relatively common complication of sphincterotomy, with an overall frequency of 0.8 % to 3.2% [Masci et al. 2001] depending on the definition. Severe bleeding has been reported in 0.3% to 0.5% of sphincterotomy cases [Freeman et al. 1996, Christensen et al. 2004]. The vast majority of all episodes of haemorrhage usually ceases without treatment or managed successfully within minutes by standard haemostatic endoscopic procedures. As a last resort, severe bleeding can be managed either by angiographic or surgical methods.

Perforation

Perforations caused by sphincterotomy are rare and occur in about less than 1% of all procedures. They are usually retro-duodenal and are therefore classified anatomically as retroperitoneal perforations. Intraperitoneal perforations are very rare, but are more severe. Generally speaking, intraabdominal perforations can be extremely dangerous for the patient if not treated in time, and fatality rates of 8% to 14% have been reported [Freeman et al. 1996, Christensen et al. 2004]. A majority of perforations are small and appear to be able to be managed by conservative treatment. However, the recommendations in the literature vary widely from conservative treatment to early open operation, endoscopic intraductal drainage with a biliary stent, or nasobiliary tube placement, depending on the clinical course. Since delayed recognition is associated with poor outcomes, the challenge is to identify the perforation early in the course of the event and select those patients who will not respond on conservative treatment.

Prevention of post-ERCP pancreatitis (PEP)

Endoscopic pancreatic duct stent: Prophylactic pancreatic stenting is recommended to prevent post-ERCP pancreatitis in conditions that are considered high-risk cases [Choudhary et al. 2011, Kawaguchi et al. 2012], including SOD [Smithline et al. 1993, Tarnasky et al. 1998], difficult cannulation [Fazel et al. 2003], endoscopic papillectomy [Harewood et al. 2005], and papillary balloon dilatation [Aizawa and Ueno 2001], (EG: Ib, RG: A). Prophylactic pancreatic stents are designed to overcome temporary ERCP-related papillary oedema. After their function has been performed, more than 95% will dislodge spontaneously within days after the procedure, mitigating the need for a second-look endoscopy. There seems to be no doubt about the efficacy of prophylactic pancreatic stents in high-risk patients [Andriulli et al. 2007a, Singh et al. 2004]. On the other hand, there are controversies concerning whether stenting should be performed in patients with an average risk of developing PEP, especially since the incidence of PEP has been reported to be as high as 65% among patients in whom cannulation of the pancreatic duct has failed [Freeman et al. 2004]. However, a recent prospective multicenter randomized trial that included 37 high-volume centres in Japan, which compared prophylactic pancreatic stent placement versus non-stent placement in an unselected patient cohort regardless of risk factors, found post-ERCP pancreatitis in 7.9% of the prophylactic stent group and 15.2% of the non-prophylactic stent group [Sofuni et al. 2011]. The success rate of pancreatic stent placement was 88.3%. However, the difference between groups was not statistically significant in the intention-to-treat analysis, probably due to a relatively small sample size.

Pharmacological prevention of post-ERCP pancreatitis

A number of forms of pharmacological agents have been suggested over the years to prevent PEP. However, available data are conflicting. There are examples where the early data was promising but was then tempered by larger, more carefully-designed studies that failed to find a statistically-significant benefit for the drug in question. Agents that have been shown to be ineffective include pharmacological drugs that reduce the pressure of the sphincter of Oddi such as glyceryl trinitrate (nitroglycerin) [Shao et al. 2010], botulinum toxin [Gorelick et al. 2004], epinephrine [Matsushita et al. 2009], lidocaine [Prat et al. 2002], and nifedipine [Sand and Nordback 1993], or antioxidant agents such as allopurinol [Andriulli and Annese 2008], N-acetylcysteine [Katsinelos et al. 2005] and β -Carotene [Lavy et al. 2004] or anti-inflammatory agents such as glucocorticoids [Bai et al. 2008], heparin [Li et al. 2012], interleukin-10 [Sherman 2009b], pentoxifylline [Kapetanios et al. 2007], or semapimod [van Westerloo et al. 2008], or recombinant platelet-activating factor acetylhydrolase [Sherman et al. 2009a], or antibiotics [Brand et al. 2010]. Prophylaxis with antisecretory drugs (e.g. somatostatin analogues) and antiprotease drugs (e.g. gabexate, ulinastatin, nafamostat mesylate) showed some benefit in smaller trials, but they were found to be ineffective in patients with an average and high risk for post-ERCP pancreatitis when they were evaluated in a large meta-analysis [Andriulli et al. 2002, Seta and Noguchi 2011].

According to the European Society of Gastrointestinal Endoscopy (ESGE), the only prophylactic drug that could be recommended in clinical practice for limiting the development of PEP are non-steroidal anti-inflammatory drugs (NSAIDs) given as a single dose (diclofenac 100 mg) administered rectally (EG: Ia, RG: A) [Dumonceau et al. 2010]. However, similar studies with NSAIDs administered intramuscularly [Senol et al. 2009] or intravenously [Bhatia et al. 2011] have not shown any reduction of post-ERCP pancreatitis. So far, no pharmacological drug has been universally recommended in the purpose to reduce the incidence of post-ERCP pancreatitis.

2 AIMS

The aims of the studies in the present thesis were as follows:

- Paper I** Primary: To evaluate the efficacy of RV-ERCP in a routine clinical setting.
Secondary: To study whether the method is safe in terms of complications associated with ERCP and to determine whether the prolonged operation time compared with conventional LC influences the hospital stay.
- Paper II** Primary: To evaluate 10 years of clinical experience with peroral intraductal mother-baby endoscope assisted lithotripsy with EHL or LL treatment of difficult CBDS, focusing on the success rate of stone clearance.
Secondary: To evaluate the long-term clinical outcome concerning stone recurrence, cholangitis and biliary associated pain.
- Paper III** To examine whether the use of RV-ERCP could prevent post-ERCP pancreatic damage compared with conventional ERCP cannulation in patients treated for CBDS.
- Paper IV** Primary: To investigate the relation between cannulation techniques (RV-ERCP versus conventional ERCP) and the risk of developing PEP.
Secondary: To identify risk factors other than cannulation technique associated with PEP after ERCP on non-sphincterotomized papillas.

3 PATIENTS AND METHODS

3.1 PAPER I

Design and data collection

All data were collected and analyzed retrospectively from medical charts and included patients demographics, operative and radiographic findings, the success rate of stone clearance, procedural time, per- and postoperative complications, and the length of hospital stay. The study period covered two years (January 2000 to December 2001) of cholecystectomies at the Karolinska University Hospital Huddinge. The department uses IOC policy on a routine basis. Out of all cholecystectomies, we identified all patients treated with RV-ERCP as a result of IOC findings of CBDS and compared this group with the large cohort of cholecystectomies.

Surgical procedure

LC was conducted with the four trocar technique *ad modum* Olsen [Olsen 1991] together with peroperative cholangiography through a small incision in the cystic duct (cysticotomy). When the cholangiogram suggested a common bile duct stone, the endoscopy team was alerted. After the endoscopist had positioned the duodenoscope *en face* in front of the papilla, an RV-ERCP with sphincterotomy was conducted according to previous description. See figures 12 and 13. If stone clearance was incomplete, an indwelling plastic biliary stent was placed as a bridge to final postoperative endoscopic treatment. After the RV-ERCP was terminated, the LC could proceed accordingly to the standard protocol.

Logistic protocol

A basic logistical chart was created for using RV-ERCP during office hours. Among other things, there were instructions for the operating staff about arranging the endoscopic equipment, X-ray apparatus and anaesthetic machine in the operating theatre during the waiting time for the endoscopy team to arrive. In addition, a trolley was purchased to transport the necessary endoscopic equipment and the duodenoscope.

Statistical analyses

Baseline characteristics and comparative data were calculated and quantitative data was presented as mean values, median values and standard deviations. The level of significance (α -value) was 5% ($p=0.05$).

3.2 PAPER II

Design and data collection

In this retrospective study, all data was collected through medical charts from all identified patients who were treated consecutively for difficult CBDS with mother-baby scope-assisted lithotripsy at two different Swedish surgical units, the Karolinska University Hospital and Östersunds County Hospital, during the period from December 1995 to September 2006. In the cohort, we analyzed data concerning the following: patient demographics, preoperative clinical features, previous treatments, per procedural endoscopic and radiographic characteristics of stones, success rates of stone fragmentation and ductal stone clearance, procedural times, per- and postoperative complications, length of hospital stay, and long-term follow-up. Information concerning long-term follow-up data was collected from medical charts or by contacting patients directly by telephone at the time of the follow-up evaluation.

Surgical procedure

Lithotripsy within the CBD was performed under direct optic surveillance by two endoscopists, with one endoscopist monitoring a per oral cholangio-endoscope (baby-scope) that in turn was supported by a second endoscopist who positioned the baby-scope through the instrumental channel of a duodenoscope (mother-scope). The lithotripter was advanced through the instrumental channel of the baby-scope. The fragmentation was conducted either by EHL, using a 1.9 Fr coaxial electrode probe or by pulsed dye LL, using a 200 µm fine-caliber laser fiber at a wavelength of 504 nm. All procedures were performed under general anesthesia with the patient in the supine position. Intravenously-administered antibiotics were used prophylactically in all patients. If complete stone clearance was not accomplished, an indwelling plastic biliary stent was placed as a bridge to the next treatment session.

Statistical analyses

All patients referred for intraductal treatment for difficult CBDS were analyzed as an intention to treat. Baseline characteristics and descriptive data were calculated and data were presented as mean values, median values, and ranges.

3.3 PAPER III

Design and data collection

A prospective comparative controlled trial on patients undergoing ERCP in two different endoscopic treatment settings due to CBDS. Preoperative screening data was recorded concerning the following: physical examination, baseline laboratory values, radiographic imaging (ultrasound, CT-scan or MRCP) in order to confirm the presence of CBDS and to rule out ongoing pancreatitis and/or cholecystitis, which in turn could influence the results.

Three study groups were identified. Regardless of the suspicion of CBDS, every patient with cholecystolithiasis who was fit for general surgery was prepared for a standard LC. According to the results of the IOC, patients were allocated to one of two groups: RV-ERCP (if IOC was positive for CBDS) or LC alone (if IOC turned out to be negative). The latter group became a control group. The conventional ERCP group consisted of previously cholecystectomised patients with a high suspicion of choledocholithiasis.

The endoscopist documented all data according to the protocol immediately after the procedure. All patients were hospitalized for a minimum of 24 hours and had a clinical examination and collection of blood samples at 4 hours, 8 hours and 24 hours postoperatively. All postoperative clinical examinations and the 30-day follow-up interview were performed by a nurse assigned to the study.

The primary objective was to compare the incidence of pancreatic injury estimated as leakage of pancreatic enzymes in the cohorts assigned to the different treatment groups. Secondary objectives were to study the rate of PEP, successful cannulation, and CBDS clearance.

3.3.1 Surgical procedures

Laparoscopic cholecystectomy (LC)

LC was performed using standard laparoscopic technique *ad modum Olsen*, [Olsen, 1991] with pneumoperitoneum, introduction of four troachars, and isolation of the cystic duct. All procedures included peroperative cholangiography through a small incision in the cystic duct, in order to exclude CBDS and to delineate the bile duct anatomy.

Combined laparoendoscopic ERCP with rendezvous- assisted cannulation (RV-ERCP)

Performed according to the previous description, see figures 12 and 13.

Conventional ERCP

All patients were investigated under general anesthesia, and ERCP was performed by experienced endoscopists, using conventional duodenoscope and biliary retrograde cannulation by wireguided cannulation (WGC) through a sphincterotome, **see figures 2 and 3**. If cannulation failed, pre-cut techniques was used, **see figure 6**. After sphincterotomy, stone extraction was carried out with retrieval balloons or baskets. If stone clearance was incomplete, a biliary endoprosthesis was inserted.

Laboratory analysis

Blood samples were collected in ice-cold EDTA (ethylenediaminetetraaceticacid) tubes within 30 minutes; plasma was obtained after centrifugation and stored at -70°C until further analysis. Procarboxypeptidase B and trypsinogen-2 was determined in plasma by use of in-house double-antibody enzyme-linked immunosorbent assays (ELISA) developed at the Department of Surgery, Clinical Sciences, Malmö Skåne University Hospital. Pancreatic amylase and C-reactive protein (CRP) were collected in venous blood and analyzed consecutively at the Department of Clinical Chemistry at the Karolinska University Hospital in Huddinge. All samples were coded at analysis.

3.3.2 Statistical analyses

Sample size estimation

We made a sample size calculation based on following assumptions: significance level of $\alpha=0.05$, power of 75% ($\beta=0.25$), and a reduction of the outcome pancreatic enzyme leakage from 14% in the conventional ERCP group to 1% in the RV-ERCP group. This estimation was based on previous studies of proCAPB and post-ERCP pancreatitis [Petersson *et al.* 2002].

Statistical Analysis

Pancreatic amylase, proCAPB and trypsinogen-2 were analyzed using a mixed linear model with one between-group factor, *i.e.* conventional ERCP, rendezvous ERCP and control group, and one within-group factor, which was time (0, 4 hours, 8 hours and 24 hours), and the subsequent interaction between the factors. In the case of significant interactions (p -values less than 0.05), simple main effect tests were performed, *i.e.* effects of one factor holding the level of the other factor fixed.

Results were presented as mean, SD, and 95% confidence intervals. The variables with positively skewed distributions (e.g. proCAPB, trypsinogen-2, pancreatic amylase) were log-transformed before the formal analyses. The binomial responses were subsequently analysed by fitting a generalized estimating equations model with the Genmod procedure. These latter parameters were presented as odds ratios (OR) and 95 % CI. P values less than 0.05 were considered statistically significant.

In order to investigate the strength of correlation between 8-hour results for enzyme leakage (pancreatic amylase and proCAPB) and possible associative variables; The Spearman Rank Order Correlation was used for analysis of age, procedure time, number of cannulation attempts, pancreatic duct cannulation, and contrast injection variable. The Mann-Whitney U Test was used to analyse gender, use of a precut technique. The Kruskal-Wallis ANOVA by Ranks Test was used for ASA-classification.

3.3.3 Definition of outcome measures

Post-ERCP pancreatitis (PEP)

PEP was defined according to the 1991 Consensus Guidelines [Cotton *et al.* 1991] as a post-procedural onset of upper abdominal pain persisting for at least 24 hours combined with an increase in serum pancreatic amylase equivalent to at least three times the upper limit of normal. The severity of PEP was graded according to the same guidelines.

Pancreatic Amylase

Measurement of pancreatic amylase is generally used in clinical practice to support the diagnosis of acute pancreatitis and was used in this study as a surrogate marker for pancreatic injury caused by ERCP intervention. Hyperamylasemia was defined as amylase levels more than three times the upper limit of normal 4 to 24 hours after ERCP.

Procarboxypeptidase B (proCAPB)

Procarboxypeptidase B (proCAPB) is by definition an inactive proenzyme to the activated carboxypeptidase B (aCAP) and is one of the major digestive proteolytic enzymes synthesized in the pancreatic acinary cells. Under normal physiological conditions, it is activated in the duodenum by trypsin, in company with other proteolytic, amylolytic, and lipolytic enzymes [Geokas *et al.* 1975]. ProCAPB is a large (45 kDa) stable protein and, in normal conditions, is found in low concentrations in both serum and urine [Müller *et al.* 2003]. Therefore, proCAP was used in the current study as a surrogate variable for injury of the pancreatic gland.

Trypsinogen-2, Human anodal trypsinogen (HAT)

Trypsinogen is an inactive precursor of trypsin, which is the key enzyme for activation of all proteolytic enzymes in the duodenum and also an important protagonist in the early stage of acute pancreatitis. Trypsinogen appears in two major forms in pancreatic juice: trypsinogen-1 (cathodal trypsinogen) and trypsinogen-2 (anodal trypsinogen) [Kimland *et al.* 1989]. Elevated levels of both trypsinogen 1 and 2 are associated with acute pancreatitis and represent intracellular leakage from disrupted acinar cells in the pancreas [Regnér *et al.* 2008]. In the current study, trypsinogen-2 was used as a surrogate variable for pancreatic injury.

Difficult cannulation

Difficult cannulation was defined as more than six cannulation attempts for deep biliary cannulation or the need for pre-cut techniques.

3.4 PAPER IV

3.4.1 Design

A nationwide population-based nested case-control study was conducted within the cohort of ERCP procedures in Sweden, all recorded in a nationwide quality registry during a period of three years, 2007 - 2009.

3.4.2 The source of data; GallRiks

The data were collected from the Swedish Registry for Gallstone Surgery and ERCP (GallRiks), a nationwide quality registry. GallRiks has been collecting data since it was established in 2005 under the direction of the Swedish National Board of Health and Welfare (Socialstyrelsen) and the Swedish Surgical Society (Svensk

Kirurgisk Förening, Svensk Förening för Övre Abdominell Kirurgi, Svensk förening för Innovativ Kirurgisk Teknologi), which also appoints the members of the GallRiks board. GallRiks is administered by the Uppsala Clinical Research Center (UCR), which is a national center of excellence for quality control registers. An increasing number of Swedish hospitals have joined GallRiks since its inception, and 72 hospitals are currently affiliated with GallRiks, including all 9 university hospitals, all 21 county hospitals, and 42 small county hospitals. This corresponds to almost all hospitals in Sweden.

Data coverage:

The coverage of the presented data represents 75% of all ERCPs performed in Sweden in the year 2007 and more than 87% during the period 2008-2009. The coverage was estimated by cross-linkage to the Swedish Hospital Discharge registry (Slutenvårdsregistret) in which the Swedish National Board of Health and Welfare has been collecting information on individual hospital discharges since 1965 [Persson *et al.* 2010]. GallRiks is also linked to the registry of Causes of Death (Dödsorsaksregistret).

Data completeness:

A validation program has been instituted with periodic audits at each institution at least every third year. So far, the results from the first 25 audited hospitals indicate a complete match between the medical records and the GallRiks data base in 97.3% of ERCP cases [Enochsson *et al.* 2010].

Data registration:

The GallRiks registry uses an internet platform (www.ucr.uu.se/gallriks) with online data registration of ERCPs and cholecystectomies. The online questionnaire allows over 100 different variables to be described for each case with multiple choice functions depending on the complexity of the procedure. Compulsory data include patient characteristics, the indication for ERCP, mode of admission, type of anesthesia, cannulation technique, diagnostic findings, therapeutic measures in biliary-pancreatic ducts, procedure time, and per-procedural complications. Data is recorded prospectively by the endoscopist at the time of the procedure. The questionnaire is closed after registration of each individual case, and further alterations of the index information is not readily possible. Follow-up data is collected locally 30 days after the ERCP by each institution, usually by an appointed coordinator.

3.4.3 Study Base

We identified all patients in whom ERCP was performed for the first time (i.e. on a non-sphincterotomised papilla) between January 1, 2007, and December 31, 2009. All patients registered as having PEP were considered cases in the analyses, while all registered ERCP patients without a registered PEP were classified as control subjects. The complete cohort was further analysed with respect to sex, age, comorbidity, indication for ERCP, RV-ERCP and pre-cut assisted cannulation techniques, therapy, procedure time, and hospital volume.

3.4.4 Definition of variables and outcome measures

Post-ERCP pancreatitis

The diagnosis of PEP was defined according to the 1991 Consensus Guidelines and was recorded at the time of the 30-day follow-up. However, severity of PEP is not recorded in GallRiks.

Rendezvous cannulation

Biliary cannulation with rendezvous technique is achieved by using an existing guidewire that has been introduced in an antegrade fashion by PTC technique or at cholecystectomy. Basically there are three

different approaches, all of which were described previously in detail, **figures 12-17**. In GallRiks, however, there is no way to distinguish between the various rendezvous techniques mentioned above.

Conventional ERCP cannulation

Conventional ERCP cannulation techniques see **figures 2-4 and 9** and pre-cut cannulation techniques see **figures 6-7 and 10-11**, have been described in detail in a previous chapter:

Statistical analyses

The quantitative variables were calculated as mean \pm standard deviation [SD], and the categorical variables as frequencies and/or percentages. The chi-square test was used except in cases where the expected frequencies were low, when the Fisher's Exact Test was used instead.

Odds ratios (OR) and their 95% CI, derived from unconditional logistic regression, were used to assess the association between the potential risk factors under study and the risk of PEP, registered 30 days after the procedure. Linear trends of the association were tested in a multivariate model by treating categorical variables as continuous.

Any potential confounding effects of the variables under study were tested by introducing them one by one into the multivariate logistic regression model, and exposures shown to be significant in the univariate analysis were tested for possible statistical interactions. The level of statistical significance was specified to be 0.05, and the fit of the model was tested.

4 RESULTS

4.1 PAPER I

Basic characteristics

During the period of two years, a total of 674 patients underwent cholecystectomy because of cholelithiasis. Of these, 612 (90.8%) patients were completed as laparoscopic procedures. Conversion from LC to open cholecystectomy occurred in 37 (5.5%) patients. Another 25 (3.7%) patients were electively initiated as open cholecystectomies. A total of 592 (87.8%) IOC was completed. Of all the 674 patients, 54 (8.0%) patients turned out to have radiological evidence of CBDS, and in 34 (5.0%) of those RV-ERCP was conducted with intention to treat. There were 20 (3.0%) patients with CBDS, managed otherwise (laparoscopic transcystic approach, n=2; open surgery, n=5; post-operative ERCP, n=13).

Baseline characteristics are outlined in **table 1, see Paper I**. Gender and age profiles were about the same between the two groups, with a domination of female sex (cholecystectomy group 70.9% versus RV-ERCP 82.4%), and the mean age was close to 48 years. However, there was a significant difference between the groups with respect to whether the procedure was planned or performed under acute admission. RV-ERCP was performed to a larger degree under conditions in which patients were admitted acutely compared with the cholecystectomy group (LC group 19% versus RV-ERCP 35%).

Peroperative data

The total operating time was significantly extended by an average of 82 minutes when RV-ERCP was performed. However, the average operation time decreased considerably after the first year of observation, from 216 minutes to 166 minutes, which to a large extent can be explained by the learning curve and improved logistical routines. For patients undergoing cholecystectomy without ERCP, the operation time of 110 minutes was consistent throughout the study period.

Successful cystic duct cannulation during RV-ERCP was completed in all 34 (100%) patients, which was a prerequisite for performing IOC for the detection of common bile duct stones. All 34 (100%) patients had deep biliary cannulation, and in 26 out of 34 (76%) it was a complete RV-ERCP. Complete stone clearance with sphincterotomy and balloon extraction of a visible stone was obtained in 29 (93.5%) of 31 patients. In three patients, the endoscopist was not sure whether he actually saw the stone or not during the extraction procedure. Complete duct clearance was accomplished in 32 (94.1%) of the 34 patients; the other two (1.9%) patients were completed successfully after a second ERCP (one patient with multiple stones and one patient with a solitary large difficult common bile duct stone). No peroperative complications were observed when RV-ERCP was added to the operation, and all 34 operations could be completed as laparoscopic procedures. No clinical signs of PEP were reported among the 34 patients.

Postoperative data

Adding an ERCP to the laparoscopic cholecystectomy did not significantly affect the average length of hospitalization, which was 2.6 ± 0.4 days (median value 2, range 1-9) for the RV-ERCP group, compared with 2.1 ± 0.1 days (median value 1, range 1-43) in the cholecystectomy group. Readmission due to complications was observed in one (2.9%) patient in the RV-ERCP group, compared with a readmission rate of 11.3% in the cholecystectomy group.

4.1.1 Comments

We could show that RV-ERCP was feasible under routine conditions in a clinical setting. Even though the average operation time was extended compared with cholecystectomy alone, the procedure itself did not have any negative effects concerning the outcomes of complication rate, success rate or duration of hospitalization compared with cholecystectomy alone. The unchanged length of hospitalization can probably be attributed to the fact that RV-ERCP can be conducted under the principle of minimal invasive surgery as a one-stage procedure. At our study point in 2004, our data was on par with other case-series reports by Tatulli et al. [Tatulli et al. 2000], Filauro et al. [Filauro et al. 2000] and Tricarico et al. [Tricarico et al. 2002] who used the same RV-ERCP approach as we did.

When IOC was used, the indication for ERCP became highly specific. For instance, in almost half of the cases with positive findings of CBDS, IOC revealed clinically unexpected stones. Unfortunately, we did not have any information on the number of patients who had a preoperative suspicion of common bile duct stones that later proved to have a clean IOC. However, a prospective randomized controlled trial by Rábago et al. [Rábago et al. 2006] that compared two-stage versus single-stage treatment showed that 57.6% of all patients with a preoperative suspicion of common bile duct stones (according to clinical features, liver function tests and ultrasound) turned out to have a completely normal IOC. These two examples illustrate how unpredictable common bile duct stones can appear and disappear at the time of surgery and underlines how essential it is to have a functional routine in daily practice when stones are frequently detected incidentally.

Weak points of our investigation and other previous reports were the retrospective design of the study and the relatively small sample size. So, in that respect, we cannot draw any conclusions from the observation that we virtually had no cases of PEP. However, that finding generated our next hypothesis that antegrade rendezvous cannulation might prevent pancreatic injury (see Paper III).

4.2 PAPER II

Basic characteristics

A cohort of 44 patients was identified who were treated with mother-baby endoscopy assisted intraductal lithotripsy during a period of 10 years. The distribution between genders was equal (22 female/22 male). The mean age (74 years) was remarkably high among the patients, and 50% of the patients were 80 years old or older. The medical history of a majority of the patients included a substantial number of co-morbidities, and nearly half of the cohort had a poor physical status (ASA class 3 or worse) with an overall average physical ASA-class status of 2.3. Moreover, 6 (14%) patients were considered too poor in their physical status to undergo any general surgery. At the time of the lithotripsy treatment, all 44 patients had undergone at least two (range 2-9) unsuccessful conventional ERCP investigations, and 43 (98%) patients had a need for permanent biliary drainage due to previously suffering from recurrent biliary symptoms including jaundice (87%), abdominal pain (75%) and cholangitis (20%).

Peroperative data

By the end of the treatment period, complete duct clearance had been achieved in 34 (77%) patients and had failed in 10 (23%) patients. In the subgroup of patients who were 80 years of age or older, 19/22 (86%) were stone free at the end of the treatment period. The median diameter of the stones was 15 mm, and 72% of the stones had a diameter larger than 15 mm. In two-thirds of the cases, the stones were solitary, and the majority (86%) were located in the CBD. Total duct clearance after complete or partial fragmentation was obtained in half of the cases on the first attempt and another quarter of the cohort became stone free after an additional

ERCP session. There was no difference in the success of fragmentation whether EHL or laser lithotripsy was performed. The median duration of the procedures was 120 min (range 25-210 min).

Postoperative data

Early complications were observed in four (9%) patients. One patient died unexpectedly of myocardial infarction at home 10 days after a successful LL with complete ductal clearance and without signs of complications associated to the procedure. Another three early post-procedural complications occurred; acute cholangitis (n=2) and mild post-ERCP pancreatitis (n=1). The patient flow chart and rate of stone clearance is depicted in **figure 20**.

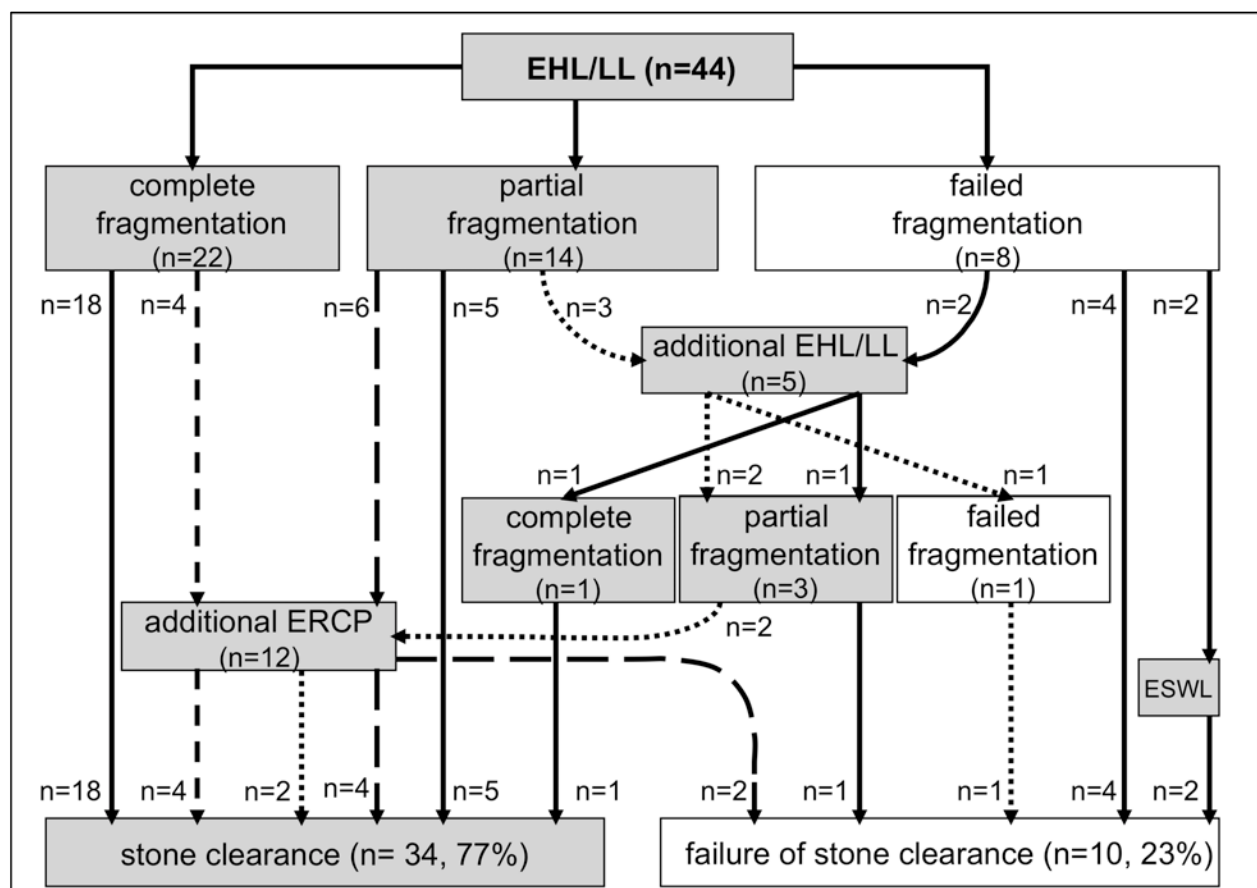


Figure 20. Flowchart and results.

Long-term follow-up evaluation

The remaining 43 patients (the early death mentioned above has been excluded) were followed up for a median of 53 months (range 9-126 months). At the end of the follow-up, 13 patients had died at a median age of 84 years, approximately 50 months (median value) after the index treatment and with a range of 12 to 88 months. The causes of death were not related to biliary disease. At completion of the study, the median age of the 30 patients still living was 83 years (range 43-95 years) and 6 (14%) patients had experienced late biliary symptoms or complications (cholangitis n=2, cholecystitis n=1, suspicion of recurrent stone n=3), events that occurred within the first two years after the index procedure. In the cohort of patients with an age of 80 or more who had a successful CBDS clearance, all remained free from biliary symptoms after an average of 45 months follow-up until death or the end of the study period.

4.2.1 Comments

The current study included virtually all cases of mother-baby-assisted lithotripsy performed in Sweden between 1995 and 2006, and our case series also represents the first Scandinavian report. It is important to stress that cases of difficult CBDS, resistant to first and second line treatment modalities, are very rare. They represent the most complex segment of endoscopic management of CBDS. Moreover, the population suffering from giant CBDS contains a disproportionate number of older patients and age-related comorbidities.

We showed that clear visualization of the stone and close contact with the lithotripter probe are prerequisites for successful fragmentation and subsequent stone clearance. Gigantic stones, greater than 20 mm in diameter, were undoubtedly the most difficult to handle. In eight of the ten failures recorded, the diameter was 20 mm or larger, although complete stone removal was obtained for 60% of the 20 patients with stones that size. Repeated sessions were necessary in a quarter of the cases in order to obtain complete ductal clearance. If fragmentation failed completely on the first attempt, the chance to succeed in a subsequent attempt was poor; only one (13%) out of eight became stone free. If partial fragmentation was achieved, the rate of success at a second endoscopic attempt was 50%. We had an overall stone clearance rate of 77%, which is on par with other larger case series [Arya *et al.* 2004, Adamek *et al.* 1996, Neuhaus *et al.* 1993, Hui *et al.* 2003]. However, our cohort represented the oldest patient group ever reported, with an average age of 74 years and a median age of 80 years.

Case series like this one, in which a number of patients undergo a treatment and are observed without any control group or selection by randomization, is generally considered to be a weaker form of scientific evidence. On the other hand, there is no reason to discount the data simply because it is from a retrospective study. A well-conducted retrospective study can add important scientific information, and in this particular case, it would have been more or less impossible to use a prospective randomized design for a trial like this, since this particular situation is extremely rare.

Since the cases were admitted and treated at two different sites, there may be a potential risk of both selection bias and misclassification bias. A difficult stone at one hospital might be a non-difficult stone at another. On the other hand, all patients in the cohort had undergone one or several ERCP attempts at their home hospital before they were referred to our hospitals, and we consistently tried conventional methods before we scheduled the patient for a mother-baby-endoscopy. One should also be aware that it is not always a matter of stone size that makes a stone difficult to handle; there are other contributing factors such as strictures, the anatomic location of the stone and miscellaneous technical aspects.

Another source of bias is the process of determining whether a stone was divided into pieces completely or partly. All imaging (X-ray and endoscopy pictures) were investigated by radiologists before and after treatment. A standard was decided: stones that were reduced up to 50% in size were to be categorized as partly fragmented, and complete fragmentation was obtained if destruction of the stone was more than 50% of its size. The arbitrary threshold was found to be meaningful in the sense that patients who were judged as having complete fragmentation all became stone free, while partially fragmented stones needed complementary ERCP to a greater extent (60%) to obtain duct clearance, and clearance failed in two cases (14%). Cases, in which the stone was undistorted, with an exception of a small chip, were classified as failed fragmentation. One possible source of error that we could not control was whether there could have been a change in the stone's physical strength as a result of pressure energy, but this does not seem to have affected the outcome in our limited series.

The strength of this study was its demonstration that it is sensible to treat even very old, frail patients and the data showing that patients over 80 years old can continue to live many years without experiencing late biliary

symptoms. There is also an example of how endoscopy can offer proper therapeutic intervention of a surgical nature for patients who are not eligible for conventional surgical treatment because of medical reasons.

4.3 PAPER III

Basic characteristics

In total, 139 patients were enrolled in the study; another 17 patients were excluded for various reasons shown in the flowchart, **figure 21**. Relevant preoperative demographic characteristics did not differ between the three study groups in terms of gender, BMI, physical status according to ASA classification, baseline laboratory values for CRP, pancreatic amylase, proCAPB, or trypsinogen-2. However, there was a difference in age, with the conventional ERCP group being somewhat older. In addition, there was, as expected, a difference between the control group and the other two groups with respect to bile duct diameter, ALP, and bilirubin levels but no significant difference between the rendezvous and conventional ERCP group.

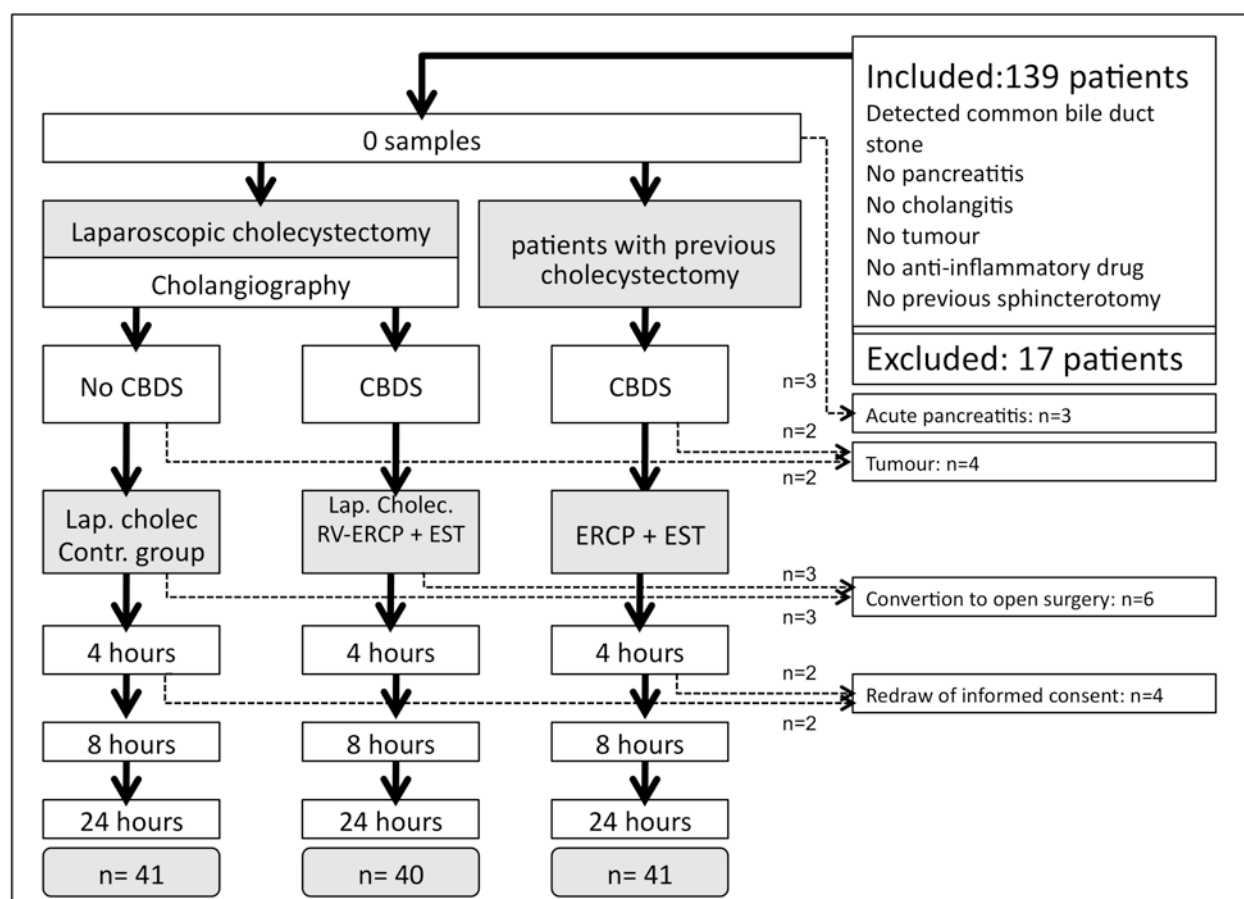


Figure 21. Flowchart of the study.

Peroperative data

In the RV-ERCP group, transcystic antegrade biliary cannulation was successful in all 40 (100%) patients compared with the 38 (93%) successful retrograde cannulations in the ERCP group, which had three (7%) failures due to difficult cannulations. Unintentional injection of contrast medium into the pancreatic main duct

was observed in 11 (27%) of the conventional ERCP cases compared to no patients in the RV-ERCP group. Complete CBDS clearance at the index procedure was achieved in 38 (95%) of the RV-ERCP procedures versus 29 (71%) patients in the conventional ERCP group ($p=0.01$), even though there was no significant difference in stone size ($p=0.40$) or procedure time ($p=0.11$) between the two study groups. After an additional ERCP, the bile ducts in all patients, including the three cases with initial cannulation failure, were clear of retained CBDS. None of the 41 patients in the control group had pancreatic duct opacification during cholangiography, acute pancreatitis, or hyperamylasemia.

Postoperative data

PEP developed in three (7%) of the 41 patients cannulated with conventional ERCP, compared with no cases among patients cannulated by RV-ERCP ($p=0.24$). According to the Cotton criteria [Cotton *et al.* 1991], one of these cases of pancreatitis was classified as moderate and two as mild. Two major postoperative complications were recorded in the LC group: one patient had postoperative intraabdominal bleeding that was treated by conservative means and one had postoperative bile leakage from the cystic duct, which was successfully treated by temporary endoscopic stent placement.

Laboratory markers

The post-procedural time course of pancreatic amylase, procarboxypeptidase B and trypsinogen-2 are depicted in the three figures below. In the patients treated with conventional ERCP, a significant increase in all three markers was seen after 4 hours and levels remained elevated during the entire observation period. Patients treated with RV-ERCP had virtually the same trend as the control group that underwent cholecystectomy alone.

Figure 22-24, demonstrates serum values at all times (0, 4, 8 and 24 hours) and Y-axis values are logarithmically transformed. Vertical bars denote 95% CI. P-values indicate differences between conventional (CV) ERCP vs. rendezvous (RV) ERCP.

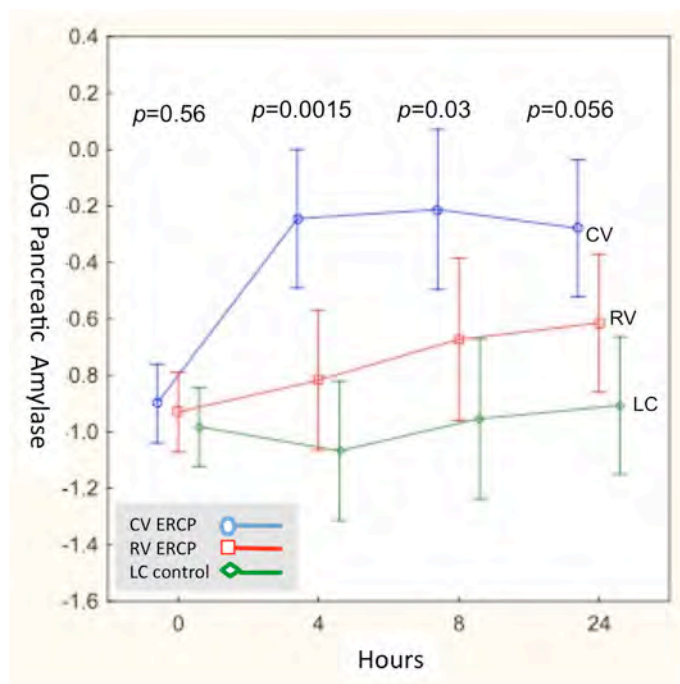


Figure 22. Pancreatic amylase (microcat/L)

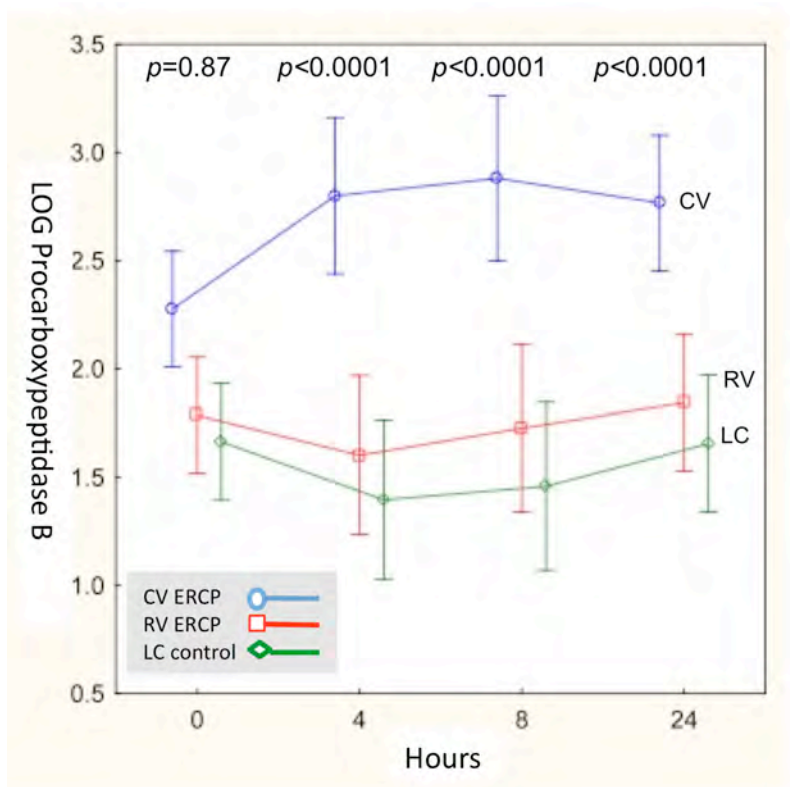


Figure 23. Procarboxypeptidase B (nmol/L)

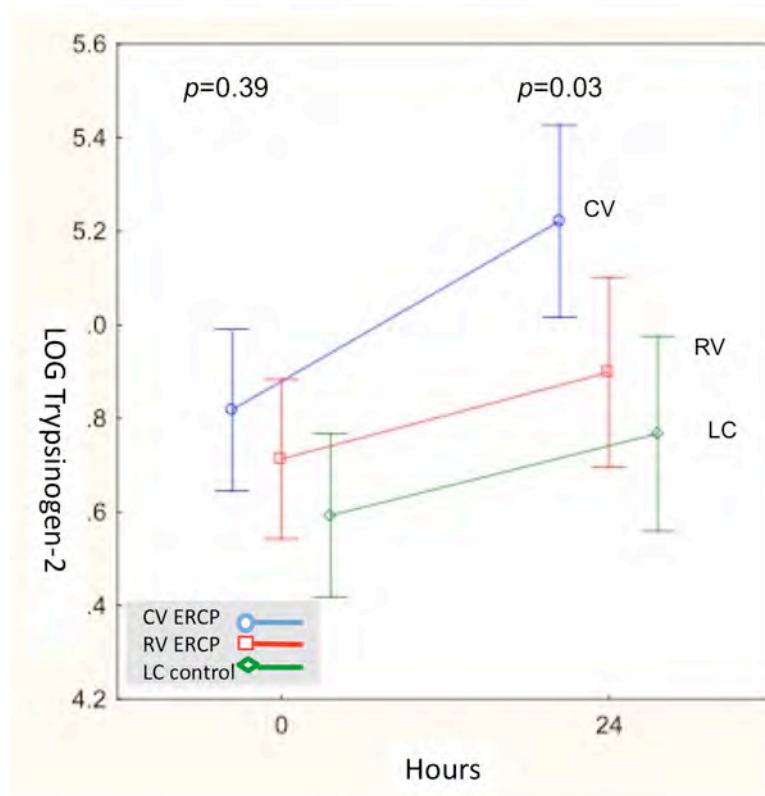


Figure 24. Trypsinogen-2 (microg/L)

4.3.1 Comments

This study showed that transcystic guidewire-assisted rendezvous cannulation at ERCP followed by bile duct stone clearance was not associated with post-procedural pancreatic enzyme leakage. This observation supports the hypothesis that rendezvous cannulation can prevent the development of post-ERCP pancreatitis. Basically, it is the complete avoidance of pancreatic duct contact together with the absence of difficult cannulation that makes the profound difference when the antegrade cannulation technique is used instead of retrograde cannulation. In fact, inadvertent contrast injection into the pancreatic duct during conventional ERCP was the factor most obviously associated with leakage of pancreatic enzymes into the systemic circulation and the subsequent risk of developing PEP.

There are inborn methodological difficulties and challenges associated with studies directed towards various aspects of ERCP performances and PEP development. In order to estimate an effect of an uncommon event, a large cohort of patients is required to achieve sufficient statistical power. According to our own data from GallRiks, the average risk of developing PEP is approximately 4%. If this example is used, as the basis for designing a RCT, in which we want to demonstrate a significant ($p < 0.05$) rate reduction of PEP from 4% to 2%, we would need to recruit a sample size of at least 2300 patients distributed 1:1 in order to reach a sufficient statistical power of 80%. No such study has been reported in the literature.

Because clinical trials demand considerable resources, pilot studies are required to guide the formation of the final trial design. Therefore, it is vital to use clinically-relevant biochemical markers as surrogate variables of the pancreatic inflammatory response. However, the use of surrogate endpoints is controversial, for good reason, and there are numerous examples in which surrogate markers have shown benefits from a particular treatment but the effects of the treatment later turned out to be non-significant or even harmful [Psaty *et al.* 1999].

In order to get a powerful representative surrogate variable, it is crucial to show strong, consistent, independent associations from well-validated trials that will support the use of a particular surrogate variable as a true risk factor for the outcome. This was one of the reasons that we wanted to use a more relevant and valid surrogate variable than pancreatic amylase, which has a rather low specificity around 71% to 98% and a sensitivity between 81% to 95% [Yadav *et al.* 2002]. We chose proCAPB and trypsinogen-2 since both have been shown to be stable, early markers of acute pancreatitis and to be superior to lipase and pancreatic amylase, especially if the objectives are to distinguish mild from severe pancreatitis [Kylänpää-Bäck *et al.* 2002, Kempainen *et al.* 1997, Kobayashi *et al.* 2011, Petersson *et al.* 2002] and to discriminate PEP from other non-pancreatic disorders with an accuracy of 95% to 99% [Müller *et al.* 2003, Regnér *et al.* 2008]. The latter distinction is essential, because patients in two of our three study groups were subjected to additional surgical trauma in the form of laparoscopic cholecystectomy, which might have increased unspecific inflammatory responses.

Our first intention was to perform an RCT, which was also an early proposal by the local Ethics Committee. We decided to abandon the idea because of ethical considerations that it might be in conflict with the statements according to the ethical principles of the Helsinki Declaration and its fifth article: that the well-being of human subjects should take precedence over the interests of science [Helsinki 2001]. What were the arguments for not performing a RCT? First, ERCP is an invasive endoscopic procedure with the potential of causing serious adverse events. If we designed a randomized trial with a treatment arm that would lead to a sequential procedure, e.g. pre- or postoperative ERCP, it would result in an appreciable amount of negative investigations that in turn could result in a number of unnecessary and potentially harmful ERCP-associated complications. Second, a study design with a treatment arm that included post-operative ERCP could end up with a worst-case scenario with additional surgical CBD exploration if endoscopic biliary cannulation failed.

Third, if we designed the study as a one-stage procedure, the conventional ERCP would be conducted in the operating theatre during on-going surgery, an environment less suited for conventional ERCP than the endoscopy suite. Under such suboptimal circumstances for conventional ERCP, the study would be seriously undermined because methods should be compared under optimal conditions for each. Suboptimal conditions for ERCP would also put those patients at risk for a higher complication rate associated with difficult cannulation. After we had explained our reasoning, we received full approval of our study design from the Ethical Committee who urged us to proceed since they thought that the clinical issue was of great importance.

All patients admitted to our hospital due to cholecysto/choledocholithiasis were considered for inclusion in the RV-ERCP group. Patients admitted because of CBDS who had undergone a previous cholecystectomy were invited to participate in the conventional ERCP group. This inclusion procedure created a risk for selection bias in that patients selected for laparoscopic cholecystectomy with or without rendezvous ERCP were younger than those selected for conventional ERCP, most of whom had already had their gallbladder removed. Therefore, age could serve as a possible confounder for the outcome. However, this is counterbalanced to a degree by the fact that young age in itself has repeatedly been found to be an independent risk factor for PEP [Christensen *et al.* 2004, Cheng *et al.* 2006, Loperfido *et al.* 1998, Freeman *et al.* 2001], whereas older patients may be protected by, for example, age-related pancreatic atrophy [Laugier *et al.* 1991]. Accordingly, this age imbalance is likely to underestimate than overestimate an association.

With the type of intervention-based study that we used, it is impossible to conduct the investigation in completely blinded fashion, because the performing endoscopist is obviously aware of the group to which the patient belongs. In designing the study, we wished to address the following concern: An endoscopist who is performing a conventional ERCP in a preoperative two-step setting or during a cholecystectomy may not have the same strong urge or time to use all endoscopic alternatives, such as pre-cut techniques in order to achieve successful biliary cannulation compared with the more demanding postoperative situation when there is no readily available surgical solution to lean on. Therefore, we only included postoperative ERCP cases in our study. As a result, the endoscopists for the patients in our conventional ERCP group all had the same reasons to perform a thorough ERCP and obtain complete stone clearance. Most importantly, this study design did not raise the ethical concerns associated with a randomized trial.

Despite the caveats due to ethical considerations, we achieved the primary goal in this pilot study, which was to test the hypothesis that rendezvous cannulation can avoid pancreatic injury.

4.4 PAPER IV

Basic characteristics

A total of 17,787 patients who had undergone ERCP were identified in the registry. Of these, 3,337 (18%) were not eligible due to previous ERCP with sphincterotomy and 1,732 could not be included because of incomplete 30-day follow-up data, **figure 25**. Thus leaving 12,718 patients for further analysis. Out of those, 6,982 (55%) were females. Physical status was assessed according to the ASA classification system. Two-thirds of the patients were classified as ASA class 1-2 before ERCP. A majority (69%) of the patients were admitted acutely, and the most common indication for ERCP was common bile duct stones (28%). PEP was recorded in 452 (3.6%) of the patients (**Table 2** in Paper IV). According to the GallRiks registry, a total of 455 patients received RV-ERCP, and 274 of these procedures were conducted as a one-step RV-ERCP. The other 181 patients were cannulated with one of the two-step RV-ERCP procedures described in chapter 1.3.11.

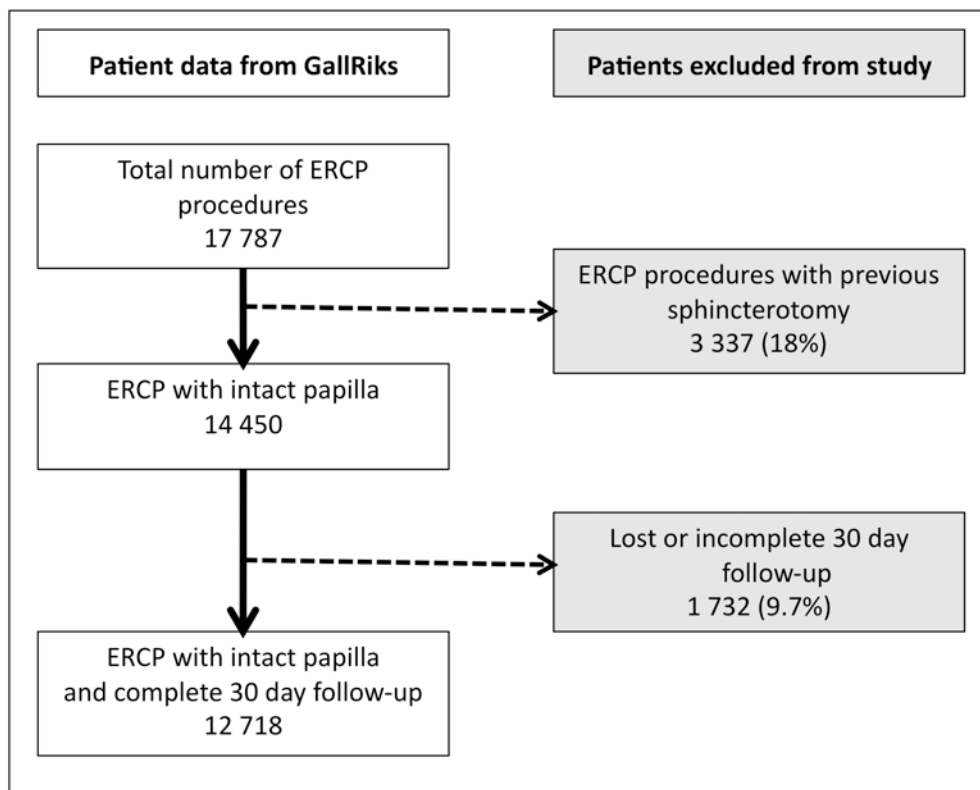


Figure 25. Cohort selection from the GallRiks database.

Risk factors for post-ERCP pancreatitis

Among the 455 patients in whom rendezvous ERCP cannulation was performed, there was a 50% decrease in the risk of PEP compared with patients who were cannulated by conventional means (OR 0.5; 95% CI 0.2-0.9), see **table 1**.

There was a dose-dependent increase in the risk of PEP with decreasing age. In the multivariate analysis, patients younger than 60 had a risk of developing PEP that was more than twice as high as that of patients older than 82 years (OR 2.3; 95% CI 1.7-3.2). Female gender carried a slightly higher risk of PEP (30%) compared with men, and this was statistically significant (OR 1.3; 95% CI 1.1-1.6). Physical status did not significantly influence the risk of developing PEP, even though there was a trend towards a lower risk of PEP with increasing level of co-morbidity. The risk of PEP was higher among patients who were treated electively compared with those who were admitted acutely (OR: 1.3; 95% CI 1.1-1.6). The actual technique of the endoscopic sphincterotomy, such as pre-cut, did not affect the risk of PEP and biliary stone extraction. Biliary stent placement was associated with a significantly lower risk of developing PEP. Long duration of the ERCP procedure was associated with an increased risk of PEP, with the point estimates increasing linearly with the duration of the procedure. Procedures lasting longer than 40 minutes had a 2.5 times higher risk than procedures lasting less than 20 minutes (OR 2.5; 95% CI 1.8-3.5). The annual volumes of ERCP examinations per hospital did not affect the risk of PEP.

| | Number | | Univariate | | P value | Multivariate | | P value |
|------------------------------------|--------|----------|------------|------------------|-------------------|--------------|------------------|-------------------|
| | Cases | Controls | OR | 95% CI | | OR | 95% CI | |
| Age (years) | | | | | | | | |
| >82 | 60 | 3035 | 1.0 | (reference) | | 1.0 | (reference) | |
| 72-<82 | 109 | 3105 | 1.8 | (1.3-2.4) | | 1.7 | (1.2-2.3) | .6258 |
| 60-<72 | 114 | 3068 | 1.9 | (1.4-2.6) | | 1.7 | (1.2-2.3) | .5963 |
| <60 | 169 | 3017 | 2.8 | (2.1-3.8) | | 2.3 | (1.7-3.2) | < .0001 |
| P value for linear trend | | | | | < .0001 | | | < .0001 |
| Sex | | | | | | | | |
| Male | 176 | 5560 | 1.0 | (reference) | | 1.0 | (reference) | |
| Female | 276 | 6706 | 1.3 | (1.1-1.6) | .0070 | 1.3 | (1.1-1.6) | .0058 |
| Comorbidity (ASA*) | | | | | | | | |
| ASA class 1 | 155 | 2883 | 1.0 | (reference) | | 1.0 | (reference) | |
| ASA class 2 | 199 | 5738 | 0.7 | (0.5-0.8) | | 0.8 | (0.6-1.0) | .5154 |
| ASA class 3 | 89 | 3187 | 0.5 | (0.4-0.7) | | 0.7 | (0.5-0.9) | .7776 |
| ASA class 4 | 9 | 444 | 0.4 | (0.2-0.7) | | 0.5 | (0.3-1.0) | .1641 |
| P value for linear trend | | | | | < .0001 | | | .0462 |
| Indication for ERCP | | | | | | | | |
| Acute | 263 | 8565 | 1.0 | (reference) | | 1.0 | (reference) | |
| Elective | 189 | 3701 | 1.7 | (1.4-2.0) | < .0001 | 1.3 | (1.1-1.6) | .0012 |
| Assisted cannulation technique | | | | | | | | |
| Pre-cut (no) | 386 | 11,024 | 1.0 | (reference) | | 1.0 | (reference) | |
| (yes) | 66 | 1242 | 1.5 | (1.2-2.0) | .0035 | 1.3 | (0.9-1.8) | .1445 |
| Rendezvous (no) | 445 | 11,821 | 1.0 | (reference) | | 1.0 | (reference) | |
| (yes) | 10 | 442 | 0.6 | (0.3-1.1) | .0883 | 0.5 | (0.2-0.9) | .0162 |
| Therapy | | | | | | | | |
| Sphincterotomy (no) | 170 | 4022 | 1.0 | (reference) | | 1.0 | (reference) | |
| (yes) | 282 | 8244 | 0.8 | (0.7-1.0) | .0341 | 1.1 | (0.8-1.4) | .5928 |
| Stone extraction (no) | 347 | 8572 | 1.0 | (reference) | | 1.0 | (reference) | |
| (yes) | 105 | 3694 | 0.7 | (0.6-0.9) | .0013 | 0.7 | (0.5-0.9) | .0016 |
| Biliary stent (no) | 331 | 8293 | 1.0 | (reference) | | 1.0 | (reference) | |
| (yes) | 121 | 3973 | 0.8 | (0.6-0.9) | .0107 | 0.7 | (0.6-0.9) | .0026 |
| Duration of ERCP (minutes) | | | | | | | | |
| <20 min | 55 | 2526 | 1.0 | (reference) | | 1.0 | (reference) | |
| 20-29 min | 94 | 3046 | 1.4 | (1.0-2.0) | | 1.6 | (1.1-2.2) | .4216 |
| 30-40 min | 118 | 3020 | 1.7 | (1.3-2.5) | | 2.0 | (1.4-2.8) | .0350 |
| >40 min | 185 | 3669 | 2.3 | (1.7-3.1) | | 2.5 | (1.8-3.5) | < .0001 |
| P value for linear trend | | | | | < .0001 | | | < .0001 |
| Center-related (volume: ERCP/year) | | | | | | | | |
| low <100 | 78 | 2104 | 1.0 | (reference) | | 1.0 | (reference) | |
| medium 100-500 | 259 | 7378 | 0.9 | (0.7-1.2) | | 1.1 | (0.8-1.4) | .9100 |
| high >500 | 115 | 2784 | 1.1 | (0.8-1.5) | | 1.2 | (0.7-1.6) | .3474 |
| P value for linear trend | | | | | .3694 | | | .5933 |

* American Society of Anesthesiologists (ASA) physical status classification system²⁷

Table 1. Associations between patient-, procedure-, and volume-related risk variables and post-ERCP pancreatitis. Bold values indicate $p < .05$.

4.4.1 Comments

This nationwide population-based case-control study showed that RV-ERCP gave a significant (50%) risk reduction in PEP. There have been at least 12 published cases series [Tatulli et al. 2000, Filastro et al. 2000, Iodice et al. 2001, Borzellino et al. 2010, Tricarico et al. 2002, La Greca et al. 2007, Enochsson et al. 2004, Saccomani et al. 2005, Ghazal et al. 2009], including three randomized trials [Lella et al. 2006, Rábago et al. 2006, Morino et al. 2006], that suggest that RV-ERCP is associated with lower PEP rates. However, our study was the first to have a cohort large enough to reach statistical significance. In addition, our study minimized the risk of selection bias and therefore had high internal validity, since all previous studies were

based on single-center data. Furthermore, the population-based design used also offers high external validity, i.e. it is representative of the Swedish population at large.

In order to address our hypothesis with statistical strength, we collected data from one of the many Swedish case-based quality registers; the Swedish Registry for Gallstone Surgery and ERCP (GallRiks). Ideally, case-control studies are conducted in a well-defined source population, so that individuals (cases) with the disease being studied arise in that source population, and individuals without the disease (*controls*) are a representative sample of the same source population. The term nested refers to the situation when the source population is well-defined with a known sample size, as in the current source population, which consists of patients registered in GallRiks. The calculation gives an Odds ratio that is an estimation of the incidence rate ratio in a population without having to obtain individual information on every patient in the population. A nested case-control study can be preferable to a full-scale cross-sectional cohort study when the actual disease prevalence is low. A nested case-control study also allows evaluation of multiple possible risk factors. However, the design only allows us to measure one disease variable (PEP), and the result will provide less statistical precision in estimating the true prevalence or incidence compared with a cohort study.

In the design of any epidemiological study, it is important to control two major errors that can occur: random error and systematic error. A way to control random error is by increasing the sample size. With a cohort that includes more than 12,000 patients, the numbers are large enough to produce valid precision. Systematic errors, on the other hand, can be difficult to identify and are impossible to correct satisfactorily afterwards if they are outside a multivariate modeling and remain unchanged regardless of sample size. Selection bias is a systematic error due to a non-random sample of a source population that causes some subjects to be less likely to be included than others. By using a nested design, we could precisely identify the source population and assure that both the cases and controls were selected from the exact same population source. Since the cohort represents about 85% of all ERCPs performed in Sweden during the observation period, almost all hospitals are represented. Therefore, there is no selection bias with respect to performance level and expertise or center volume. All risk group categories for developing PEP are equally represented in the cohort. Moreover, limiting the enrollment period to three years minimizes the risk that the results might have been influenced by alterations in the technique or by the introduction of modernized or novel equipment.

Information bias can arise because the information collected is erroneous. One type of information bias is misclassification, which could be the case if there were faulty registrations in GallRiks. From the GallRiks validation program, we know that the completeness of information is very high, with an overall mismatch less than 3% between GallRiks and medical charts [Persson *et al.* 2010]. The internet-based design of the GallRiks questionnaire helps ensure that the amount of missing data is kept to a minimum since all compulsory data must be entered before the internet file can be sent to the registry. Possible non-differential misclassification bias for data entered into the GallRiks registry is measurement faults that are not related to the outcome of PEP and should be equally distributed between cases and controls. Nevertheless, a recall bias is a plausible misclassification bias among patients who had a short episode of mild PEP that could easily be neglected at the time of follow-up 30 days later, leaving a group of patients under-diagnosed for mild PEP. This experience is also reflected in prospective controlled trials in which PEP incidence is somewhat higher compared with the prevalence of PEP recorded in retrospective ERCP studies.

An important objection to the present design is the lack of stratification between the three different types of RV-ERCP procedures presented in the paper. Although they all share the same concept of antegrade cannulation, two of them rely entirely on two-stage management with post-operative ERCP that could lead to an unintentional pancreatic main duct contact. If the registry could have discriminated between RV-ERCP techniques, that might have, at least in theory, strengthened the analysis.

Confounding is always a central issue for epidemiologically-designed studies. Confounding can be defined simply as confusion or mixing between the variable being investigated and some other factor (the confounder) that appears irrelevant but is actually the one that leads to the outcome. The confounding variable must have an effect on the outcome to be recognized as a true confounder. In non-experimental studies, the best defence strategies against confounding are stratification of variables, using multivariate adjustment in logistic regression analysis, and matching. In the current study, we controlled for confounding by multivariate logistic regression modelling; introducing identified variables one by one in backward, forward, and stepwise exception analyses. When doing this, we did not observe any significant alterations of Odds ratio or confidence interval (CI) in risk variables. However, there are some variables in our study that need to be discussed. Comorbidity is a well-known confounder in epidemiological research since there is a strong association between advanced age and comorbidity. In our study we found that patients in higher age groups and those who had a poorer ASA-classification status had a lower risk of developing PEP compared to those who were younger and had a better physical status. A speculative conclusion is that it is more dangerous to expose a young, healthy pancreas to ERCP compared with one that is old and worn. This fact could support our current recommendation that older, more fragile patients with CBDS are best treated with ERCP only. Young, healthy patients should be offered, depending on preferences, laparoscopic or laparoendoscopic CBDS management as a first-line treatment. The duration of ERCP procedure is another ambiguous variable that includes a plurality of factors that may obscure the reason why extended procedure time leads to an increased risk of developing PEP. A speculative explanation could be that prolonged cannulation procedure due to difficult cannulation may influence the exposure of long investigations.

Center-related exposure is another variable that is difficult to interpret since it includes everything from the skills of individual endoscopists to a different case-mix of patients or differences in the complexity and invasiveness of procedures. In Sweden, there are two high-volume hospitals performing more than 500 ERCPs annually (22% of the total) and 15 intermediate volume hospitals performing 100-500 ERCPs each year (56% of the total). The other 22% of ERCPs are done at low-volume hospitals performing less than 100 ERCPs on annually basis. There are about 177 individual endoscopists report cases to GallRiks. Of these, 8 (4.5%) endoscopists performs more than 100 ERCPs per year and 55 (31%) endoscopists do fewer than 10 ERCPs on an annual basis [Enochsson *et al.* 2010]. With this huge range of different conditions, one might expect that there would be differences in outcomes for PEP. Nevertheless, our data are in line with other published data [Williams *et al.* 2007, Colton and Curran 2009, Testoni *et al.* 2010], since we could not find a significant difference in the outcome of PEP between the three categories of hospital volume.

5 GENERAL DISCUSSION

New techniques have provided us with a number of different strategies for removing CBDS, and we have seen a proliferation of scientific publications in the quest to find the superior or ideal approach. However, there seems to be no standard recommendation about how to treat CBDS in conjunction with cholecystectomy. In the clinical guidelines published in 2006 by the European Association for Endoscopic Surgery (EAES) [Treckman et al. 2006, Paul et al. 2006] and by the British Society of Gastroenterology in 2008 [Williams et al. 2008], the alternatives given are either an open or laparoscopic approach or ERCP performed separately before or after cholecystectomy. These guidelines do not mention combined laparoendoscopic RV-ERCP as a viable alternative. Therefore, the central question is whether RV-ERCP could challenge the prevailing doctrine.

5.1.1 Is laparoscopic cholecystectomy with rendezvous ERCP superior to open cholecystectomy with common bile duct exploration?

In the era of minimally invasive surgery, we must not forget that in most non-Western countries open cholecystectomy together with choledochotomy is still regarded as the first-line treatment for CBDS. Even in Sweden, the open approach is still a valid and trusted last resort for a limited group of patients when minimally invasive approaches appear to be impossible or complex. During almost 30 years of experience with minimally invasive surgery, LC has gradually superseded open cholecystectomy as the operation of choice for uncomplicated biliary stone cases. Even though open CBD exploration is still regarded as the benchmark to which other treatment modalities are compared, it is surprising that there are no published studies comparing the outcome of open CBD explorations with laparoscopic CBD exploration. Likewise, there are no randomized trials between open common bile duct exploration and peroperative ERCP [Gurusamy and Davidson 2010]. The question is whether those studies would ever be conducted, since the general opinion is that open CBD exploration is associated with a higher degree of postoperative pain, a prolonged hospital stay and recovery, a longer time before normal activity, and a less cosmetically-appealing result. There is no evidence to suggest that a surgeon should have any misgivings about proceeding with open CBD surgery in order to obtain stone clearance if a laparoscopic or RV-ERCP procedure failed. Nevertheless, studies have demonstrated an increased risk of morbidity, mostly post-operative bile leakage into the abdominal cavity, when it is necessary to use a T-tube to obtain biliary downstream control [Moreaux 1995]. Open operations are associated with higher mortality rates (around 4% to 10%) in elderly patients and may be as high as 20% among elderly and frail patients undergoing open biliary emergency procedures [Siegel and Kasmin 1997, Gonzales et al. 1997]. These figures contrast with those for laparoscopy and ERCP, where advanced age and comorbidity do not seem to be associated with such high rates of mortality [Ceulemans et al. 2004].

5.1.2 Is laparoscopic cholecystectomy with rendezvous ERCP superior to complete laparoscopic management?

Laparoscopic CBD exploration performed either by a transcystic route or by direct choledochotomy, has advantages that are similar to those of RV-ERCP in many respects. For instance, CBDS can be identified at IOC and managed with minimally invasive means in a one-step procedure. Indeed, low rates of complications have been reported for laparoscopic transcystic CBD exploration, and the length of hospital stay for the procedure is about the same as for LC [Strömberg et al. 2008a, Lauter and Froines. 2000]. However, there

are a number of reasons why the complete laparoscopic approach is unlikely to become accepted as an optimal treatment for choledocholithiasis. The overall stone clearance rate of the complete laparoscopic approach is lower than that of RV-ERCP [La Greca et al. 2009]. Even though the laparoscopic approach may be an excellent method of choice for handling small, single stones preferably located below the confluence of the cystic duct [Lezoche and Paganini 2000], it is not as suitable for handling intrahepatic stones, multiple stones, or large common bile duct stones or for exploring a common bile duct that is surrounded by inflammation or has a ductal diameter less than 10 mm [Fitzgibbons and Gardner 2001]. In addition, a transcystic or transcholedochal approach does not seem to be the best way to manage a situation in which there is an unclear peroperative cholangiogram with obscure images of biliary contrast defects or delayed transpapillary contrast passage to the duodenum, which are circumstances that are not uncommon. In contrast, RV-ERCP provides transpapillary downstream control by sphincterotomy and allows placement of an indwelling stent regardless of the pathology involved.

In general, laparoscopic choledochotomy is considered to be a rather complex procedure that requires excellence on the part of the surgeon. Surgeons with average skills may encounter situations in which they need to either convert the operation to an open choledochotomy or leave a common bile duct stone for a precarious post-operative ERCP. Compare this situation with RV-ERCP, which requires the surgeon to bring down a transcystic guidewire through the cholangiogram catheter and the endoscopist to perform a facilitated ERCP procedure when the guidewire is in place in the duodenum. Both of these steps can be performed by non-experts.

Some opinion leaders are reluctant to suggest conventional ERCP in the OR. The most common arguments are that it is difficult to conduct ERCP with the patient in a supine position and that it is harder to work if some of the customary endoscopic and advanced X-ray equipment is not available. These arguments may be valid for conventional ERCP, but the RV-ERCP procedure can be done well even under operating room conditions. Another strong argument against using ERCP has been the justifiable fear of causing PEP. However, the evidence from our study and others indicates that ERCP-associated injuries of the pancreatic gland can be minimized by using rendezvous cannulation and that PEP is more related to the maneuvers used to achieve biliary access rather than to patient characteristics or endoscopic experience [La Greca et al. 2010]. By using the rendezvous concept, the endoscopist will have instant biliary cannulation success on the first attempt, regardless of experience [Hong et al. 2006, ElGeidie et al. 2011]. On the other hand, pancreatitis has also been reported as a rare complication (<1%) after laparoscopic CBD exploration, possibly as a consequence of antegrade instrumentation or dilatation of the papilla [Tranter and Thompson 2002]. A further argument against ERCP instead of the laparoscopic approach is the risk of future consequences due to biliary sphincterotomy, a concern that now can largely be dismissed, see 1.3.10.

5.1.3 Is laparoscopy cholecystectomy with rendezvous ERCP superior to a two-stage strategy with pre- or postoperative ERCP?

In many parts of Sweden and other Western countries, when there is a high suspicion of CBDS during the preoperative period, the strategy that is currently most widely-used is to ask the endoscopist to perform an ERCP. A subsequent LC is usually planned shortly thereafter. This two-stage approach may be convenient for the endoscopists and the surgeons because it allows both groups to treat the patients in an environment that is tailored to their own needs and routines. However, this may not serve the patients' best interests. There are two small prospective randomized trials [Rábago et al. 2006, Morino et al. 2006] that compared RV-ERCP with sequential pre-operative ERCP and found a significantly higher rate of CBDS clearance when RV-ERCP was performed. In addition, morbidity (which was dominated by PEP) was almost three-fold higher in the patients who were treated with conventional ERCP. These results are in line with our findings in study III.

Regarding the difference between complete laparoscopic management versus sequential ERCP treatment, the evidence is stronger. A number of RCTs including a Cochrane report [Martin *et al.* 2006], showing that the outcomes associated with a one-stage laparoscopic CBD approach are comparable to those of sequential management by LC and ERCP in terms of efficacy, morbidity and mortality. This seems to apply regardless of whether sequential ERCP is performed as a pre-operatively or post-operatively strategy [Rhodes *et al.* 1998, Cushieri *et al.* 1999, Martin *et al.* 2006]. However, one-stage based strategies are likely to be more cost effective with shorter hospital stays compared to two-stage procedures [Urbach *et al.* 2001].

Post-operative ERCP in conjunction with LC is usually performed on the basis of a positive IOC. Under such circumstances, the yield of finding CBDS is considerably higher, above 70% [Tham *et al.* 1998]. Even though most of the ERCP procedures are successful, there is always a potential risk of cannulation failure or unsuccessful stone clearance, which can necessitate a second surgical procedure when adopting a post-operative ERCP strategy. One particular situation may arise in connection with RV-ERCP. If the surgeon for some reason does not manage to introduce the transcystic guidewire, the options are then to either conduct a laparoscopic CBD exploration or convert to open surgery. A viable endoscopic alternative could be to perform a conventional per-operative ERCP with the intention of obtaining stone clearance or at least a plain duodenoscopy to judge, while the patient is still lying on the operating table, whether it is feasible to conduct ERCP in a post-operative scenario if cannulation would actually fail and end up in a reoperation.

A final and sometimes overlooked argument is the patient experience and preference. During laparoscopic procedures, the patient is totally unaware of the treatment since it is performed under general anesthesia. Pre- or post-operative ERCP is often performed under sedation, which can result in serious discomfort for the patient and at times be difficult for the endoscopist to control fully. It is also an inconvenience for the patient to be treated twice.

5.1.4 Some final arguments for using rendezvous

Implementation of the rendezvous concept in Sweden started on a modest scale, probably in 1997 at Norra Älvsborgs Länssjukhus (NÄL), a county hospital in Trollhättan [Johanson *et al.* 1999]. Today, 15 years later, more than 30 surgical units in Sweden have adopted RV-ERCP in conjunction with cholecystectomy as the method of choice in the management of CBDS. They have come to depend on the way the method treats CBDS in a very straight-forward fashion within a reasonable and predictable time frame during cholecystectomy. Some endoscopists have found that when they are challenged by a difficult stone case, it is more effective to terminate the ERCP by placing an indwelling stent and then let the surgeon complete the cholecystectomy in a reasonable time. The patient can then have a subsequent elective ERCP in the regular endoscopy suite to complete the stone removal. Another reason why RV-ERCP can be implemented successfully, especially at a county hospital, is that only a small investment is required because only a guidewire is needed in addition to the standard equipment for laparoscopy and ERCP. In general one could state that the endoscopist experience is usually very positive with RV-ERCP approach because of the minimization of some procedural steps, foremost the simple and swift cannulation. To our knowledge, we have not seen any report about surgeons and endoscopists who have abandoned RV-ERCP once it is fully implemented.

6 CONCLUSIONS

The present study provides data to support the following conclusions:

- Difficult CBDS, unmanageable by conventional endoscopic first- and second-line methods, can be treated successfully and safely with intraductal EHL or by LL under the guidance of direct visualization by a per oral mother-baby cholangioscopy system.
- Intraductal EHL or LL biliary treatment can be used in old and/or frail patients. A majority of these patients can live many years thereafter free from biliary symptoms, with minimized need for hospitalization due to biliary symptoms.
- Elective laparoscopic cholecystectomy with RV-ERCP is a safe and efficient method for removing CBDS and can be conducted in a routine clinical setting. Even if the total operation time is prolonged, RV-ERCP does not influence hospital stay compared with laparoscopic cholecystectomy alone.
- RV-ERCP minimizes leakage of pancreatic amylase, procarboxypeptidase B and trypsinogen-2 compared with conventional post- or pre-operative ERCP. The RV-ERCP induced enzyme leakage was identical to that after cholecystectomy without ERCP and therefore seems to reduce the risk of developing PEP compared with conventional ERCP.
- It seems that RV-ERCP has all the important qualities that lead to an effective ERCP without causing PEP. RV-ERCP provides swift, single-attempt, direct biliary cannulation at all times regardless of the appearance of the papilla, and it can be performed in the same way regardless of the endoscopist's skills and level of experience.

These results concerning RV-ERCP will challenge the current guidelines for treatment of CBDS, at least if ERCP is included in the treatment algorithm in conjunction with cholecystectomy.

7 PROPOSALS FOR RELATED CLINICAL RESEARCH IN THE FUTURE

While it appears that RV-ERCP is safe and efficient, further trials comparing the rendezvous procedure with sequential ERCP and complete laparoscopic management are needed. RCT of all forms of laparoscopic common bile duct explorations would not only validate our current results but also allow assessment of secondary outcomes where current data are inadequate. In terms of future trials and designs, the following studies are proposed:

- A descriptive presentation of the entire Karolinska experience, comprising of more than 300 RV-ERCP procedures.
- A national survey of methods used to treat common bile duct stones in conjunction with laparoscopic cholecystectomy.
- A randomized clinical trial of laparoscopic common bile duct exploration (transcystic and/or choledochotomy) versus laparoendoscopic ERCP with rendezvous. It would be worthwhile to determine whether there are any statistically-significant differences in morbidity, duct clearance, and cost effectiveness.
- A randomized controlled trial with intention to treat between patients presenting with small CBDS, for example 5-6 mm, treated during LC by any peroperative method compared with leaving the CBDS in situ and observing whether the stones pass spontaneously within 6 months. This would help determine which CBDS in the smaller size range need to be cleared up front.
- A randomized trial with intention to treat of sequential ERCP in conjunction with laparoscopic cholecystectomy compared with one-stage laparoendoscopic ERCP with rendezvous, with particular focus on the patients' experiences and health economy.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

År 2012 kan vi fira att det var 130 år sedan den tyske läkaren Carl Langenbuch i Berlin 1882 utförde världshistoriens första kolecystektomi, det vill säga att man på kirurgisk väg tar bort gallblåsan. Patienten, en 43-årig man, fick dagen efter operationen äran att tillsammans med kirurgen röka cigarr för att fira händelsen och samtidigt uttrycka sin tacksamhet över att slippa de kroniska buksmärtor han lidit av under många år till följd av gallsten.

Trots att dagens gallblåseoperationer numera utförs med titthålskirurgi så råder det samma grundprincip idag som förr, det vill säga att man avlägsnar organet där gallsten bildas. Gallstenssjukdom kan i vår del av världen betraktas som en verklig folksjukdom då mellan 25 till 50 procent av befolkningen förr eller senare i livet kommer att utveckla gallsten, och av dessa utgörs två tredjedelar av kvinnor. Lyckligtvis känner majoriteten av gallstensbärarna aldrig av några påtagliga symtom och studier har visat att det bara är mellan 10 och 40 procent av de drabbade som till slut behöver opereras. Även om det rör sig om låga procenttal så representerar siffrorna i det här sammanhanget ett betydande antal patienter och ansemliga kostnader, varje år opereras 11 500 personer för gallstenssjukdom i Sverige.

Den här framlagda avhandlingen kretsar kring den speciella omständighet när gallsten av olika skäl anträffas i området som kallas den gemensamma gallgången. Den gemensamma gallgången är den viktiga rörformiga förbindelsen mellan levern (där gallan bildas) och tolvfingertarmen, där gallan bidrar till matsmältningen. Beroende på förutsättningarna kan sten i den gemensamma gallgången utgöra en direkt fara för patienten då tillståndet förutom smärta kan förorsaka leverskada på grund av stopp i gallflödet, gallgångsinfektion eller bukspottkörtelinflammation, om en sten täpper till bukspottkörtelgångens mynning som anatomiskt sett delar samma utförsmykning som gallgången.

Gallblåseoperation med titthåls teknik utförs idag som en rutinoperation och tar cirka en timme i anspråk att genomföra. Under pågående operation kan man göra en kontraströntgen av gallvägarna, med avsikten att bekräfta eller avfärda förekomst av sten i gallgången samt säkerställa anatomin. Skulle det finnas tecken på sten i gallgången finns det i princip tre olika strategier att välja mellan:

Öppen kirurgi är den klassiska operationen där man gör ett större snitt genom bukväggen strax under höger revbensbåge, avlägsnar gallblåsan och öppnar den gemensamma gallgången för att bortskaften stenen. Den här tekniken har fördelen att den är kirurgiskt tillförlitlig och ger mycket goda resultat gällande stenfrihet. Nackdelen är att den medför en större kroppslig belastning i återhämningsfasen vilket kan vara besvärande för äldre och skörare patienter. Vårdtiden på sjukhus är ofta drygt en vecka längre jämfört med de ett till två dygn som titthålsopererade patienter behöver.

Under 1990-talet introducerades *titthålskirurgi* med stor framgång och används rutinmässigt vid nio av tio gallblåseoperationer. Det finns stora fördelar att använda titthåls teknik, inte minst när det gäller patientens tillfrisknande, som kortare vårdtid och ett mer kosmetiskt tilltalande ärr på bukväggen. Viljan att fullända titthålsstrategin har också radikalt förändrat sättet att hantera sten i gemensamma gallgången. Men att genomföra en komplett utrymning av sten i den gemensamma gallgången med titthålskirurgi är dock tekniskt komplicerat och tidskrävande, därtill är resultaten något sämre jämfört med öppen kirurgi, vilket förklarar varför denna teknik tillämpas och behärskas av få kirurger i landet.

Den metod som varit helt dominerande sedan 1990-talet är *endoskopisk retrograd cholangio-pankreatoskopi (ERCP)*. Det är ett ingrepp där man via munnen för ner ett slangliknande instrument till tolvfingertarmen, för att därifrån med en tunn kateter komma in i gallgången, klyva dess förslutningsmuskel och avlägsna en gallgångsten. ERCP är i många avseenden ett alldeles utmärkt förfaringssätt för att erhålla stenfrihet och har dessutom den stora fördelen, som nämndes ovan, med att klyva den försnäva förslutningsmuskeln och därmed undvika att ytterligare stenar ska kunna fastna där. Om misstanke på gallgångsten väcks i anslutning till operation kan ERCP utföras före operation (pre-operativ ERCP) alternativt efter (post-operativ ERCP).

Ur logistisk synvinkel har den här strategin varit praktisk både för operatören och för endoskopisten, men problematisk för sjukvården då den inneburit ett förlängt vårdbehov, eller två separata vårdtillfällen, dessutom, inte alldeles ovanligt, ett onödigt ingrepp för patienten i de fall stenen har försvunnit spontant före ERCP-undersökningen. En annan risk, men liten, är att man inte lyckas komma in i gallgången vid den efterföljande ERCP-undersökningen, vilket i enstaka fall kan medföra ny operation.

Men ERCP är inte en ofarlig teknik då en av de mest fruktade komplikationerna är akut bukspottkörtelinflammation, eller som den kallas post-ERCP pankreatit (PEP) eftersom den orsakas av ERCP, vilket statistiskt sett drabbar ungefär var tjugonde patient. Visserligen visar PEP sig oftast, i nio fall av tio, som en mild till måttligt stark men övergående buksmärta, utan framtida skadeverkningar. Om det emellertid skulle tillstå en allvarlig bukspottkörtel-inflammation kan det ske till priset av en okontrollerbar inflammatorisk utbredning till många livsviktiga organ, med intensivvårdskrävande organsvikt och i värsta fall risk för död.

Ett av flera syften med denna avhandling var att studera hur man rutinmässigt kan kombinera de båda teknikerna för tithålskirurgi och ERCP. Målet med kombinationen är att kunna erbjuda patienter med gallgångssten en komplett tithåls- och endoskopi-baserad behandling vid ett och samma narkostillfälle, med hög grad av stenfrihet och med reducerad risk för PEP genom så kallad rendezvous-ERCP. Rendezvous innebär i det här sammanhanget att kirurgen för ner en tunn ledare via en kateter i gallblåsans gång och vidare, via den gemensamma gallgången, ner till tolvfingertarmen. Samtidigt kan ERCP-undersökaren med instrument, via munvägen, möta upp i tolvfingertarmen och fånga ledaren (rendezvous), v.g. se **figur 12-13**. Därmed får ERCP-undersökaren direkt tillträde tillgallgången utan kontakt med bukspottkörteln huvudgång, med mindre risk för komplikation.

I det första delarbetet visades att det gick att kombinera gallblåseoperation med rendezvous-ERCP och att det kunde utföras säkert och framgångsrikt på 34 patienter. Resultaten visade att samtliga patienter kunde undersökas i gallgången, de flesta patienter (32 av 34) blev stenfria vid första operationstillfället och resterande två kunde åtgärdas vid senare tillfälle med vanlig ERCP teknik. När förslutningsmuskeln är kluven så är det betydligt lättare och ofarligare att utföra ERCP. Några ERCP-associerade komplikationer, inklusive PEP, observerades inte. Visserligen förlängdes arbetstiden på operationssalen men vårdtiden blev den samma jämfört med vanlig gallblåseoperation utförd med tithålsteknik.

Delarbete två var att studera kort- och långtidsresultatet för de patienter som behandlats med ERCP-teknik i kombination med laser (LL) eller elektrohydrauliskt (EHL) alstrad stötvågsbehandling i gallgången, d.v.s. på så stora gallgångsstenar att de inte kunnat behandlas med vanliga ERCP-metoder. I undersökningen presenteras tio års samlade erfarenhet på 44 patienter som behandlats med så kallad mother-babyskopi assisterad sönderdelning av stora komplicerade stenar i gallgången med LL respektive EHL, v.g. se **figur 19**. Närmare åtta av tio patienter kunde bli helt stenfria, vissa dock först efter upprepade försök. Det unika med studien var den mycket höga medelåldern där hälften av patienterna var 80 år eller äldre och där ett flertal tidigare hade bedömts vara i allt för dåligt fysiskt skick för att klara av öppen bukkirurgi. Vid uppföljningen, som i medeltal skedde omkring fem år efter ingreppet, kunde man summera att majoriteten av patienterna under uppföljningstiden levde utan tecken på gallgångsbesvär eller av denna anledning haft behov av ny kontakt med sjukvården.

I det tredje delarbetet gjordes en jämförande pilotstudie mellan 40 patienter som behandlades med rendezvous-ERCP och 41 patienter åtgärdade med vanlig ERCP. Hypotesen var att ERCP med rendezvous-teknik leder till lägre grad av bukspottkörtelskada, beroende på mängden av ERCP-orsakat enzymläckage från bukspottkörteln. Mätvärden registrerades för tre enzymer (pankreasamylas, procarboxypeptidase-B och trypsinogen-2) fyra, åtta respektive tjugofyra timmar efter behandling och vars halt i blodet befanns vara statistiskt säkerställt högre efter vanlig ERCP jämfört med rendezvous-ERCP. Dessa 40 rendezvous-patienter hade i stort sett samma enzymprofil som kontrollgruppen på 41 patienter som bara hade genomgått sedvanlig gallblåseoperation med tithålskirurgi, d.v.s. bukspottkörteln tycks inte påverkas i nämnvärd utsträckning med RV-ERCP.

I fjärde delarbetet gjordes en epidemiologisk studie omfattande tre års (2007-2009) registrering i ett nationellt kvalitetsregister för gallkirurgi och ERCP (GallRiks), vilket omfattade 12 718 ERCP-undersökningar, utförda på patienter med tidigare orörd gallgångsmynning och med komplett 30-dagars uppföljning. Totalt, för hela gruppen, var risken för PEP 3,6 procent. Det visade sig med god statistisk säkerhet att patienter behandlade med rendezvous-ERCP har 50 procent lägre risk för att utveckla PEP jämfört med vanlig ERCP-teknik. Den patientgrupp som löper störst risk att drabbas av PEP är patienter som är yngre än 62 år, med 130 procent högre risk, jämfört med de patienter som är äldre än 82 år. En annan riskgrupp är kvinnor som löper 30 procent större risk jämfört med män.

Sammanfattningsvis åskådliggjorde dessa delarbeten (studie I, III, IV) att kombinerad titthålsoperation av gallblåsan och ERCP med rendezvous-teknik kan genomföras som ett rutinartat ingrepp utan att det tillför risker som normalt är associerade med ERCP. Graden av komplett stenfri behandling är i paritet med öppen kirurgi, men vårdtiden på sjukhus är den samma som för vanlig okomplicerad gallblåseoperation med titthålskirurgi.

Kombinerad titthålsoperation för gallblåsa och ERCP kräver inte mer avancerad utrustning eller kompetens utöver den som krävs för standardkirurgi eller ERCP-endoskopi, vilket borde vara en god förutsättning för spridning av ingreppet på såväl universitets-, läns- som länsdels-sjukhus. Den åtgärd som krävs är en fungerande logistik mellan ERCP-team och operationsavdelning. Med hänsyn till de behandlingsresultat som erhållits i studierna så kan så kan rendezvous-ERCP rekommenderas i samband med gallblåseoperation som en förstahandsmetod för patienter med röntgenbekräftat fynd av sten i gallgången. För svårbehandlade stora stenar kan mother-babyskopi-assisterad ERCP, med fragmentering av mycket stora stenar i gallgången, rekommenderas som behandlingsmetod även för gamla och sköra patienter.



A gallbladder illustration from Andreas Vesalius (1514-1564). Saunders, J.B. deC. M. & O'Malley, Charles Donald, Facs: Cleveland and New York, The world Publ. Comp. 1950 (Hagströmer Medico-Historial Library).

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