Surgical treatment of choledochocystolithiasis
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Chapter 1

General introduction and thesis outline
GENERAL INTRODUCTION

Epidemiology
Cholelithiasis is derived from the Greek words χολή (bile), λίθος (stone) and ἴασις (sickness/process) and means the presence of gallstones. The words -cysto (sac) and -docho (duct) are added to specify the location of gallstones; Choledochocystolithiasis is the term used for the presence of gallstones in the gallbladder and bile duct.

The earliest known gallstone was found in a mummy from the 21st Egyptian dynasty (1085-945 B.C.). The prevalence of cholecystolithiasis varies enormously worldwide, from near 0% in the Masai from Eastern Africa to 70% of female Pima Indians in Arizona. Overall, in Western countries the prevalence is between 9.5-18% in men and 13-25% in women. Sonographic surveys conducted in China, Taiwan, Thailand, Japan and Korea found a prevalence of 3-11%. Precise and recent data from Africa are scarce because most studies are 20-40 years old and are mostly based on surgery or autopsy reports.

Pathogenesis
Gallstone formation is a process caused by changes in concentration of bilirubin, bile salts and acids, phospholipids or cholesterol. Dependent of the percentage of cholesterol, gallstones are divided into 2 groups: cholesterol and pigment stones.

In Western society, cholesterol stones account for 70-80% of all gallstones. They are the result of oversaturation of bile with cholesterol leading to the formation of cholesterol crystals, microlithiasis (“sludge”) and eventually gallstones. Risk factors include female gender, increasing age and genetic factors like ethnicity or familiar predisposition. Worldwide, women are twice as likely to develop gallstones in comparison with men, and in the reproductive age this ratio reaches up to 4 to 1. Other risk factors include obesity, pregnancy, rapid weight loss, hypertriglyceremia, hypomobility of the gallbladder, diabetes mellitus and parenteral feeding and severe weight loss.

Pigment stones are more common in Asia and are most often secondary to hemolytic disease, liver cirrhosis, cystic fibrosis, or diseases of terminal ileum. A subset of pigment stones are formed in the (intrahepatic) bile ducts as a result of infection with Clonorchis sinensis or Ascaris lumbricoides. These worms and their eggs cause mechanical obstruction and changes in the composition of bile favourable for secondary bacterial infection.

The risk of symptomatic cholelithiasis, independently of gender, varies from 10% in the first 5 years after discovery to 18% after 20 years. Of women between the ages of 20-69 with proven cholecystolithiasis eventually up to 39% will finally end up with symptomatic gallstone disease. Symptoms of gallstone disease are biliary colic pain (as defined by the
“Rome criteria”), acute cholecystitis, obstructive jaundice caused by choledocholithiasis, cholangitis and biliary pancreatitis.\textsuperscript{19} When obstruction or infection plays a role (1-3% per year in patients with symptomatic gallstones) than it’s referred to as complicated gallstone disease.\textsuperscript{20}

Treatment
The treatment for symptomatic cholecystolithiasis is a cholecystectomy. The first successful cholecystectomy is attributed to Carl Johan August Langenbuch on July 15th 1882.\textsuperscript{21} In 1985 Professor Erich Mühe performed the first laparoscopic cholecystectomy, which nowadays is the golden standard.\textsuperscript{10,22,23} In the Netherlands over 21,000 cholecystectomies are performed annually, and more than 700,000 in the United States of America.\textsuperscript{24,25} It is one of the most performed abdominal procedures. Of patients with symptomatic gallbladder stones 3-10% have concomitant common bile duct (CBD) stones.\textsuperscript{26-29} If small enough, they are able to pass through Oddi’s sphincter and be eliminated via the duodenum. However the narrowing anatomical configuration of the sphincter often leads to impaction of stones. These patients will present with colic pains, jaundice, or (potentially deadly) infectious complications such as cholangitis or biliary pancreatitis. Treatment consists of the combination of antibiotics and decompression of the CBD by extracting the ductal stones. In the pre-laparoscopic time span stone removal and cholecystectomy was performed surgically in one setting; patients underwent open cholecystectomy and common bile duct exploration.\textsuperscript{30-33} In the 1970’s endoscopic retrograde cholangiopancreaticography (ERCP) with endoscopic sphincterotomy (ES) became available as treatment for CBD stones.\textsuperscript{34,35} Patients’ CBD stones could be treated endoscopically and this became a general accepted alternative for open bile duct exploration.\textsuperscript{36,37} For a while the need for cholecystectomy after endoscopic stone extraction was questioned. However, trials showed that patients who had undergone ES and stone removal should still be offered cholecystectomy to prevent future biliary complications.\textsuperscript{31,33} The popularity of endoscopic stone extraction further increased when laparoscopic cholecystectomy became the golden standard and surgeons lacked the experience and equipment for laparoscopic common bile duct exploration (LCBDE). Even though the popularity of LCBDE is growing, endoscopic sphincterotomy is still the treatment of choice in many countries. Two RCTs have shown that laparoscopic cholecystectomy should be offered to patients after ES to prevent biliary complications, even in patients over 60 years old.\textsuperscript{38,39} A recent systematic review confirmed these findings.\textsuperscript{40} The timing of the cholecystectomy has been a debate for a long time, even in the frame of open cholecystectomies. Surgeons worldwide propagated delayed cholecystectomy, usually after 6 weeks or longer. The rationale behind this decision was
that many surgeons believed that manipulation of Oddi’s sphincter causes bacterial colonization of the biliary tract. This would lead to inflammation of the hepatoduodenal ligament, hindering the dissection of Calot’s triangle. This concept was reinforced after early prospective and observational studies showed a high conversion rate after endoscopic sphincterotomy, up to 55%. An observational study however, revealed in contrast that timing and delay might be of influence. The conversion rate of patients operated within 2 weeks was 4%, compared to 31% in patients operated after 2-6 weeks. This effect had not yet been studied in a randomized fashion. Another potential drawback of the delayed cholecystectomy was the development of biliary events in the waiting period before surgery. An observational study of 167 patients after endoscopic sphincterotomy showed that 20% of patients suffered from biliary events in the time interval cholecystectomy. These events lead to patients’ discomfort and possible morbidity.

**THESIS OUTLINE**
Considering the above mentioned controversy in the management of symptomatic gallstone disease the studies presented in this thesis will focus on the surgical aspect of patients with complicated gallstone disease, choledochocystolithiasis in particular. Several important clinical aspects in the treatment of choledochocystolithiasis and acute cholecystitis are investigated, aiming to improve outcome of surgical treatment of gallstone disease. In the first part of this thesis we investigated the influence of timing on the perioperative outcome of laparoscopic cholecystectomies after endoscopic sphincterotomy. In the second part we evaluated the effect of subspecialization of surgeons on the outcome of laparoscopic cholecystectomy and analyzed literature on laparoscopic common bile duct explorations.

**Chapter 2** describes a randomized clinical trial which evaluates the timing of laparoscopic cholecystectomy after endoscopic sphincterotomy for choledochocystolithiasis. Patients are randomized between early (<72 hours after endoscopic sphincterotomy) and delayed (>6-8 weeks) laparoscopic cholecystectomy. Performing early laparoscopic cholecystectomy can be quite logistically demanding on a hospital’s OR planning and its staff. In **Chapter 3** we describe a prospective study which evaluates if early laparoscopic cholecystectomy after endoscopic sphincterotomy as standard treatment is logistically feasible in a large teaching hospital. In **Chapter 4** we present a prospective study measuring the differences in difficulty of laparoscopic cholecystectomy and length of the procedure between patients undergoing laparoscopic cholecystectomy with and without previous endoscopic sphincterotomy.
Bile is sterile under normal circumstances. Endoscopic sphincterotomy destroys Oddi’s sphincter, allowing intestinal flora into the common bile duct and potential colonization and infection of the biliary tract. Chapter 5 focuses on the bacterial changes occurring in bile after endoscopic sphincterotomy. Intraoperatively obtained bile cultures are compared for the presence of micro-organisms. We also analyzed if the outcome of bile cultures influenced surgical outcome in patients.

The laparoscopic cholecystectomy is generally considered to belong in the armamentarium of the general surgeon. However, nowadays with increasing subspecialization it has been suggested that perhaps in selected cases they should only be performed by dedicated laparoscopic surgeons. Chapter 6 is aimed on evaluating the impact of subspecialization of surgeons on the outcome of elective and emergency laparoscopic cholecystectomy.

Endoscopic sphincterotomy followed by laparoscopic cholecystectomy is still the most common treatment for combined choledochocystolithiasis in most European countries. However with increasing skill in laparoscopic surgery, common bile duct exploration can be safely performed by an increasing number of surgeons. This “single stage” treatment (cholecystectomy combined with laparoscopic CBD clearance) is advocated as the better treatment compared to the two stage treatment of endoscopic sphincterotomy and subsequent laparoscopic sphincterotomy in some studies. Chapter 7 we perform a literature search on comparative studies between the two treatment options and subjected them to a systemic review.

Chapter 8 summarizes and discusses the presented studies and presents future perspectives.


Chapter 1

REFERENCES


22. Reynolds W. The first laparoscopic cholecystectomy. JSLS. 2001; 5:89-94.


