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ASPECTS OF TREATMENT OF COMMON BILE DUCT STONES

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Those are my principles. If you don't like them I have others.
Groucho Marx

ABSTRACT

Background: Gallstone disease is a major cause of morbidity and at least 10 000 cholecystectomies are performed annually in Sweden. At the time of surgery about 5-15% of the patients also have common bile duct stones (CBDS). Introduction of new techniques like Endoscopic Retrograde CholangioPancreatography (ERCP) and laparoscopy have changed the treatment for these patients.

Aims: To analyze how CBDS has been treated in Sweden 1965-2009 and to calculate mortality connected to the different procedures, to assess the risk of malignancy after ERCP in benign disease and identify risk factors for death within 90 days. To evaluate the short term clinical outcome and identify risk-factors for failure in laparoscopic transcystic common bile duct exploration (LTCE).

Methods: Data on all patients with an in-patient procedure code of common bile duct exploration or ERCP 1965-2009 were collected from the Swedish Hospital Discharge Register and those with a diagnosis of malignancy in the bile ducts, liver or pancreas were excluded. The outcome death was identified by cross-linkage to the Registry of Causes of Death and readmission in the Swedish Hospital Discharge Register. For assessment of cancer risk a cohort study of all patients in Sweden having had an ERCP before the end of 2003 without a diagnosis of malignancy at the time of the procedure or within two years after it was performed. To calculate mortality and analyze risk-factors for death after ERCP a case-control study based on the population of Stockholm 1990-2003 was performed. Cases were defined as patients having died within 90 days of the procedure and controls were randomly chosen among those who did not die. Data were collected prospectively on patients having a cholecystectomy at S:t Göran's Hospital 1994-2002, in 155 patients a LTCE were attempted and the outcome analyzed.

Results: The Swedish Hospital Discharge Registry contained records of 126 885 procedures for treatment of common bile duct stones in 110 119 individuals, without a diagnosis of malignancy at the time of the procedure, during 1965-2009. The 90-day mortality was 0.24 % after open surgery, 0.90% after ERCP, 0.67% after combined procedures and 0% after laparoscopic surgery. After adjustment for confounding factors, mainly age and comorbidity, in the multivariate analyses there was no significant difference in mortality between open surgery and ERCP. The risk of malignancy in the bile ducts alone and in the bile ducts, liver and pancreas together was significantly elevated in the cohort of individuals having had an ERCP before 2003, irrespective of if an ES was performed or not. The risk of malignancy diminished with increasing follow-up time. Patients ever having had a cholecystectomy had a significantly lower risk of the studied malignancies**.** In Stockholm County during 1990-2003 the 90-day mortality after ERCP was 1.6%. Advanced age, severe comorbidity, high complexity of the procedure and the occurrence of a complication were associated to death within 90 days, whereas a previous cholecystectomy or the simultaneous performance of an endoscopic sphincterotomy reduced the risk. An attempt of transcystic CBD exploration with complete stone clearance in the 155 patients at S:t Göran's Hospital could be fulfilled in 85 %. The median operating time was 184 minutes (range 89-384 minutes) and the median postoperative hospital stay was one day. There was a significant 3-fold increase in risk of failure of clearance of the bile ducts among patients with stones of >5 mm compared to patients with stones ≤5 mm.

Conclusions: Common bile duct stones were mainly treated endoscopically. ERCP and open surgery were associated with a similar mortality after adjustment for confounding factors. Laparoscopic treatment was chosen in younger and healthier patients, probably with a less severe disease, and no 90-day mortality was recorded. The risk of malignancy in the bile ducts, liver or pancreas was elevated after ERCP in benign disease. However, ES did not seem to affect this risk. Old age and comorbidity were the main risk factors for death after ERCP but a complex procedure or the occurrence of a complication also seemed to increase short term mortality. The performance of a sphincterotomy may decrease the risk of death, possibly by facilitating adequate drainage. Previous cholecystectomy may also decrease the risk of dying after ERCP. Laparoscopic transcystic exploration of the CBD had a high frequency of stone clearance and low morbidity in the present study. Moreover, large stones were a risk factor for failure in stone clearance.

LIST OF PUBLICATIONS

I. *Strömberg, C, Nilsson M*
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Stone Clearance and Risk Factors for Failure in Laparoscopic Transcystic Exploration of the Common Bile Duct.
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CONTENTS

LIST OF ABBREVIATIONS

CBDS	Common bile duct stones
ERCP	Endoscopic retrograde cholangiopancreatography
LTCE	Laparoscopic transcystic common bile duct exploration
CBD	Common bile duct
ES	Endoscopic sphincterotomy
BC	Before Christ
IAP	International Association of Pancreatology
MRCP	Magnetic resonance cholangiopancreatography
CT	Computed tomography
MR	Magnetic resonance
EUS	Endoscopic ultrasound
ESWL	Extra-corporeal shock-wave lithotripsy
SILS	Single incision laparoscopic surgery
NOTES	Natural orifice transluminal endoscopic surgery
IOC	Intraoperative cholangiography
ICD	International classification of disease
HR	Hazard ratio
CI	Confidence interval
SIR	Standardized incidence ratio
OR	Odds ratio
E	Expected
O	Observed
ERC	Endoscopic retrograde cholangiography
BFF	Best friends forever

1 INTRODUCTION

Gallstone disease is a major cause of morbidity world-wide. About 10-15 % of Europeans have gallstones and though many of them are asymptomatic and need no treatment at least 10 000 cholecystectomies are performed annually in Sweden. About 5-15 % of the patients also have stones in the common bile duct at the time of surgery. When open surgery was performed these stones were removed at the same time through a choledochotomy. Treatment of common bile duct stones has changed, first by the introduction of endoscopic retrograde cholangiography with endoscopic sphincterotomy in the 1970s and later by the revolution of laparoscopic cholecyst-ectomy. The endoscopic treatment was initially used in patients who had had a previous cholecystectomy or when surgery was considered too risky. When laparoscopic cholecystectomy was introduced several alternative techniques were used to treat patients with simultaneous stones in the common bile duct: conversion to open surgery, combinations of laparoscopic and endoscopic methods in one or two stages and finally, laparoscopic treatment of the common bile duct stones as well, either by laparoscopic transcystic exploration or by a laparoscopic choledochotomy. Presently all techniques are being used and which one to choose is probably often decided by local tradition.

1.1 HISTORY OF GALLSTONE DISEASE AND TREATMENT

Concerning the liver and the biliary tract there are early records of observations by man. About 2000 B.C. the Babylonians described the gallbladder and the extrahepatic biliary tree in sacrificial animals and made a clay model of them, currently on display at the British Museum. The Babylonian and Assyrian priests examined organs to interpret omens and the model is believed to have been used to instruct their students [1].
The liver was believed to be the centre of the soul, which gives light to the extreme gravity of Prometheus' fate, that was to have his liver plucked by vultures in eternity, a punishment for defying Zeus and bringing fire to mankind [2].

Biliary tract stone disease has tormented man since ages. The oldest gallstone known was found in Gotland, in the remnants of a tomb dating back to the Stone Age, approximately 4000 years old [3].

The mummy of a priestess of the 21st dynasty in ancient Egypt (about 1000 B.C.) was found with a preserved liver with a gallbladder containing 30 gallstones. The mummy was presented at the Royal College of Surgeons in London in 1909, but destroyed in the bombings during World War II, now only photographs remains [1, 4].

Alexander the Great died at the age of 34. The cause of his death is believed to have been malaria or an overdose of Hellebore (Christmas rose) but the course of his disease was also compatible with perforation of the gallbladder or associated pancreatitis. After a party of excess alcohol intake and overeating he deceased after eleven days of fever and abdominal pain [1].

The earliest description of biliary stones and colic is probably to be found in the works of Alexander of Tralles, a Greek physician of the fifth century, however neglected in favour of the theories of Galen, who thought that the yellow bile (one of the four body fluids in humoral pathology) was produced in the gallbladder and disorders of it was held responsible for diseases like cholera [1].

In 1556 an autopsy was performed on Saint Ignatius of Loyola, the founder of the Jesuit Order, by Realdo Colombo, an anatomist from Padua. Numerous gallstones were found in the gallbladder and also a large stone impacted in the common bile duct which had eroded into the portal vein. This was one of the earliest descriptions of adverse effects of stones in the biliary tree but successful treatment lacked for a long time. The famous English anatomist Francois Glisson stated in 1678 that "only death was the solution for biliary colic" [4].

Elective surgery of gallstone disease was first proposed by J L W Thudichum in 1859, a description of which was published in the British Medical Journal the same year [5]. His method of choice was the forming of a biliary fistula by fixing the gallbladder in an abdominal wound and then removing gallstones after crushing them. J L W Thudichum didn't use the method himself but it was adopted by several other surgeons, including Theodor Kocher [6, 7].

The first cholecystectomy was performed in 1882 by Carl Langenbuch in Berlin. A 43-year old man with recurrent attacks of biliary colic and obstructive jaundice was purged for five days prior to surgery. The operation was performed through a "macroinvasive"

incision, a “T” with one limb of 10-15 cm below the right costal margin and the other of the same length along the lateral margin of the rectus abdominis muscle. The cystic duct was ligated with silk and the gallbladder removed. The patient had a cigar the following morning and was strictly forbidden to leave his bed for twelve days. He survived and was discharged from hospital seven weeks later [8]. The new method was ignored and even received with contempt by Langenbuch’s contemporary colleagues and not adopted until the end of the century.

The first common bile duct explorations were done in London in 1889 by Knowsley Thornton and in Basel in 1890 by Ludwig Courvoisier who introduced the use of a T-tube for safer closure of the common bile duct [4, 9, 10]. However, surgery of the common bile duct remained to be a “risky business” illustrated by the fact that William Halsted, the famous American surgeon, watched his mother die of complications of common bile duct stones even though she had been operated on by her legendary son. Ironically he himself died of the same disease in 1922 in spite of the fact that his former students and colleagues at Johns Hopkins University in Baltimore performed three operations on him. The autopsy showed a large common bile duct stone, impacted in the papilla [4, 11].

The surgeons blamed the gastroenterologists for referring the patients too late thereby causing an overrepresentation of hopeless cases and a high mortality. The mortality after surgery was indeed very high, in the first decades of the 20th century reports were published with a mortality of 8-9 % after cholecystectomy with exploration of the common bile duct and 6 % after simple cholecystectomies [3].

In 1974 gastroenterologists from Japan and Germany described an endoscopic alternative to treat common bile duct stones by Endoscopic Retrograde Cholangiopancreatography (ERCP). The papilla of Vater where the common bile duct and the pancreatic duct enter the duodenum was localized, the common bile duct cannulated and if common bile duct stones were diagnosed they could be removed after the performance of an endoscopic sphinterotomy (ES) of the biliary sphincter of Oddi. The technique was recommended to be used in patients with stones impacted in the ampulla of Vater and used exclusively in patients who had had a prior cholecystectomy or in those considered unfit for surgery [12, 13].

A major change in the treatment of gallstones occurred in the late 1980s when laparoscopic cholecystectomy was introduced. The French surgeon and gynaecologist Philippe Mouret performed a laparoscopic cholecystectomy in 1987 starting a revolution in surgery [14, 15]. The technique was not new, in fact a German surgeon, Eric Mühe, from Böblingen had performed a similar operation a few years earlier [16] and the Swedish physician Hans Christian Jakobaeus had described laparo- and thoracoscopy as early as 1912 [17]. It was however the invention of a video computer chip that allowed the image to be shown on a television screen that started the laparoscopic era [18].

1.2 ABOUT GALLSTONE DISEASE

1.2.1 Prevalence

The prevalence of gallstone disease varies around the world. Ultrasound studies reveal gallstone disease in about 10-15% of adult individuals in Western countries and in 3-5% of African and Asian populations [19]. A very high prevalence is seen among adult Pima Indian women in south Arizona (73 %) [20] while in Sweden the frequency is estimated to be 11% in women [21]. It rises with age from 11% in 40 year old women, 25% in 60 year women and in 77-78 year old women 51 % have gall stone disease or have had a cholecystectomy. Gallstone disease is not so common in Swedish men, it is found in 4% of 40 year old men and 15 % in the 60 year old [22, 23]. The difference between men and women concerning prevalence of gallstone disease has been explained by Jorgensen to be related to estrogen therapy and child birth [24]. About 60-80 % of gallstones are silent, giving no symptoms, and need no treatment [25]. With the high prevalence of gallstone disease the remaining symptomatic gallstones will raise a demand on national health care. In the Scandinavian countries the cholecystectomy rate annually is 6-12/10 000 inhabitants [26] and presently in Sweden 10 000-11 000 cholecystectomies are performed every year [27].

1.2.2 Pathogenesis

Gallstones are divided into three major categories: Cholesterol, brown pigment and black pigment stones depending of their composition and pathogenesis. They can also be divided into two categories depending of their origin; the gallbladder or the intrahepatic bile ducts.

In Western countries about 75-80% of the stones are cholesterol-based [28] and female gender, fecundity and a family history of gallstone disease are strong risk factors as well as the metabolic syndrome for development of cholesterol gallstones [29]. Dietary constituents are more questionable, Cuevas et al stress the fact that high energy simple sugar and saturated fat favours cholesterol gallstone formation while fibres and alcohol consumption reduces the risk [30] but legume intake is also identified as a risk factor for gallstone formation [31].

Cholesterol is made soluble in bile by micelle formation with bile salts and phospholipids and precipitation occurs when the bile is hypersaturated with cholesterol or hyposaturated with phospholipids. The supersaturated cholesterol nucleates into crystals and the crystals form into stones [29, 32] in the gallbladder [33] from where they can migrate through the cystic duct or through the wall of the gallbladder into the bile ducts [34]. Impaired gallbladder motility is a risk factor for gallstone formation though it may be a secondary effect of the biliary cholesterol supersaturation [35].

Pigment stones have an estimated prevalence rate of about 20-25% among patients undergoing cholecystectomy [36] and while black pigment stones form in the gallbladder and is associated with biliary hypersecretion of bilirubin or impairment of the enterohepatic recycling of bilirubin [37], brown pigment stones form in the intrahepatic bile ducts as a result of bacterial infection and biliary stasis [33]. Brown pigment stones are more common in Asia while in western countries cholesterol stones are predominant.

1.2.3 Symptoms

In many cases biliary stones are asymptomatic [25] and otherwise non-specific. Symptoms of gallbladder stones such as biliary colic are considered to be caused by the impaction of one or several stones in the gallbladder neck. The most common symptom is abdominal pain with radiation to the upper back with onset more than an hour after a meal. However, abdominal pain for other reasons is common in the population and biliary stones are often silent [38, 39]. Muhrbeck found abdominal symptoms to be as common in individuals with gallstones as in those without [40].

In a Swedish study of asymptomatic patients with gallstones about 10% develop symptoms or complications that require treatment within five years [41] which is

compatible with the literature review made by Friedman [42] but higher incidences have also been reported [43].

Food intolerance is commonly believed to be a symptom of gallstone disease and is typically described as a tendency of abdominal pain related to intake of fatty or fried food and fruit and vegetables with thin skins. Festi et al found abdominal pain related to intake of fatty food in a significantly larger extent in gallstone patients [44], in opposition to other studies [38, 45]. It has been argued that the food intolerance is not related to the gallstones themselves and could persist after surgery [46]. In summary, symptoms of uncomplicated biliary stones are often vague and hard to interpret.

1.2.4 Radiology in Diagnosis of Gallstone Disease

Since gallstone disease gives non-specific symptoms the establishment of a correct diagnosis could not have been easy before the introduction of radiological methods. In 1890 plain x-ray was introduced and gallstones could be detected if they were calcified which occurs in only about 10-15%. In 1924 Evarts Graham and Warren Cole performed a cholecystography, the gallbladder was visualized after intravenous injection of tetrabromphenolphthalein and failure to obtain a shadow was interpreted as cholecystitis [47]. Several roentgenograms were taken during a period of 32 hours. Today the diagnosis of gallstone disease is quite easily made by ultrasound, introduced in the 1970s, no preparations other than six hours of fasting is needed and a correct diagnosis is set in >90% [48, 49] of gallbladder stones.

1.2.5 Indications for Treatment in Gallstone Disease

Gallbladder stones are asymptomatic in many cases and no treatment is necessary [50] [51], however some authors have recommended prophylactic surgery in children, due to the unknown natural course of gallstone disease among pediatric patients [52]. There have been suggestions that asymptomatic stones should be treated in diabetic patients, due to a higher incidence of infectious complications and that cholecystitis presents unexpectedly and proceeds quickly in diabetics [53], but that strategy is refrained from since later studies showed no benefit. Prophylactic treatment is no longer recommended [54, 55]. On the other hand, in symptomatic gallbladder stones treatment is recommended [56, 57], since the risk of development of a complication is higher. The importance of a proper assessment before surgery was illustrated by Halldestam et al

who found that patients who had typical pain location and specific food intolerance had a lower risk of persistent abdominal pain after elective cholecystectomy [58].

1.2.6 Complications

Simple gallstone disease could be complicated by cholecystitis, acute pancreatitis, gallstone ileus, gallbladder carcinoma and finally common bile duct stones the latter being the scope of this thesis. The risk of complications has been correlated to the patient's age at the time of onset of biliary symptoms [59] and also to the severity of the symptoms [42, 60, 61], older age and more severe symptoms being risk factors for the occurrence of a complication.

1.2.6.1 Acute Cholecystitis

Acute cholecystitis is caused by an obstruction of the cystic duct by gallstones or sludge impacted in Hartman's pouch, leading to an increased pressure in the gallbladder in presence of bile hypersaturated with cholesterol [62]. The distension enhances prostaglandin formation giving a vicious circle since the prostaglandins further activates the epithelial cells to secrete fluid [63], also explaining why prostaglandin inhibitors relieve pain [64]. The inflammation is often sterile and the bacterial growth demonstrated in 40-60% of cases is believed to be secondary [65, 66]. Acute cholecystitis is generally considered to be an indication for surgery, either in the acute stage or as a delayed procedure. In high-risk patients needing treatment a cholecystostomy could be performed as a temporary solution [67].

1.2.6.2 Gallstone Pancreatitis

Biliary pancreatitis is the most frequent form of acute pancreatitis in western countries [68] and it occurs in about 3-8% of patients with symptomatic gallstones [69]. Microlithiasis has been detected in a substantial part of patients previously classified as having idiopathic pancreatitis [70, 71]. The pathogenesis of biliary pancreatitis may be multifactorial but two mechanisms could be of importance: reflux of bile into the pancreatic duct, as proposed by Claude Bernard already in 1856 and transient ampullary obstruction, caused by a stone or sludge passing through the ampulla of Vater into the duodenum or impacted in the ampulla [72]. The obstruction gives a raise of the pressure in the pancreatic duct and thereby an activation of digestive enzymes [73, 74].

In Denmark a 30-day mortality of 5% and one-year mortality of 11% has been reported [75] and in a literary review a decreasing mortality (<10%) is reported in later studies compared to 15-21% in the earlier from 1960-1985 [76]. Mortality rises with age and by the severity of the pancreatitis. Many scoring systems have been used for predicting the subsequent occurrence of multiple organ failure causing death since the severity is not always clinically apparent at admission [77-79].

In biliary pancreatitis indication for definite treatment of gallstones is very strong since recurrence rate otherwise is as high as 25-61% [80, 81]. However, the timing of the procedure has been a topic of debate. During the days of open surgery Kelly and Wagner did a prospective study of mortality and morbidity in early and delayed surgery and found it to be much higher in early surgery. On the other hand Burch et al reported similar mortality but a higher incidence of recurrent biliary attacks in the delayed group [82]. More recent reports during the laparoscopic era have shown an advantage of early surgery. In a Swiss study of 112 patients no difference in mortality or morbidity could be shown, but early cholecystectomy gave a lower risk of new biliary attacks [83]. Uhl et al recommend early (within 7 days) surgery in cases of mild pancreatitis, while in severe cases surgery should be postponed at least three weeks, due to increased risk of infection [84]. In the IAP guidelines for surgical management of acute pancreatitis three grade B guidelines concerning surgery to prevent future attacks of biliary pancreatitis are stated: cholecystectomy should be performed to prevent further attacks, in mild biliary pancreatitis surgery should be performed as soon as the patients have recovered, ideally during the same admission, and in severe gallstone-pancreatitis cholecystectomy should be delayed until the patient has recovered with sufficient resolution of the inflammatory response [85]. The indication for early ERCP in gallstone pancreatitis has also been much debated. Fan et al reported beneficial effects of ERCP performed within 24 hours of admission in terms of lower incidence of biliary sepsis [86] and Neoptolemos found benefits concerning morbidity but not mortality, [87] while Petrov in a metaanalysis found no reduction of mortality or complications of early ERCP in patients with predicted mild or severe gallstone pancreatitis but without cholangitis [88].

1.2.6.3 Gallstone Ileus

Gallstone ileus is a rare complication of gallstone disease. It arises mostly in the elderly and accounts for about 1-4% of all cases of mechanical bowel obstruction [89]. It

occurs when a gallstone erodes the gallbladder wall into the intestinal lumen and gets impacted in the valvula of Bauhini although impaction in other locations of the gastrointestinal tract has been described [90, 91]. The management is associated with high morbidity and also mortality and consists of enterotomy with retrieval of the gallstone. A laparoscopic approach has also been described [92]. Whether a biliary procedure should be added and the timing of such a procedure remains a controversy. The literature consists mainly of single centre experiences of small numbers of patients collected over many years and in a recent review Ravikumar and Williams argued that future case series would hardly help decision making [93].

1.2.6.4 Gallbladder Carcinoma

There is a strong association between gallstone disease and gallbladder cancer since gallstones are present in a vast majority of gallbladder cancer patients [94, 95] and the size of gallstones is a major risk factor, the bigger the stones the bigger the risk of development of a carcinoma [96]. However, the causal relationship between stones and development of carcinoma remains unclear [97].

1.3 COMMON BILE DUCT STONES

1.3.1 Prevalence

About 5-15 % of patients with symptomatic gallstones have common bile duct stones (CBDS) at the time of surgery [43, 98, 99], the portion grows with increasing age and duration of symptoms. CBDS that appear after common bile duct surgery or endoscopy are defined as retained if they are diagnosed less than six months postoperatively, otherwise as recurrent. Retained stones, mostly due to incomplete clearance, are reported in a frequency of 4-10% after both surgery and ERCP [100-102]. The rate of recurrence after ERCP is estimated to be 10-20% and as risk-factors for recurrence a gall-bladder left in situ (if it contains gallstones), a bile duct with a diameter > 15mm and the existence of a periampullary diverticula have been identified [103-105] . The risk of recurrence after ERCP is about the same as after open surgery [100] but it may be lower after laparoscopic common bile duct surgery [106, 107].

1.3.2 Pathogenesis

Most common bile duct stones form in the gallbladder and migrate through the cystic duct to the common bile duct and are composed as gallbladder stones, i.e. in Europe predominately of cholesterol, but they may also form primarily in the common bile

duct. Brown pigment stones, however uncommon in the Western world, form in the intrahepatic bile ducts in patients with infections and obstruction.

Mirizzi syndrome was originally described in 1948 as jaundice caused by a gallstone impacted in the gallbladder neck compressing the bile duct and thereby causing obstruction. It has later been classified by Csendes et al into four categories. In type I obstruction is caused by the external compression originally described, in type II a cholecystobiliary fistula is present with destruction of less than one-third of the diameter of the bile duct. In type III the fistula involves up to two thirds of the duct diameter while in type IV there is a complete destruction of the bile duct [108]. Mirizzi syndrome is known to be difficult to diagnose. In a British retrospective study of 33 patients it was found that the diagnosis was most easily set with MRCP [109].

1.3.3 Symptoms

The natural history of common bile duct stones is unpredictable, varying from no symptoms at all to life-threatening conditions. Rosseland found asymptomatic CBDS in up to 10% of patients scheduled for laparoscopic cholecystectomy [110], making the prevalence of common bile duct stones at the time of cholecystectomy hard to predict in spite of the use of scoring systems [111-113]. CBDS may also pass spontaneously into the duodenum without causing symptoms or reside in the bile duct for a long time and still be asymptomatic, in a literature review Metcalfe et al found that to be the case in 85% of patients with stones discovered unexpectedly during surgery [114].
The most common symptom is biliary colic while jaundice, cholangitis and pancreatitis would rather count as complications of common bile duct stones.

When a bile duct stone gets impacted in the papilla it will cause obstructive jaundice, often fluctuating, when jaundice clears the stone may have passed into the duodenum but it may also have floated up in the bile duct.

Cholangitis is a result of an infection complicating obstructive jaundice and has been reported with a mortality of 13-88% if left untreated [115]. The classical symptoms of Charcots triad (jaundice, fever and pain) is encountered in about 75% of the patients but in some this life-threatening condition is presented with vague symptoms [116]. Stones passing the papilla may also induce a pancreatitis by obstructing the pancreatic duct (se above).

In longstanding obstruction secondary biliary cirrhosis and portal hypertension may develop [102].

Patients with symptomatic common bile duct stones could have a higher risk of developing a complication, studies have shown a risk of 25-50% of jaundice, cholangitis or pancreatitis if the stones were left untreated [116] and in a Dutch study of 175 patients with complicated gallstone disease half of the patients had had "warning" colic attacks five months before the complication occurred [116, 117].

1.3.4 Radiology in Diagnosis of Common Bile Duct Stones

Ultrasound is frequently used in the diagnosis of gallbladder stones but is less trustworthy in terms of sensitivity in diagnosing common bile duct stones, especially if they don't cause dilatation of the bile duct [116] which is the case in about half of the patients [118]. The sensitivity for detection of intraductal stones is 10-63% [119-121] but since the specificity is high ultrasound remains an important tool and is often used as primary imaging modality.

At computed tomography (CT) biliary stones are heterogenic in appearance from heavily calcified too less radiopaque than bile when containing mainly cholesterol. They can also have gas attenuation due to nodules of nitrogen gas [118]. The sensitivity for detection is reported to be 69-88% and the specificity 83-97% [122-124]. Contrast material excreted in the bile can be injected intravenously for better sensitivity but the use is not wide-spread, perhaps because the excretion is variable and reduced when serum bilirubin is high. It is also believed to cause more severe allergic reactions than conventional intravenous contrast material [118] and no water-soluble iodine-based contrast material with affinity to the liver is available for use in Sweden [125].

Magnetic Resonance (MR) imaging is generally better than CT in diagnosing common bile duct stones [118] and with special techniques it has the advantage of permitting imaging of the whole biliary tract within one breath-hold [126]. T2 weighted MR cholangiography is highly sensitive and specific in the detection of CBDS while T1 weighted images give a more variable appearance [118]. Sensitivity is reported to be 88-100% and specificity 72-97% [127-129]. However, when the stones are small (< 3 mm) sensitivity of detection by MR is low, maybe as low as 50% [130].

Endoscopic ultrasound (EUS), where an ultrasonic probe is placed in the duodenum under endoscopic guidance, gives a detailed imaging especially of the distal common bile duct [131]. EUS has been used the last twenty years for diagnosing CBDS and in two meta-analyses the pooled sensitivity and specificity were 89-94% and 94-95% respectively [132, 133], comparable to the sensitivity and specificity of MR. EUS is useful for diagnosing microlithiasis (stones < 3 mm) in pancreatitis and in "idiopathic pancreatitis" the cause can be identified in up to two-thirds of the patients [70] where other modalities have failed but otherwise the choice between MR and EUS is decided by local availability [102].

The evolvement of new less invasive modalities has gradually replaced ERCP as a diagnostic tool and it is nowadays used mainly as a therapeutic procedure [102]. Routine use of preoperative mapping of the bile ducts, such as intravenous cholangiography, MRCP or ERCP, to detect asymptomatic common bile duct stones and to reduce the risk of a bile duct injury by identifying anatomic anomalies, has been a topic of much debate [134]. Scoring systems containing a history of colic pain and/or jaundice, dyspepsia, cholecystitis, ultrasound describing number and size of stones in the gallbladder and the level of transaminases and/or alkaline phosphatase have been used to try to predict the existence of silent common bile duct stones prior to laparoscopic cholecystectomy thereby reducing the need of preoperative radiology [111, 112]. In patients with no history of jaundice or pancreatitis, normal liver function tests and a normal sized common bile duct (≤ 5 mm) Majeed et al reports a 6% risk of common bile duct stone [135]. Preoperative evaluation of the bile ducts is now much abandoned and in a Swedish study Järhult found it unnecessary since it had no impact on preventing bile duct injury or on the frequency of retained common bile duct stones [136].

1.3.5 Indications for Treatment of Common Bile Duct Stones

Ammori et al has suggested a policy of leaving small stones found unexpectedly in bile ducts of normal width at surgery and wait and see if symptoms occur before removing them [137], on the other hand Collins found no correlation between the number or size of silent stones or size of ducts and spontaneous passage [138]. However, it is generally agreed that all symptomatic bile duct stones should be removed [102, 111, 139].

Obstructive jaundice should be treated as an emergency due to potentially dangerous complications such as cholangitis, renal failure, cardiovascular dysfunction or coagulopathy [52, 102].

1.4 TREATMENT

Several attempts have been made to dissolve gallstones. In traditional Chinese medicine different herbs have been used and in Europe artichoke and hawthorn in wine were believed to have a dissolving effect. Aeter is also known to be able to dissolve gallstones and was used for many years before the era of surgery. It was probably one of the ingredients in " Liquor anodynus mineralis Hoffmanni" [140, 141] used from the 18th century in many conditions like colic and hysteria [142].

Gallstones consist mainly of cholesterol in individuals of industrialised countries and are thereby susceptible to dissolution by bile acids, first described in 1937. A high success rate (80 to 90% in one year) has been reported in small calculi, but the recurrence rate is high [143]. Extracorporeal shock-wave lithotripsy (ESWL) has been used to disintegrate gallstones but it also has the disadvantage of a high recurrence rate [144] to some extent prevented by post- ESWL medication with bile acids. However Nicholl et all found that ESWL did not relieve symptoms and that it was not cost-effective [145] and surgery was recommended as first line treatment of symptomatic gallstones. ESWL has also been used to fragment big common bile duct stones [146] but a randomized study of 60 patients with difficult common bile duct stones by Neuhaus et al showed intracorporal laser lithotripsy to be more efficient in clearing the bile ducts [147]. ESWL is still recommended as treatment for intrahepatic stones [148].

1.4.1 Surgery

Cholecystectomy was first performed in 1882 and exploration of the common bile duct in 1889, initially and in the first decades of the last century with high mortality and morbidity, however with growing experience and the introduction of antibiotics in the 1940s the mortality and morbidity decreased [3, 85, 87, 149, 150]. In the 1970s small-incision cholecystectomy was introduced and morbidity and complications seemed to decline [151]. Laparoscopic cholecystectomy was introduced in 1987 and became quickly the method of choice even though scientific evidence of its superiority were lacking [152]. A recent Cochrane report concluded a low mortality (< 0.09%) regardless of the method of access to the abdominal cavity chosen, no difference in

complications or risk of bile duct injury, but a shorter hospital stay and sick-leave for both mini-invasive procedures. Small-incision cholecystectomy had a shorter operating time and a lower cost than laparoscopic cholecystectomy [153] but the latter is by far the predominant procedure. In recent years new techniques have been introduced, single incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES), to reduce the number of incisions and thereby morbidity [154-156]. These methods need to be evaluated.

The most feared complication of surgery is a bile duct injury, a lesion that has been reported to be more common in laparoscopic surgery, especially when the technique was introduced [157, 158]. The risk was increased in hospitals doing less than 100 procedures yearly [159], to some extent similar to the findings of Andrén-Sandberg et al during the era of open surgery, that most bile duct injuries are caused by surgeons under training [160]. The increase has been explained to be a result of the learning curve but Waage et al found that not to be the case [161].

Whatever access is chosen to the abdominal cavity the rest of procedure is more or less the same. The gallbladder in dissected either from above (fundus-first), a technique often used in open surgery and also recommended to be used in laparoscopic surgery [162] , though Dolan et al point out that using fundus-first technique could lead to a higher incidence of retained common bile duct stones[163], or from below. The critical point is the dissection of the triangle of Calot and the correct identification of the ducts, in laparoscopic cholecystectomy made easier by lateral traction of the infundibulum of the gallbladder [164] and unintentional thermal damage could be avoided by careful use of electro-cautery in this area [165].

The use of intraoperative cholangiography (IOC) was introduced by PL Mirizzi in 1931 [166] and in Sweden by Hulten in Uppsala in 1937 [167] and since then there has been a debate of whether a routine use of peroperative cholangiography should be recommended or not [161, 168-170]. The main advantage would be that it would lower the risk of serious bile duct injuries [158, 161] while other studies find no such correlation [171, 172]. The main disadvantage would be that it is time-consuming and sometimes difficult to perform [173, 174]. It is however accepted that it should be done prior to an exploration of the bile ducts, thereby reducing the number of unnecessary explorations [170, 175].

During the era of open cholecystectomy surgical removal of CBDS found under operation was considered gold standard and in a randomized trial between surgery alone and preoperative ERCP followed by biliary surgery Neoptolemos et al found no advantage of the two-stage procedure [176]. The introduction of laparoscopic surgery caused a change of therapeutic strategy since, at least in the beginning, no method of treating CBDS laparoscopically existed, instead a variety of options developed. The laparoscopic cholecystectomy could be converted to open surgery when CBDS were revealed or laparoscopic cholecystectomy could be combined with ERCP and ES either as a one-stage procedure or as a two-stage one where the endoscopy could be performed either before or after surgery. Laparoscopic techniques of common bile duct exploration have later evolved and CBDS can be removed either by a transcystic approach or by a choledochotomy (see below).

1.4.2 ERCP

When ERCP with endoscopic sphincterotomy (ES) was introduced in the 1970s [12, 13] as treatment of common bile duct stones (CBDS) it was reserved for patients who had had a previous cholecystectomy or were considered unfit for surgery. After the introduction of laparoscopic cholecystectomy treatment of CBDS by ERCP and ES of the biliary sphincter of Oddi has become a routine procedure world-wide [102] even in young patients without previous cholecystectomy, a fact that could be alarming, since ERCP is known to cause complications in a substantial extent. Short-term consequences as perforation of the bowel, hemorrhage, cholangitis and pancreatitis are reported in 3-23% of cases with a mortality of 0-6% [177-180]. Late complications include cholangitis and stone recurrence reported in 10-15% of cases [179-181]. The splitting of the sphincter of Oddi has been reported to increase the risk of cholangiocarcinoma in the long run, thought to be an effect of long-standing bacterial overgrowth in the bile ducts due to an ascendant infection from the duodenum [181]. In patients scheduled for laparoscopic cholecystectomy a policy of performing preoperative ERCP will result in a number of unnecessary potentially dangerous procedures [182, 183] since only 27-54% of the patients believed to have CBDS according to screening tests actually have so [184]. If on the other hand a postoperative ERCP is chosen a problem could be that the ERCP will sometimes fail, the papilla might be impossible to cannulate or clearance of the bile ducts may be difficult, Rhodes et al found a 93% clearance of the bile ducts when using postoperative ERCP [185].

Randomized trials have however found that a two-stage procedure has the same efficacy in treating CBDS compared to a single-stage one but implies a longer hospital stay and higher costs [185-187].

During laparoscopic cholecystectomy insertion of a soft-tipped guide-wire through the cystic duct and sphincter of Oddi out in the duodenum could facilitate cannulation [187-189]. A single-stage rendez-vous procedure has been described by Enochsson et al, if the intraoperative cholangiography showed CBDS the guide-wire was introduced to duodenum through the IOC catheter by the surgeon while waiting for the endoscopy team to arrive. The endoscopist caught the guide-wire with a polypectomy snare and after pulling it through the working channel of the endoscope a sphincterotomy could be introduced. After ES the stones could be removed using a balloon or a basket and after the endoscopic intervention the surgeon could complete the laparoscopic cholecystectomy [188]. With this rendez-vous technique Rabago et al found morbidity as well as post-procedure pancreatitis to be reduced, probably because injection of contrast material in the pancreatic duct could be avoided [187]. If intraoperative ERCP for some reason is refrained from, the guide-wire can be left in place after completed surgery an used to facilitate postoperative cannulation as a two-stage procedure [190]. ERCP and ES are still, as in the beginning, used also in patients who have had a prior cholecystectomy and as only treatment in biliary stone disease in elderly with a severe comorbidity. However, a recent Cochrane report concluded that there was a higher mortality if cholecystectomy was deferred from after ERCP and endoscopic clearance of common bile duct stones [191] in contrast to what earlier was recommended [192-194].

1.4.3 Laparoscopic Exploration of the Common Bile Duct

Laparoscopic exploration of the common bile duct could be done either by a transcystic approach or by a choledochotomy [195-197]. In the transcystic technique a guide-wire is placed through the cystic duct into the CBD. After balloon-dilatation of the cystic duct a thin choledochoscope is placed over the guide-wire and the stones are retrieved one by one. Good results have been published with a clearance of 85% or more [198, 199] but the technique has limitations, big stones are not possible to pull through the cystic duct, intrahepatic stones may be impossible to reach and when there are numerous stones in the biliary tract the technique can be time-consuming.

The laparoscopic choledochotomy has no limitations in size of stones [195, 200] but carries a higher morbidity that could be due to the use of a T-tube when closing the incision in the common bile duct [201]. Alternative techniques have been described, the common bile duct could be closed either by a direct suture or over a stent instead of T-drain [202]. In a Cochrane review dated 2007 Gurusamy and Samray found no evidence of benefit of the use of a T-tube or not [203] but in 2008 Leida et al published a randomized study of 80 patients and found a primary closure of the choledochotomy to be superior to the use of a T-tube by a shorter hospital stay, lower costs and less postoperative and biliary complications [201].

2 AIMS

Paper I aimed to analyze how CBDS has been treated in Sweden 1965-2009 and to calculate mortality and morbidity related to the different procedures.

Paper II aimed to evaluate the relationship between ES for benign disease and subsequent development of malignancy in the biliary tract. A secondary aim was to study the relation between severe CBDS exposure and malignancy in the biliary tract.

Paper III aimed to identify risk factors for mortality within 90 days of the procedure in patients who have had ERCP in non-malignant disease. The main hypothesis was that a potentially dangerous procedure like ES would be one such risk factor.

Paper IV aimed to evaluate the short term clinical outcome, especially the stone clearance rate, of LTCE as well as to examine potential risk factors for failure in stone clearance in the use of this technique.

3 MATERIAL AND METHODS

3.1 PAPER I, II AND III

We used data from the Swedish Hospital Discharge registry ("slutenvårdsregistret"), where the Swedish National Board of Health and Welfare has been collecting data on individual hospital discharges since 1965. The coverage of the Hospital Discharge Register was 60% in 1969, 85% in 1983, and included all Swedish hospitals from 1987 and thereafter [204]. By cross-linkage to the Swedish National Cancer Registry ("cancerregistret") we identified individuals with a diagnosis of malignancy in the bile ducts, liver or pancreas. Cross-linkage to the registry of Causes of Death was performed to ascertain death as an outcome or censoring in the event of death and Domestic and International Relocations for censoring in the event of emigration of a cohort member. The Swedish National Cancer Registry is 98% complete [205] and the registry of Causes of Death ("dödsorsaksregistret") is also essentially complete [206, 207]. A detailed description of the methods used in these studies has been described elsewhere [208].

3.2 PAPER I

3.2.1 Study Base

Using the national registration numbers we identified all individuals who had had at least one in-hospital episode with a discharge procedure code of open or laparoscopic exploration of the common bile duct, ERCP or ES (JKB00, JKB01, JKB11, JKB20, JKB21, JKE00, JKE02, JKE12, JKE15, JKE18, JKE25, UJK02, UJK05, UJK12, UJK15, 5300, 5302, 5304, 5351, 5352, 5356, 5357, 5388, 5394 and 9014 [209, 210]) during the years 1965-2009. This total cohort was divided into four sub-groups in the further analyses, open surgery (JKB00, JKB20, 5300, 5302, 5351 and 5352), ERCP (JKE02, JKE12, JKE15, JKE18, JKE25, JKE96, JKW96, UJK02, UJK05, 5388, 5394 and 9014), laparoscopic common bile duct exploration (JKB01, JKB11, JKB21) and finally surgery combined with ERCP (any ERCP-code and any code for open or laparoscopic common bile duct exploration during the same hospital stay).

The outcome death was identified by cross-linkage to the Causes of Death Registry. All individuals with discharge code or a code in the Swedish National Cancer Registry of

malignancy in the bile ducts, liver and pancreas (ICD 7 155-157 or corresponding codes in the later classification) within 90 days of the procedure were excluded.

3.2.2 Registry Data

From the Swedish Hospital Discharge registry we collected information on the age, sex, time-period, co-morbidity, complications and length of hospital stay, readmissions and redo procedures of the cohort members.

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3.2.3 Statistical Analyses

Survival among patients who have undergone treatment of common bile duct stones by open surgery, ERCP, laparoscopic exploration or combination of endoscopic and surgical methods was assessed by the Kaplan-Meier method.

Cox proportional Hazard ratios (HR) and their 95% confidence intervals (CI) were used for univariate and multivariate assessment of the association between potential risk factors and the hazard of death within 90 days of the procedure. The potential risk factors used in the regression modeling were categorized in order to facilitate the analyses. Potential confounding effects were tested by introducing the variables under study stepwise into the multivariate regression model, and the risk factors were also tested for possible interactions. Statistical analyses were performed using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, IL). The level of statistical significance was specified to be 0.05.

3.3 PAPER II

3.3.1 Study Base

From 1965 to 2003, we identified all individuals with at least one in-hospital episode with a discharge procedure code for ERCP or endoscopic sphincterotomy (Swedish Classification of Operations and Major Procedures, codes 9014, UJK02, UJK05, UJK12, UJK15 for ERCP or 5388, 5394, JKE 02, JKE 12, JKE 15, JKE 18, JKE 25, JKE 98 for ES or procedures for which ES normally is a prerequisite). This total ERCP cohort was in the further analyses divided into two subgroups: 1. Patients having at least one procedure code registration for ES or any other endoscopic biliary procedures for which an ES normally is a prerequisite (Swedish Classification of Operations and Major Procedures, codes 5388, 5394, JKE 02, JKE 12, JKE 15, JKE 18, JKE 25, JKE

98). 2. Patients in the cohort without any procedure code registration for ES or any other endoscopic biliary procedure implying ES.

Those patients who had a diagnosis of malignant or benign tumour in the bile ducts, liver or pancreas at the time of the procedure or within two years after it were excluded from further analyses to avoid bias, since the registered ERCP in these cases may have been performed because of the tumour or due to symptoms caused by a tumour that was still undiagnosed. Considering the poor prognosis of malignancies in the biliary tract, liver and pancreas it is highly unlikely that a tumour causing symptoms would be diagnosed more than two years later. The cohort was then followed from entry until diagnosis of an outcome malignancy (primary malignant tumours in the liver, bile ducts including ampullary region and pancreas, but excluding gallbladder malignancy, ICD7 codes: 155 and 157, but excluding 1551), death, emigration or end of follow-up (December 31st 2003), whichever occurred first.

3.3.2 Statistical Analyses

Several patients had ERCP or ES procedures registered at more than one point in time. As index procedure for cancer relative risk analyses were, first of all, every first time procedure for every patient. If the first time procedure included or implied ES the patient's person-time was only included in the ES subgroup. If, on the contrary, a patient's first time procedure was non-ES or ES-implying, and followed by a subsequent procedure including a code for, or implying, ES, this patient had two index procedures. One without ES, with person-time counted in the non-ES subgroup from two years after this procedure until the subsequent, second index procedure ES, after which person-time was counted in the ES subgroup from two years after that procedure and on.

The standardized incidence ratio (SIR), the ratio of the observed to the expected number of malignancies, was used to calculate relative risk. The expected number of cancers occurring in the entire Swedish population was calculated by multiplying the observed person-time by age- (in 5-year groups), sex- and year of entry-specific cancer incidence rates. The standardized incidence ratios are inherently adjusted for confounding by age at follow-up, sex and year of entry. The 95% confidence intervals (CI) of standardized incidence ratios were calculated assuming that the observed numbers followed a Poisson distribution [211].

To assess the general risk of malignancy in the cohort the SIR for all malignancies (ICD 7: 140 – 209) was performed. Moreover, the SIR for lung malignancy (ICD 7: 162 – 163) was calculated as an indirect estimate of tobacco smoking exposure in the cohort, since smoking may be a relevant confounder, especially concerning pancreatic cancer risk analyses.

3.4 PAPER III

3.4.1 Study Base

In the cohort used in paper II we identified all individuals of the population in Stockholm County with one or more in-patient episodes with a discharge code of any ERCP-procedure but without a diagnosis of malignancy at the time of the procedure from a Stockholm County hospital during 1990-2003.

3.4.1.1 Case Identification

Cases were defined as individuals in the study base who had died within 90 days of the procedure. For those registered as having undergone several procedures, the last one counted as index procedure. Of the 323 patients initially identified 90 were eligible to study.

3.4.1.2 Selection of Controls

The controls were randomly chosen from the study base among individuals not identified as cases and, as in the cases, when several procedures were registered, the last one counted as index procedure. Written informed consent was obtained from the control subjects who were still alive.

3.4.2 Exposures

The exposures studied were age, sex, hospital volume, time-period, co-morbidity, previous cholecystectomy, indication for the procedure, complexity of the procedure, pancreatic duct contrast injection, ES and finally the occurrence of complications. For age, sex, hospital volume, time-period, co-morbidity and previous cholecystectomy, registry data were used. Concerning indication for the procedure, complexity of the procedure, pancreatic duct contrast injection, ES and complications, data were collected by reviewing the medical records. The part of the medical record concerning the ERCP

procedure, including indications and complications, was coded with a number for each study subject and reviewed blinded for case or control status.

3.4.3 Statistical Analyses

Means and frequencies of exposures were calculated according to the outcome variable death or not. Data were presented as means ± standard deviations for continuous variables and proportions for dichotomized variables. Significant differences between groups were determined using Student's t-test for comparisons of means and Chi-square test for comparisons of proportions.

Odds ratios (OR) and their 95% confidence intervals (CI), derived from unconditional logistic regression, were used for univariate and multivariate assessment of the association between potential risk factors and the outcome death within 90 days of the procedure. The potential risk factors used in the logistic regression modeling were categorized in order to facilitate the analyses. Potential confounding effects were tested by introducing the variables under study stepwise into the multiple logistic regression model, and the exposures shown to be significant in the univariate analysis were tested for possible statistical interactions. Statistical analyses were performed using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, IL). The level of statistical significance was specified to be 0.05 and the fit of the model was estimated by the Hosmer and Lemeshow goodness-of-fit test [212].

3.5 PAPER IV

3.5.1 Study Base

Laparoscopic transcystic common bile duct exploration (LTCE) was attempted in 155 patients at S: t Göran's Hospital during the years 1994-2002. Data on all patients having cholecystectomy was collected prospectively and registered in a database. During the time period a total of 3106 patients underwent cholecystectomy. In 273 patients the intraoperative cholangiogram suggested CBD stones and in 118 of them the surgeon chose other methods of stone clearance (conversion to open surgery, ERCP or laparoscopic choledochotomy). The 155 patients in whom LTCE was attempted were included in this study. The patients were followed up six week postoperatively including analysis of liver enzymes. If the tests were normal and the patient was well, no further follow-up was done.

3.5.2 Statistical Analyses

All LTCE procedures registered were classified as either successful or failed with regard to stone clearance. Stone clearance was considered successful if a second intraoperative or postoperative cholangiogram after the attempted clearance showed no stones.

The success rate was then analyzed with regard to age, sex, procedure priority, common bile duct diameter, number of stones, stone size, intrahepatic stones and length of hospital stay. In significance testing Fischer's exact test was used for dicotomized discrete variables and the nonparametric Wilcoxon method for comparisons between means.

Odds ratios (OR) and their 95% confidence intervals (CI), derived from unconditional logistic regression were used for univariate and multivariate assessment of the association between studied potential risk factors and the risk of failure in stone clearance. Linear trends of the associations were tested by treating categorical variables as continuous in the logistic regression model. Potential confounding effects were tested by introducing the variables under study one by one into the model.

4 RESULTS

4.1 PAPER I

During the period 1965-2009 a total of 126 885 procedures of open or laparoscopic common bile duct exploration or ERCP were performed in 110 119 patients without a diagnosis of malignancy in the bile ducts, liver or pancreas at the time of the procedure or within 90 days after it. The distribution of the different procedures by five-year terms is shown in Figure 1. Endoscopic procedures have gradually replaced open surgery as treatment for common bile duct stones, only to a small extent challenged by laparoscopic methods.

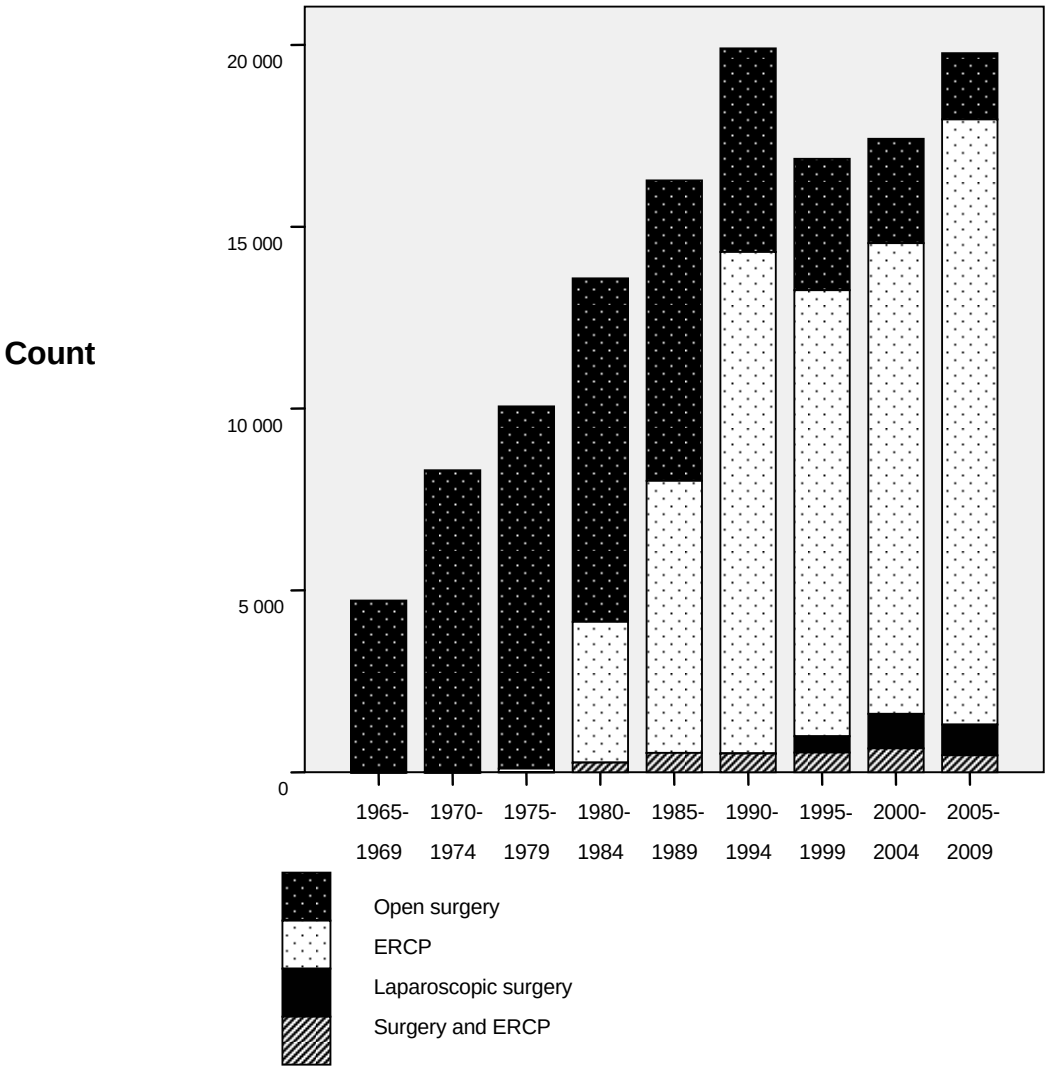

Figure 1. *Treatment of Common Bile Duct Stones in Sweden 1965-2009.*

The profile of age, sex and co-morbidity differs between the cohorts where the ERCP patients tend to be older, to a larger extent of male sex and to have more severe co-morbidity according to the Charlson index. On the contrary, patients treated with laparoscopic CBD exploration are significantly younger, more often women, and tend to have less comorbidity. Pancreatitis, which may be either a complication of the biliary stone disease or a complication of the procedure, is reported in 0.6% of patients after open surgery, in 5.9% after ERCP and in 3.4% after laparoscopic exploration (Table 1).

Both the 30- and 90-day mortality is around 3-fold higher after ERCP than after open CBD exploration. Also in this respect laparoscopic CBD exploration differs markedly from the other interventions as 90-day mortality is 0 in this cohort. The proportion that has a reintervention within 90 days after ERCP is also significantly, i.e. up to 5-fold higher, than in the laparoscopic and open CBD exploration cohorts.

The Kaplan-Meier survival curves (Figure 2) confirm that crude survival is higher after laparoscopic common bile duct exploration and then gradually decreases for open surgery, surgery and ERCP and is lowest after ERCP alone.

	OPEN CBD EXPLORATION N=54581 N (%)	ERCP N=67078 N (%)	LAPAROSCOPIC CBD EXPLORATION N= 2244 N (%)	SURGERY AND ERCP N=2982 N (%)
Age, mean (std)	60 (17)	67 (17)	48 (18)	65 (17)
Sex, male	20616 (38)	29281 (44)	577 (26)	1271 (43)
Comorbidity :				
Charlson score 0	51922 (95)	58206 (87)	2144 (96)	2720 (91)
1-2	2529 (4.6)	8007 (12)	97 (4.3)	244 (8.1)
3-4	97 (1.8)	555 (0.83)	3 (0.13)	16 (0.53)
≥5	33 (0.06)	310 (0.46)	0	2 (0.067)
90-day mortality	132 (0.24)	570 (0.85)	0	20 (0.67)
30-day mortality	56 (0.10)	188 (0.28)	0	10 (0.34)
Pancreatitis	331 (0.60)	3984 (5.9)	76 (3.4)	95 (3.2)
Septicemia	47 (0.086)	257 (0.38)	1 (0.045)	17 (0.57)
Length of stay, mean (std)	16 (14)	7.2 (10)	4.2 (5.2)	20 (15)
Readmission within 30 days	9153 (17)	11942 (18)	235 (10)	609 (20)
New procedure within 90 days	3229 (5.9)	13303 (20)	98 (4.3)	430 (14)

Table 1. *Characteristics and basic data on patients treated for common bile duct stone disease 1965-2009.*

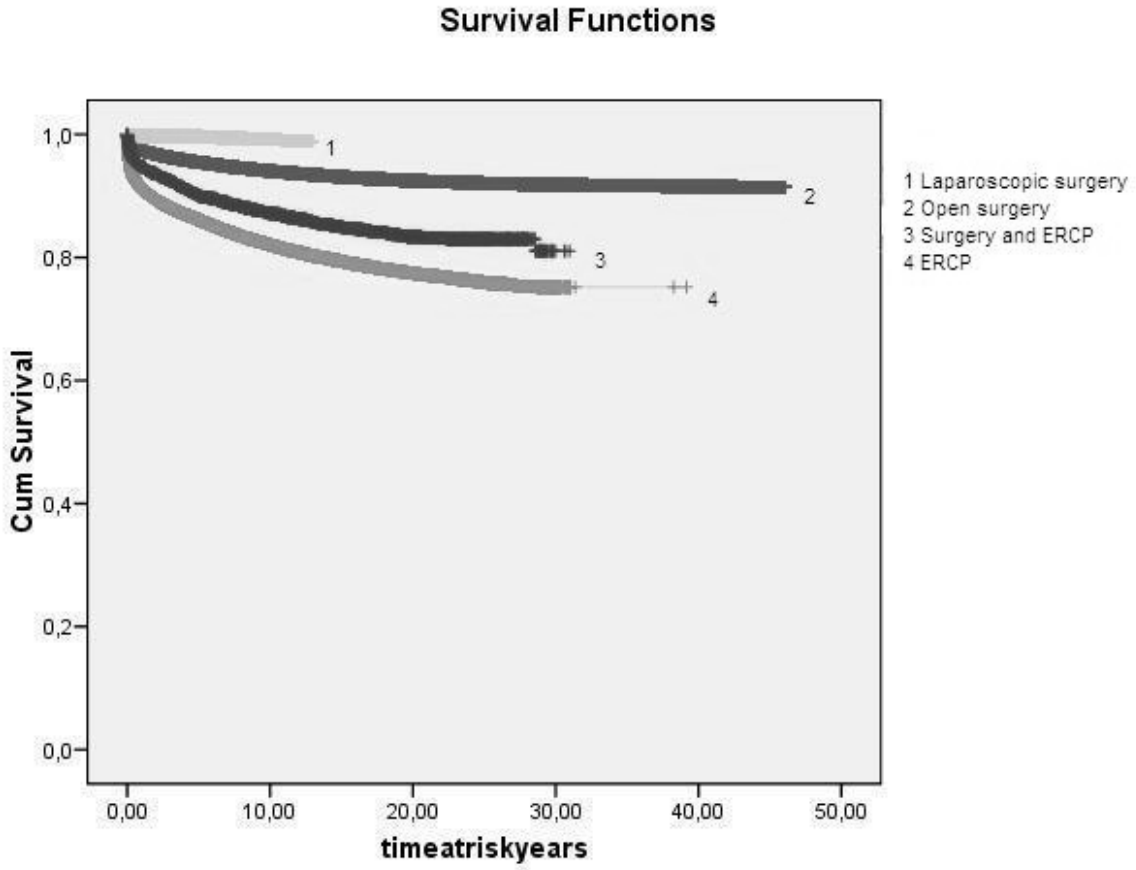

Figure 2. *Kaplan-Meier curves illustrating crude survival after treatment of common bile duct stones.*

4.1.1 Factors Influencing Survival

Both age and sex influenced survival after treatment of common bile duct stones. The influence of age was further increased in the multivariate analysis by interaction with co-morbidity (Table 2). Female sex reduced the risk of dying, a difference that remained in the multivariate analyses (adjusted HR 0.75 95% CI 0.64-0.87).

Comorbidity, measured using the Charlson comorbidity score, increased the risk of death to a high degree and the influence was enhanced in the multivariate analyses where a score ≥5 increased the risk of dying 400-fold (adjusted HR 408; 95% CI 127-1320) due to interaction with age.

Septicemia did not affect the risk of death in the multivariate analyses while pancreatitis surprisingly was associated to a significantly lower risk of dying.

The length of hospital stay had no impact on the risk of death and neither had a readmission. On the contrary the occurrence of a biliary reintervention, either endoscopic or transabdominal, within 90 days was associated to a 14-fold increased risk of dying (adjusted HR 14; 95% CI 12-17).

The type of procedure seemed to affect 90-day mortality where ERCP had a crude HR of 3.6 (95% CI 3.0-4.4) and 2.9 (95% CI 1.98-4.7) if combined with surgery compared to open surgery. However, in the multivariate analyses the effect was reduced to a non-significant trend (HR 1.6; 95% CI 0.86 – 2.8). As survival in the laparoscopic cohort was close to complete even at long term follow-up the statistical power was not sufficient for Cox regression for this exposure. It is however clear that survival in this cohort is many-fold higher than in the other intervention cohorts.

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	P	Crude HR	95% CI	P	Adjusted HR	95% CI
Age ≤51 years		1.0	(reference)		1.0	(reference)
52-67 years	<0.001	4.6	2.9-7.5	<0.001	6.2	3.6-11
68-77 years	<0.001	8.1	5.1-13	<0.001	17	9.0-32
≥78 years	<0.001	22	14-34	<0.001	77	36-165
Sex Male		1.0	(reference)		1.0	(reference)
Female	<0.001	0.59		<0.001	0.75	0.64-0.87
Comorbidity						
Charlson 0		1.0	(reference)		1.0	(reference)
1-2	<0.001	4.9	3.9-5.4	<0.001	16	9.7-26
3-4	<0.001	7.2	4.6-11	<0.001	104	38-288
≥5	<0,001	8.2	4.5-15	<0.001	408	127-1320
Pancreatitis No		1.0	(reference)		1.0	(reference)
Yes	0.004	0.40	0.21-0.75	0.05	0.54	0.29-1.0
New procedure within 90 days No		1.0	(reference)		1.0	(reference)
Yes	<0.001	15	13-18	<0.001	14	12-17
Surgery Open		1.0	(reference)		1.0	(reference)
ERCP	<0.001	3.6	3.0-4.4	0.15	1.6	0.86-2.8
Lap	0.89	0		0.89	0	
Surg+ ERCP	<0.001	2.9	1.8-4.7	0.84	1.4	0.13-5.2

Table 2. *Cox regression model with Hazard ratio and their 95% confidence intervals for risk of death within 90 days after treatment of common bile duct stone disease with respect to some potential risk factors.*

4.2 PAPER II

The final cohort of patients having undergone ERCP, for diagnostics or therapy of non-malignant disease, included 27 708 patients contributing to a total of 235 518 person-years of follow-up. Table 3 shows the steps of selection of patients from the total cohort including all ERCP procedures to the eligible final benign disease ERCP cohort. The sum of the ES and non-ES groups is larger than the all ERCP group, because 2 141 patients had an ERCP without ES before a subsequent ERCP with ES. Of these, 306 did not have a diagnosis of malignancy at the time of the first nor second index procedures and neither within two years thereafter, and were thus counted in both subgroups.

	ALL ERCP	ES	ERCP WITHOUT ES
Total	54 135	30 431	25 846
Cancer date before entry	10 085	5 734	4 764
Error registration	3 192	3 000	329
Follow-up less than two years	13 150	9 068	5 368
Eligible	27 708	12 629	15 385

Table 3. *Size of cohorts of patients having undergone Endoscopic Retrograde CholangioPancreaticography (ERCP) with or without Endoscopic Sphincterotomy (ES).*

The risk of developing malignancy in the bile ducts, liver or pancreas, excluding gallbladder malignancy, was 3-fold increased in the all ERCP cohort compared to the general population (SIR 3.0; 95% CI 2.6-3.4). Likewise it was 3-fold increased in the ES subgroup (SIR 3.0; 95% CI 2.3 – 3.8) and in the non-ES subgroup (SIR 2.9; 95% CI 2.4 – 3.3).

In the all ERCP cohort the risk of malignancy of the bile ducts, liver or pancreas decreased gradually by increasing duration of follow-up. The relative risk (SIR) was 3.6, with 95% CI 3.0 – 4.3, in the period between two and four years after the index ERCP and the point estimates for the relative risks between five and nine years, and ten years and more, after the index ERCP, were 2.9 and 2.2 respectively (Table 4). The analyses stratified by ES show a similar pattern, with decreasing point estimates for relative risks with longer follow-up. There was no significant difference between the ES and non-ES subgroups in the relative risk estimates by duration (Table 4).

YEARS AFTER PROCEDURE	ALL ERCP N= 27 708			ES N= 12 629			ERCP WITHOUT ES N= 15 385		
	E	O	SIR (95% CI)	E	O	SIR (95% CI)	E	O	SIR (95% CI)
2-4	32	113	3.6 (3.0-4.3)	13	40	3.1 (2.2-4.2)	19	72	3.8 (3.0-4.8)
5-9	31	88	2.9 (2.3-3.5)	8	25	3.0 (1.9-4.4)	22	56	2.5 (1.9-3.3)
> 10	16	35	2.2 (1.5-3.0)	1	1	0.9 (0.02-5.0)	15	28	1.9 (1.3-2.8)

Table 4. *Expected (E) and Observed (O) cases and Standardized Incidence Ratios (SIRs) with 95 % Confidence Intervals (CI) for developing carcinoma in the liver, pancreas or biliary tract after ERCP by duration.*

The risk of malignancy in the bile ducts, liver and pancreas two years or more after ERCP was significantly lower among patients who ever had had a cholecystectomy (SIR 2.3; 95% CI 1.8 – 2.9 in the all ERCP-group) compared to patients who had not (SIR 3.4; 95% CI 3.0 – 4.0). This finding was not at all affected by ES exposure.

4.3 PAPER III

During the time period a total of 5750 ERCP procedures were performed in Stockholm County in patients without a diagnosis of malignancy in the liver, pancreas or bile ducts and 90 patients died within 90 days, giving a total mortality of 1.6%. In seven cases the cause of death could be directly related to the procedure (one case of hemorrhage, two of pancreatitis and four perforations), giving a procedure-caused mortality of 0.1%. Characteristics of patients who had undergone ERCP for non-malignant disease are shown in Table 5 together with basic information on their procedures.

	CASES N=90 (%)	**CONTROLS N=146 (%)**	
Date before 1997	44 (49)	52 (36)	P=0.04
Low volume (≤200/y)	37 (41)	73 (50)	P=0.18
Mean age (st dev)	76 (14)	65 (17)	P<0.001
Sex (female %)	50 (56)	86 (59)	P=0.61
Charlson comorbidity ≥2	41 (46)	23 (16)	P<0.001
Previous cholecystectomy	12 (13)	50 (34)	P<0.001
Indication			
Gallstone	46 (51)	86 (59)	P=0.24
Complicated gallstone	13 (28)	17 (19)	P=0.27
Acute pancreatitis	20 (22)	20 (14)	P=0.083
Chronic pancreatitis	7 (8)	23 (16)	P=0.074
Other	19 (21)	28 (19)	P=0.86
Complex procedure	49 (54)	57 (39)	P=0.008
Contrast in pancreatic duct	32 (27)	59 (42)	P=0.53
Sphincterotomy	36 (40)	85 (58)	P=0.007
Inadequate drainage	19 (21)	21 (14)	P=0.19
Complication	35 (39)	31 (21)	P=0.003
LOS≥ 3 days	50 (56)	64 (44)	P=0.08

Table 5. *Characteristics of patients having had ERCP on benign indication by death within 90 days or not and data on their procedures.*

4.3.1 Age and sex

The patients who died within 90 days were older (mean 76 years) than controls (65 years) (Table 5). After categorization by the median age 73, univariate analysis gave a four-fold Odds Ratio (OR 4.0 CI 2.2-7.0) for age ≥73. This was further enhanced in the multivariate analyses due to interaction with comorbidity to 8.7 (CI 3.6-21), estimating the odds for death in those with a comorbidity score <2 and age ≥73 (Table 6). There was no significant difference between sexes.

4.3.2 Comorbidity

Charlson comorbidity index ≥2 was a strong risk factor for death, giving a four-fold increase of the Odds Ratio (OR 4.5; CI 2.4-8.2) and due to interaction with age the OR was further increased in the multivariate analysis (OR 9.2; CI 2.9-29 for those under the age of 73).

4.3.3 Indications

A history of cholecystectomy was more common among the 90 day survivors (OR 0.41; CI 0.18-0.94), but we found no difference when comparing indications for the procedure in terms of simple gallstone disease or a more severe disease with cholangitis or septicemia (OR 1.7; CI 0.8-3.4). When chronic pancreatitis was the indication for ERCP the point estimate suggested a lower risk of mortality but it was not statistically significant (OR 0.4 CI 0.14-1.1).

4.3.4 Procedure-related factors

Among those who died, a procedure classified as complex was more common (OR 2.0; CI: 1.1-3.8). Injection of contrast medium into the pancreatic duct was not associated with post ERCP death (OR 0.7 95% CI 0.4-1.5).

Complications were more common among patients who died, even though the complication per se led to death in only a few cases. Procedure-related complications increased the risk of death within 90 days approximately four-fold (OR 3.7; CI: 1.7-8.1)

Performance of an endoscopic sphincterotomy was more common among controls and thus associated with a decreased post-ERCP mortality (adjusted OR 0.36; 95% CI 0.18-0.69).

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	P	**OR**	**95% CI**	**P**	**OR**	**95% CI**
Age<73 years		1.0	(reference)		1.0	(reference)
Age≥73 years	<0.001	4.0	2.2-7.0	<0.001	8.7	3.6-21
Gender (male)		1.0	(reference)		1.0	(reference)
Gender (female)	0.61	0.87	0.5-1.5	0.73	0.89	0.46-1.7
Charlson comorbidity<2		1.0	(reference)		1.0	(reference)
Charlson comorbidity≥2	<0.001	4.5	2.4-8.2	<0.001	9.2	2.9-29
Previous cholecystectomy						
no		1.0	(reference)		1.0	(reference)
yes	0.001	0.30	0.15-0.60	0.035	0.41	0.18-0.94
Complex procedure						
no		1.0	(reference)		1.0	(reference)
yes	0.009	2.1	1.2-3.7	0.036	2.0	1.1-3.8
Sphincterotomy						
no		1.0	(reference)		1.0	(reference)
yes	0.007	0.5	0.3-0.8	0.002	0.36	0.18-0.69
Drainage						
good		1.0	(reference)		1.0	(reference)
not good	0.20	0.64	0.32-1.3	0.85	0.92	0.38-2.2
Complication						
no		1.0	(reference)		1.0	(reference)
yes	0.004	2.4	1.3-4.2	0.001	3.7	1.7-8.1

Table 6*. Risk of death after ERCP with respect to some potential risk factors.*

4.4 PAPER IV

Laparoscopic transcystic common bile duct exploration was commenced in 155 patients and was completed in 132 (85 %), without remaining CBD stones on the second cholangiogram. Hospital stay and mean operating time were significantly longer among patients where stone clearance failed. Stone size and common bile duct diameter were both significantly larger in patients where stone clearance failed, compared to

those where it was successful, using conventional significance testing. There were no significant differences between patients with successful and failed stone clearance regarding age, sex, procedure priority, number of stones and intrahepatic stone location.

In 123 out of 132 stone free LTCE patients one or more stones were extracted. In the remaining nine, no stone could be found at cholangioscopy, or in the second cholangiogram, which could either be because of false positive first cholangiograms or because of stone clearance between the cholangiogram and cholangioscopy, perhaps due to flushing of saline through the bile duct at the onset of cholangioscopy. In 24% of the patients an intrahepatic cholangioscopy was performed.

There were eight postoperative complications among the LTCE patients. Three patients had haemorrhage requiring transfusion, two had pneumonia, one had pancreatitis, one had pulmonary embolism and finally one had bile leakage needing percutaneous drainage but no further intervention. One of the patients who had haemorrhage requiring transfusion was reoperated because of an infection in the hematoma. Otherwise no reoperations were needed. There was no mortality during the hospital stay or at the follow-up six week postoperatively. Follow-up at six weeks was completed in 91% of the patients and all of them were clinically well, but one had elevated liver enzymes. A postoperative normal ERC was performed and an ES was made as a precaution, although no retained CBD stone was found. An additional patient had a postoperative ERC done due to a history of repeated biliary colic two years after surgery. The ERC showed a CBD stone that was removed after ES. Apart from that no patient was shown to have retained or recurrent stones.

In the logistic regression analyses there were no significant effects of age, sex or number of stones on the risk of failure in stone clearance (Table 7).

Univariately, there was an almost 11-fold significant increase in the risk of failure in stone clearance among patients with a common bile duct diameter of >6 mm compared with those with a diameter of ≤6 mm (OR: 10.62; 95% CI: 1.39 – 81.48). However in the multivariate analyses this effect decreased markedly and was no longer statistically significant (OR: 6.90; 95% CI: 0.87 – 54.61). This difference was due to confounding from the effect of stone size (Table 7).

	UNIVARIATE OR (95% CI)			MULTIVARIATE OR (95% CI)	
Age, years					
<55	1.00	(reference)		1.00	(reference)
>=55	1.42	(0.56 - 3.58)		1.33	(0.48 - 3.70)
Gender					
Female	1.00	(reference)		1.00	(reference)
Male	1.78	(0.71 - 4.48)		1.57	(0.58 - 4.24)
Bile duct diameter, mm					
<= 6	1.00	(reference)		1.00	(reference)
>6	10.62	(1.39 - 81.48)		6.90	(0.87 - 54.61)
Stone size, mm					
<=5	1.00	(reference)		1.00	(reference)
>5	3.95	(1.50 - 10.40)		3.13	(1.15 - 8.56)
Number of stones					
<3	1.00	(reference)		1.00	(reference)
>=3	1.65	(0.66 - 4.14)		1.43	(0.52 - 3.92)

Table 7. *Risk of failure in stone clearance in laparoscopic transcystic common bile duct exploration with regard to some potential risk factors.*

Multivariately there was a significant 3-fold increase in the risk of failure in stone clearance among patients with a mean stone size of >5 mm compared to patients with ≤5 mm (OR: 3.13; 95% CI: 1.15 – 8.56). Univariate data did not differ markedly from the multivariate result, indicating none or limited confounding effects in the analysis of stone size (Table 7).

5 DISCUSSION

During the last decades treatment of common bile duct stone disease has changed. Open surgery has gradually been replaced by endoscopic surgery and in the later years also by laparoscopic surgery to some extent. The central issue in this thesis was to try to clarify how common bile duct stone disease may be treated in these times of changes. Our hypothesis when starting the work was that laparoscopic treatment would be superior to other methods of treatment, based on the reports on short- and long-term side-effects of ERCP, especially ES. Reports on short-term side-effects included pancreatitis, perforations, hemorrhage and cholangitis causing a substantial morbidity and mortality [213] while long-term side-effects included reports on an elevated risk of cholangiocarcinoma after endoscopic sphincterotomy. The under-lying mechanism could be that the interruption of the sphincter would cause an over-growth of bacteria with longstanding carcinogenic inflammation in the bile ducts that normally are sterile [178, 181]. This could be alarming since endoscopic surgery in recent years has become a routine procedure even in young and healthy individuals and not only in the old and fragile as in the early days.

5.1 HOW HAVE COMMON BILE DUCT STONES BEEN TREATED IN SWEDEN?

To address this question we conducted a population-based retrospective cohort study (study I) which comprised all patients in Sweden 1965-2009 with an in-patient procedure code of open or laparoscopic exploration of the common bile duct or ERCP but without a diagnosis of malignancy in the bile ducts, liver or pancreas by the time of the procedure or within 90 days after it. In the majority of these patients the indication for the procedure would have been common bile duct stone disease. The cohort was divided into four subgroups: open surgery, ERCP, laparoscopic surgery and finally open and/or laparoscopic surgery combined with ERCP.

The study reflects treatment in a vast majority of the Swedish population and the registries from which the data are collected have been validated as mentioned in the methods-section giving an essentially complete follow-up. The Hospital Discharge Registry was established in 1964 and included all Swedish Hospitals from 1987 and onwards. It has been validated with a 94% agreement for surgical procedure codes [214] and 87-95% for discharge diagnoses [215, 216], however the codes and

diagnoses in this study have not been validated specifically. Misclassification could introduce information bias, although it seems unlikely that misclassification would differ between the subgroups or regarding outcome status, meaning that introduced bias would be non-differential and thereby diluting the strength of true associations. It was however not possible to analyze the procedures on an intention to treat basis and converted laparoscopic procedures are registered in the cohorts of open or combined surgery. This could imply an over-representation of severe cases in these cohorts and a corresponding under-representation in the laparoscopic cohort.

In the beginning of the studied time period open surgery was the only available method for treatment of common bile duct stone disease but from the early 1990s and on endoscopic treatment has become predominant. Laparoscopic treatment was introduced in the early 1990s and has been used in a small proportion of cases.

5.1.1 What Risk Factors for Death Could Be Identified?

Age and comorbidity were identified as main risk factors for death. There were differences between the subgroups in the way that patients treated with ERCP were older and had a more severe comorbidity than those treated with open surgery, not surprisingly, since ERCP was used in patients considered too old and frail to have open surgery, at least in the beginning of the time period. Patients treated with laparoscopic surgery were younger and healthier than the others and also more often of female sex, a circumstance connected to a significant decreased risk of dying after surgery in this study.

A new biliary procedure within 90 days, probably implying that clearance of the bile duct was not achieved at the first attempt, was a significant risk factor for death while a discharge code of acute pancreatitis was associated with a better survival. Both a redo procedure and a diagnosis of pancreatitis were more common among ERCP-patients.

5.1.2 Did Mortality Differ?

The crude 90-day mortality was significantly higher after ERCP compared to after open surgery but after adjusting for age and comorbidity this result was reduced to a trend. The results after laparoscopic surgery were excellent with no 90-day mortality at all recorded, but that must be interpreted with caution, since it to some extent could be explained by a case-selection described above. The laparoscopy subgroup consisted of

members of lower age and comorbidity and the fact that the procedure could be completed laparoscopically could imply a less severe disease.

5.2 IS THE RISK OF DEVELOPMENT OF MALIGNANCY ELEVATED AFTER ENDOSCOPIC SPHINCTEROTOMY?

A cohort study (study II) was designed to evaluate whether the longstanding inflammation caused by ascending infection after interruption of the sphincter of Oddi would lead to an increased risk of cholangiocarcinoma. The population-based cohort comprised all individuals in Sweden with a discharge code of an in-patient ERCP with or without ES and without a diagnosis of malignancy in the bile ducts, liver or pancreas at the time of the procedure or within two years after it up to the year 2003.

Since cholangiocarcinoma is a rare disease and there is a risk of missclassification between extrahepatic cholangiocarcinoma and pancreatic cancer as well as intrahepatic cholangiocarcinoma and liver cancer both cholangiocarcinoma alone and all three tumours were analyzed.

We found a three-fold elevated risk of malignancy in the whole cohort, i e disregarding if an ES had been performed or not, compared to the general population. The risk declined with time. These results imply that the elevated risk of malignancy was not a result of the ES per se but rather of some other exposure common for the entire cohort, the most likely would be gallstone disease, a notion that to some extent could support the finding that a previous cholecystectomy in this study was shown to be associated to a lower risk of malignancy.

5.3 DOES ENDOSCOPIC SPHINCTEROTOMY INCREASE SHORT-TERM COMPLICATIONS AFTER ERCP?

A case-control study (study III) was designed to evaluate short-term outcome after ERCP, especially mortality, and to study risk factors for death. The main hypothesis was that a potentially dangerous procedure like sphincterotomy would be such a risk factor. It was performed on a subgroup of patients included in paper II. Cases were defined as all individuals who had had an ERCP in Stockholm County during 1990-2003 and who died within 90 days of the procedure and as controls served a random sample from the same subgroup. The population-based design was chosen to reduce the

risk of bias in case and control selection. Risk factors for death were discerned from the medical records, to reduce information bias the parts of the medical records regarding the ERCP procedure were coded and reviewed blinded for case and control status.

The all cause mortality was 1.6% but only seven deaths (0.1%) were directly procedure-related. Advanced age and severe co-morbidity were identified as the main risk factors for death. A complex procedure, here defined as the presence of a duodenal diverticulum, multiple attempts of cannulation, difficult position of the papilla or the performance of a pre-cut sphincterotomy, was also identified as a risk factor as well as the occurrence of a post-procedural complication. A previous cholecystectomy served protective for death, possibly by reducing the severity of the common bile duct stone disease by the time of the ERCP, even though that could not be confirmed in the medical records.

In contrast to our prior hypothesis the performance of a sphincterotomy could not be identified as a risk factor for death, on the contrary it reduced the risk, a condition that remained significant in the multivariate analyses (OR 0.36, 95% CI 0.18-0.69), thereby not explained by the factors we adjusted for (age, comorbidity, date of procedure, previous cholecystectomy, complex procedure or the occurrence of a complication). A possible explanation could be that a completed sphincterotomy could reduce the risk of cholangitis by facilitating a good drainage from the bile ducts.

5.4 WHAT IS THE SHORT-TERM OUTCOME OF LAPAROSCOPIC TRANSCYSTIC COMMON BILE DUCT EXPLORATION AND WHEN DOES IT FAIL?

To address these issues we conducted a study of patients in whom LTCE were attempted at S: t Göran's Hospital during the years 1994- 2002. The study included all patients, thereby reducing the risk of selection bias. Data had been prospectively collected in a data-base and analyses showed that stone clearance was achieved in 85%. There was no recorded 30-day mortality (in agreement with the findings in study I), a low mortality and a short postoperative hospital stay. As risk factors for mortality stone size >5 mm could be identified and probably also a wide bile duct (>6mm).

5.5 GENERAL DISCUSSION

Our main hypothesis, that laparoscopic common bile duct exploration would be superior to other methods of treatment of common bile duct stones, could not be proven by this thesis. Indeed, laparoscopic treatment was safe and no 90-day mortality was reported in Sweden in cases where it could be fulfilled, yet it was applied in a minority of patients. We could identify large stones as a risk factor for failure in laparoscopic transcystic exploration, in laparoscopic choledochotomy stone size is not regarded as an obstacle [195, 200] and the reason why laparoscopic treatment was refrained from in a majority of cases is not clear. We can only speculate- perhaps the methods are regarded as complicated or the instruments fragile or difficult to handle. Laparoscopic treatment was chosen mainly in young and otherwise healthy subjects and the complexity of the bile duct stone disease could have had impact, patients with less severe disease could have been selected to laparoscopy. When laparoscopic treatment was chosen stone clearance could be achieved in a majority of cases, but not in all, and there is a need for alternative methods.

The by far most common way to treat gallstones and common bile duct stones in later years is by a combination of laparoscopic cholecystectomy and endoscopic treatment of the bile duct stones. Since ERCP and especially ES have been reported with a substantial morbidity and mortality [177-180, 217] and also with an increased risk of malignancy in the long run [181] this has been a matter of some concern. Our study showed an increased risk of development of a malignancy in all patients having had an ERCP on benign indication but the risk was elevated regardless of if an ES was performed or not and diminished with time thereby contradicting that the ES per se would be a causal factor. The 90-day mortality after ERCP was substantial in our study and as risk factors advanced age and severe comorbidity could be identified while the performance of an ES reduced the risk of dying. Our studies do not support the reports that the performance of a sphincterotomy would be a causal factor of short- or long-term mortality and morbidity after ERCP.

6 CONCLUSIONS

Treatment of patients with gallbladder stones and simultaneous stones in the common bile duct has changed. Earlier all patients had open surgery while in the recent years a combination of laparoscopic cholecystectomy and ERCP is predominant even though open surgery and laparoscopic treatment are also used.

The mortality after ERCP in benign disease was higher than after open surgery but when adjusting for age and comorbidity the difference was reduced to an insignificant trend.

Laparoscopic treatment of common bile duct stones was safe but could not be used in all patients.

The risk of malignancy in the bile ducts, liver and pancreas after ERCP on benign indication was elevated in all patients regardless of if an ES was performed or not and diminished with time contradicting that ES would be a causal factor.

The main risk factors for death after ERCP in benign disease were old age and advanced co-morbidity, while a procedure considered complex or causing a complication contributed to the risk. The performance of an ES reduced the risk of dying within 90 days after the procedure and the risk was also reduced in patients having had a previous cholecystectomy.

Stone size > 5 mm was a risk factor for failure in laparoscopic transcystic exploration of the common bile duct.

7 POPULÄRVETENSKAPLIG SAMMANFATTNING

Gallstensjukdom är vanlig och årligen utförs drygt 10 000 galloperationer i Sverige. Mellan 5-15 % av patienterna har även sten i de djupa gallvägarna (koledokussten) vid operationen. Dessa patienter behandlades under större delen av 1900-talet i en seans med öppen kirurgi. Under 1970-talet kom endoskopiska metoder där man med ett flexibelt endoskop via munnen kunde genomföra kontraströntgen och avlägsna stenar i gallvägarna efter klyvning av sfinkter Oddi, ringmuskeln runt gallvägens mynning i tolvfingertarmen (endoskopisk retrograd cholangiopankreatografi, ERCP, med endoskopisk sfinkterotomi). Sfinkterotomi visade sig vara förenad med risk för allvarliga komplikationer och reserverades först för patienter som ansågs vara för gamla eller sjuka för att klara öppen kirurgi. Farhågor framfördes också att delningen av sfinktern skulle kunna ge en kronisk infektion i gallvägarna genom tillträde för bakterier från tolvfingertarmen och att denna kroniska infektion/inflammation skulle ge en ökad risk för cancer på lång sikt.
Senare, under 1990-talet, introducerades galloperation via titthål (laparoskopisk kolecystektomi) och denna metod blev snart helt dominerande. Behandlingen av samtidig sten i gallgången blev mer varierande och öppen kirurgi, kombination av endoskopisk och laparoskopisk teknik i en eller två seanser har använts olika på olika sjukhus sannolikt beroende på lokal behandlingstradition.

Syftet med denna avhandling var att kartlägga hur patienter med samtidig sten i gallgång och gallblåsa behandlats i Sverige under denna period av förändringar (1965-2009), att beräkna dödlighet efter olika behandlingsmetoder och att identifiera riskfaktorer för död. Svängningen i behandlingstradition har inneburit att även unga patienter genomgår ERCP och sfinkterotomi vilket skulle kunna vara alarmerande om cancerrisken ökar på lång sikt, detta ville vi undersöka närmare. En ökad användning av ett potentiellt farligt ingrepp som sfinkterotomi skulle kunna vara farligt även på kort sikt varför vi ville identifiera riskfaktorer för död efter ERCP, och särskilt studera om sfinkterotomi var en sådan riskfaktor. På S: t Görans sjukhus har sedan 1994 den dominerande tekniken varit att behandla samtidig sten i gallblåsa och gallgång i en seans, där gallblåsan och stenarna i gallgången avlägsnas med titthålskirurgi och vi ville utforska resultatet samt om metoden har några begränsningar.

Fyra delarbeten ingår:

1. Behandling av koledokussten i Sverige 1965-2009, en landsomfattande populationsbaserad studie.

2. Endoskopisk sfinkterotomi och risk för malignitet i gallvägar, lever och bukspottskörtel.

3. Endoskopisk sfinkterotomi kan minska risken för död efter ERCP- en populationsbaserad fall-kontroll studie.

4. Stenfrihet och riskfaktorer för misslyckande att åstadkomma detta vid titthålsoperation av gallsten i gallvägarna.

Delarbete 1 omfattar alla personer i Sverige som vårdats inneliggande för en operation av sten i gallvägarna eller ERCP under åren 1965-2009. ERCP görs också vid cancersjukdom i gallvägar, lever och bukspottskörtel och efter samkörning med cancerregistret kunde dessa individer identifieras och exkluderas ur studien. Totalt 110 119 personer identifierades och dessa hade genomgått totalt 126 889 ingrepp. Dödligheten efter olika ingrepp skiljde sig, efter öppen operation dog 0,24 %, efter ERCP 0,90 % och efter titthålskirurgi dog ingen person inom 90 dagar. Vid närmare analys visade sig skillnaden i dödlighet efter öppen kirurgi och ERCP förklaras av att patienterna som genomgått ERCP var äldre och sjukare.

Delarbete 2 omfattar alla personer i Sverige som genomgått ERCP under åren 1965-2003 utan att ha en diagnos av malignitet i gallvägar, lever eller bukspottskörtel vid ingreppet eller inom två år därefter. I cancerregistret identifierades de som senare utvecklade malignitet. Det visade sig att risken att utveckla cancer i gallvägar, lever eller bukspottskörtel var större hos alla dessa patienter jämfört med normalbefolkningen men att risken minskade med ökande uppföljningstid och inte påverkades om sfinkter Oddi delades eller inte.

Delarbete 3 omfattar en del av personerna i delarbete 2, de som genomgått ERCP i Stockholms län 1990-2003. De som dött inom 90 dagar efter ingreppet jämfördes med slumpvis utvalda kontroller bland dem som inte dött. Som riskfaktorer för att dö kunde

hög ålder, sjuklighet, ett komplicerat ingrepp och att en komplikation tillstötte identifieras medan om personen ifråga tidigare genomgått galloperation eller om klyvning av sfinkter Oddi utfördes vid det aktuella ingreppet minskade risken för död.

Delarbete 4 omfattar alla patienter som opererats på S: t Görans sjukhus under perioden 1994-2002 där man försökt ta bort stenar i gallgången med en typ av titthålskirurgi. Den metod som användes var transcystisk exploration där gången mellan gallblåsan och djupa gallvägen öppnas och vidgas. Stenarna i gallgången fångas med hjälp av ett tunt endoskop som förs in denna väg och de kan sedan avlägsnas en efter en. Av de 155 patienter där man inlett denna operation kunde stenfrihet uppnås hos 85 % och som riskfaktor för misslyckande identifierades stenstorlek, hos patienter med koledokusstenar större än 5 mm ökade risken för misslyckande trefaldigt.

Slutsatser: Dödlighet efter behandling av choledochussten skiljer sig mellan olika behandlingsmetoder. Dödligheten är högre efter ERCP än efter öppen kirurgi men detta förklaras av att patienterna som genomgår ERCP är äldre och sjukare. Dödligheten efter laparoskopisk gallvägskirurgi är noll inom 90 dagar, dessa patienter är dock yngre, friskare och har möjligen en mindre avancerad gallstenssjukdom.
Risken för att utveckla cancer i gallvägar, lever och bukspottskörtel är högre hos alla patienter som genomgått ERCP än hos normalbefolkningen. Risken avtar med ökande uppföljningstid och påverkas inte av om sfinkter Oddi klyvs eller inte, utan orsakas av någon annan faktor som dessa patienter har gemensamt, sannolikt gallstenssjukdom.
Hög ålder, sjuklighet, svårt och komplext ingrepp ökar risken för död efter ERCP liksom om en komplikation uppträder efter ingreppet. Den potentiellt farliga klyvningen av sfinkter Oddi minskar däremot risken sannolikt p.g.a av att dränaget från gallgången förbättras och risken för uppåtstigande infektion i gallvägarna minskar.
Laparoskopisk behandling av sten i gallvägarna genom en transcystisk exploration är en metod som ger få komplikationer och kort vårdtid när den är genomförbar. Den kan dock inte användas hos alla patienter och i denna studie kunde stenstorlek över 5 mm identifieras som en riskfaktor för misslyckande.

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