Surgical treatment of mild gallstone pancreatitis

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Voor Breg en mijn ouders

TABLE OF CONTENTS

CHAPTER 1

General introduction and thesis outline

BACKGROUND

Epidemiology of Gallstone Disease

Prevalence and incidence

Gallstones (*i.e.* cholelithiasis) are very common in western society. Estimates of the prevalence of gallstones in the general population range between 8% and 25%, but they can be seen in up to 73% in certain subpopulations, implying a genetic factor.[1-3] The true prevalence of gallstones is difficult to determine, as they manifest in only around 10 to 20% of gallstone carriers.[4] Often, they are incidental findings on radiological exams. Asymptomatic gallstone carriers have an annual risk of developing symptoms of 2 to 3%.[2] When the presence of stones in the gallbladder (i.e. cholecystolithiasis) is suspected, abdominal ultrasound is the most simple and frequently used imaging modality. The most accurate methods to diagnose gallstones in the common bile duct (*i.e.* choledocholithiasis) are magnetic resonance cholangiopancreatography and endoscopic ultrasound.[5]

In most symptomatic patients, gallstones classically manifest after ingesting a meal with high fat content, as the gallbladder wall contracts against the solid stone(s). When this pain lasts for at least 30 minutes, it is defined as 'biliary colic' according to the Rome criteria.[6] It is not unusual for gallstones to migrate along the biliary tract, often passing into the duodenum spontaneously.[9] Complications arise when gallstones get lodged during this passage. A stone obstructing the cystic duct, common bile duct or ampulla of Vater can respectively cause acute cholecystitis, choledocholithiasis with or without cholangitis or pancreatitis. In rare cases, a large gallstone migrates into the duodenum or further down the small intestine, eventually obstructing the lumen causing ileus, often some 20cm proximal to the ileocoecal valve. Finally, a history of gallstone disease appears to carry a small increase in the risk of developing gallbladder cancer.[2]

Pathophysiology of Gallstone Disease and Biliary Pancreatitis

Gallstones, sludge and the biliary tract

Gallstones are solidified accumulations of cholesterol crystals (cholesterol stones), bilirubin and calcium deposits (black pigment stones) or compositions of cholesterol and calcium salts (brown pigment stones).[7] The different types of stones are formed as a result of a cascade involving various genetic, biological, dietary and other factors. Known risk factors for developing gallstones include increasing age, female sex, obesity and rapid weight loss.[2] Starting out as microscopic aggregations of crystals, they can grow to the size of small pebbles or up to several centimeters. Sludge consists of cholesterol crystals with or without calcium granules of up to 2mm embedded in the mucus layering the gallbladder wall, and can be found in the presence or absence of larger gallstones.[8]

Cholesterol stones are the most prevalent type in Western populations, accounting for approximately 70% of the found stones. This type of stone forms in the gallbladder, in part as a result of stasis of bile in between postprandial gallbladder emptying. In most cases (80 to 90%), these gallstones are asymptomatic and only found incidentally on imaging for other indications than to confirm the presence of gallstones.[4] Peristaltic contractions of the gallbladder and biliary tract drive these stones or sludge through the cystic, common bile and hepatopancreatic ducts into the duodenum.[9]

Choledocholithiasis

The presence of common bile duct stones can be appraised through various methods. Biochemical testing can indicate cholestasis through elevated serum bilirubin levels. Serum levels exceeding 70umol/l are considered highly suggestive of concurrent choledocholithiasis, as are moderately raised levels with dilatation of the bile duct on imaging.[10] Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) are both highly accurate imaging modalities to assess the bile ducts. Abdominal ultrasound or computed tomography (CT) can also be used, although their positive predictive value is less than the aforementioned methods.[5] Endoscopic retrograde cholangiopancreatography (ERCP) is nowadays used in an almost exclusively therapeutic capacity in the treatment of gallstone disease. Besides gallstone extraction and clearance of the bile ducts, it has the additional advantage of performing sphincterotomy of the ampulla of Vater, providing decent long-term protection from future gallstone-related complications.[11] Patients with suspected or confirmed choledocholithiasis with increasing signs of clinical and biochemical inflammation (*i.e.* fever and leukocytosis or c-reactive protein) should be suspected of cholangitis, a life-threatening complication of choledocholithiasis. Urgent decompression through endoscopic biliary tract clearance with sphincterotomy is advised in these patients.[12]

Biliary pancreatitis

Blockage of the ampulla of Vater, whether from gallstones or sludge, is thought to cause pancreatitis by either reflux of bile into the pancreatic duct or by ductular hypertension. Be it through chemical or mechanical stimulation, digestive enzymes produced by the pancreatic acinar cells are activated prematurely, leading to parenchymal autodigestion.[10] The subsequent inflammation of the pancreatic gland sets off a cascade of which the exact mechanisms remains incompletely understood. In most patients this inflammation will be confined to the pancreas, diminish and terminate in the span of a few days. In others it may lead to a systemic inflammatory reaction, causing end-organ hypoxemia and necrosis of the pancreas and peripancreatic tissue and failure of one or more distant organ systems. This state of acute pancreatic inflammation is a common disease, affecting around 15/100.000 persons per year in the Netherlands.[11] In part due to increasing gallstone prevalence, incidence rates have been steadily increasing over the

last few decades. In population-based studies in Western societies, gallstones represent the cause of acute pancreatitis in between a third to half of all cases.[12-14] In around 85% of these patients, the disease resolves spontaneously and patients can be discharged within a week of supporting care. This type of pancreatitis is termed 'mild' pancreatitis, as opposed to the 'moderately severe' or 'severe' types of pancreatitis which cause the patient to develop (peri)pancreatic necrosis and fluid collections with or without organ failure.[15]

Pancreatitis is diagnosed when two of the three following items are present: pain in the abdomen, an elevated serum amylase or lipase level at least three times the upper limit of normal and, if performed, cross-sectional imaging showing signs of inflammation.[18] Imaging is usually only indicated in case of diagnostic uncertainty or when pancreatic necrosis is suspected based on clinical signs of extreme distress or excessive serum inflammatory values (*i.e.* c-reactive protein and leukocyte counts).

Initial management after the diagnosis starts with supporting therapy. Analgesics and aggressive intravenous fluid replacement to counteract hypovolemia and subsequently impaired end-organ microperfusion due to third spacing will suffice in most patients.[19,20] During the first 48 hours after admission, close monitoring of vital and biochemical characteristics is critical, as the systemic inflammation reaction secondary to the pancreatitis will induce organ failure in up to 38% of patients with pancreatic necrosis. A multitude of scoring systems have been devised to predict which patients are going to develop organ failure, but thus fare none is accurate enough to supplant frequent clinical evaluation.[21]

When primary care has been initiated, the next step is establishing the etiology as this has implications for further short- and long-term management. The patient history should include queries for pre-existing gallstone disease or gallstone-like symptoms and alcohol use. Blood testing should be performed for serum liver biochemistry for signs of biliary obstruction and serum calcium and triglycerides to rule out less common etiologies. Imaging studies can then be done to establish the presence of cholecystolithiasis or choledocholithiasis. Abdominal ultrasound is traditionally the modality of choice for cholecystolithiasis as it is reliable, fast and readily available. If negative, but suspicion of gallstones persists, computed tomography, magnetic resonance imaging and endoscopic ultrasound can be employed, in increasing order of accuracy for choledocholithiasis.[5] Endoscopic retrograde cholangiopancreatography should be reserved for patients in whom ascending cholangitis is suspected, but to date there is no evidence for its use in the amelioration of pancreatic inflammation in the acute phase in patients with mild disease.[22] Its role in patients at high risk of developing pancreatic necrosis or other complications is debated and currently under investigation. As most gallstones pass into the duodenum spontaneously, stone extraction is often not necessary.[9] In patients with persisting choledocholithiasis stone extraction can be planned electively.

Cholecystectomy

First performed for biliary colics by Carl Langenbuch in Berlin, 1882, cholecystectomy has become one of the most performed operations in the Western world.[17,18] Removing the gallbladder reduces the residence time of bile in the biliary tree, thereby allowing less time for gallstone formation.[19] Introduction of the laparoscopic technique in the late 1980's was met with great enthusiasm by the surgical community and a surge in the number of cholecystectomies was seen.[20,21] However, as no standardized techniques or adequate safety measures existed for identification of the cystic and common hepatic ducts, a rise in the number of iatrogenic biliary tract injuries was observed alongside this development.[22,23] To reduce the risk of this complication, various methods to intraoperatively assess biliary anatomy were developed. These include innovative and experimental equipment such as laparoscopic ultrasound, near-infrared fluorescence cholangiography and hyperspectral cholangiography. Only two have found widespread adoption; intraoperative cholangiography and the critical view of safety.[24] Intraoperative cholangiography (IOC) is performed by introducing a cannula into the cystic duct after dissecting Calot's triangle (*i.e.* the anatomic space bordered by the liver and the cystic and common hepatic ducts), and injecting the choledochus with a radiolucent fluid followed by X-ray fluoroscopy. Its proponents praise the technique's ability to provide both information on biliary tract anatomy as well as the presence of choledocholithiasis, leading some to perform it routinely. Opponents, however, criticize the low yield of clinically relevant information against the extra effort and operating time. As a result, the indications and applications of this technique continue to be subject to debate. The most commonly used method of establishing biliary anatomy is by achieving the 'critical view of safety'. This standardized operative technique requires the surgeon to dissect the hepatocystic triangle, separate the lower third of the gallbladder from the liver and confirm that only two tubular structures can be seen entering the gallbladder (*i.e.* the cystic duct and cystic artery).[25] Achievement of these steps is ideally recorded using videoscopic imaging but always in the operation report. Despite these innovations, the overall rate of iatrogenic bile duct injuries is still between 0.5 and 1.4%.[26] In part, this is due to human error and misinterpretation of anatomical structures. However, risks of this type of injury also increase when local acute or chronic inflammation has reduced normal biliary anatomy to an unrecognizable adhesive mass of structures.

MOTIVATION FOR AND AIMS OF THIS THESIS

With its self-limiting character and low complication rate, the short-term treatment for mild acute pancreatitis leaves little room for improvement. Because of its long-term protection against recurrent disease, cholecystectomy has been the strategy of choice for decades. More recently developed alternatives such as endoscopic sphincterotomy fail to provide the same level of protection for recurrent events. On the one hand, the advent

of laparoscopy has led to an increase in the popularity of cholecystectomy. On the other, however, it has sown dissent and doubt regarding indications and, most importantly, timing of surgery. The surgical community at large currently performs cholecystectomy after an interval of around 6 weeks. This is despite many retrospective studies reporting high readmission rates for patients during this interval.

Considering the current increased emphasis on efficient and patient-oriented care, effective allocation of hospital resources and lowering healthcare costs, this thesis is aimed at improving surgical strategies for mild gallstone pancreatitis. To this end, the following questions were posed:

1. Does same-admission cholecystectomy safely reduce morbidity from recurrent disease compared with the current standard of interval cholecystectomy? What are the economic repercussions of same-admission cholecystectomy?
2. What is the prevalence of recurrent biliary events *after* cholecystectomy? And can we predict or prevent these events?
3. Are there any grounds to the notion that acute pancreatitis would obscure biliary anatomy, thereby increasing technical difficulty of the procedure? Can this be predicted according to preoperatively available variables?
4. What surgical techniques can be applied to safely complete a difficult cholecystectomy?

OUTLINE OF THIS THESIS

The role of cholecystectomy in the treatment of mild biliary pancreatitis is central in this thesis. Many consider pancreatitis an absolute indication for gallbladder removal, but several strategic and technical aspects of this approach require clarification. In this thesis the following issues will be investigated.

Chapter 2 delineates current insights in pancreatitis incidence, diagnosis and biliary tract management. Indication for endoscopic sphincterotomy and cholecystectomy are addressed in greater detail. Furthermore, overall recurrence rates of pancreatitis and other biliary events following conservative management, endoscopic sphincterotomy and cholecystectomy are investigated.

Chapter 3 investigates the issue of timing of cholecystectomy after mild acute pancreatitis in a randomized controlled trial. Having confirmed that early cholecystectomy is the strategy of choice as far as morbidity is concerned, the question whether this strategy is also cost-effective will be addressed in *Chapter 4*.

The role of cholecystectomy following gallstone pancreatitis is investigated in more detail in *Chapters 5, 6 and 7*. Knowing that cholecystectomy is not a failsafe procedure to prevent future gallstone-related complications, we studied the frequency,

type and severity of gallstone-related events following surgery in a cohort of patients with mild gallstone pancreatitis in *Chapter 5*.

Chapter 6 addresses the technical aspects of cholecystectomy following mild pancreatitis more specifically, because in the past decades the discussion on timing of cholecystectomy has been dominated by the fear of inducing additional complications by early surgery.

As discussed in the previous chapter, inflammation of the gallbladder and surrounding tissue can lead to adhesions, scarring, and ultimately disfigurement of normal anatomy. *Chapter 7* provides an overview of the literature on outcomes after partial or subtotal cholecystectomy, an increasingly used alternative to conversion to open surgery.

In *Chapter 8*, we discuss current insights on the diagnosis and management of patients in whom pancreatic inflammation has resulted in pancreatic necrosis with or without failure of vital organ systems.

In *Chapters 9 and 10*, an overall Summary and a General Discussion will be presented, respectively.

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CHAPTER 2

Endoscopic sphincterotomy and cholecystectomy in acute biliary pancreatitis

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Endoscopic sphincterotomy and cholecystectomy in acute biliary pancreatitis

ABSTRACT

Background: This review discusses current insights with regard to biliary tract management during and after acute biliary pancreatitis.

Methods: A MEDLINE and EMBASE search was done and studies were selected based on methodological quality and publication date. The recommendations of recent guidelines are incorporated in this review. In absence of consensus in the literature, expert opinion is expressed.

Results: There is no role for early endoscopic retrograde cholangiopancreatography (ERCP) in patients with (predicted) mild biliary pancreatitis to improve outcome. In case of persisting choledocholithiasis, ERCP with stone extraction is scheduled electively when the acute event has subsided. Whether early ERCP with sphincterotomy is beneficial in patients with predicted severe pancreatitis remains subject to debate. Regardless of disease severity, in case of concomitant cholangitis urgent endoscopic sphincterotomy (ES) is recommended. As a definitive treatment to reduce the risk of recurrent biliary events in the long term, ES is inferior to cholecystectomy and should be reserved for patients considered unfit for surgery. After severe biliary pancreatitis, cholecystectomy should be postponed until all signs of inflammation have subsided. In patients with mild pancreatitis, cholecystectomy during the primary admission reduces the risk of recurrent biliary complications.

Conclusion: Recent research has provided valuable data to guide biliary tract management in the setting of acute biliary pancreatitis with great value and benefit for patients and clinicians. Some important clinical dilemmas remain, but it is anticipated that on-going clinical trials will deliver some important insights and additional guidance soon.

INTRODUCTION

Gallstones cause substantial morbidity in the western world.[1, 2] Ranging from relatively harmless colics to potentially lethal pancreatitis, biliary disorders represent some of the most prevalent benign abdominal diseases.[3] Especially small gallstones and sludge are wont to migrate from the gallbladder into the duodenum.[4, 5] In the proximity of the ampulla of Vater, gallstones obstructing the biliopancreatic duct are a frequent cause of acute pancreatitis.[6] Most stones migrate into the duodenum spontaneously,[7] but persisting obstruction of the ampulla can theoretically aggravate pancreatic inflammation.[8]

Long-term management of symptomatic cholelithiasis aims at minimizing the risk of new biliary events. Recurrence rates of biliary pancreatitis up to 61% have been described when no definitive treatment was provided.[9] Cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP) are widely used to this end, although some aspects such as the timing and indication of these interventions remain unclear. This review discusses current insights in acute biliary pancreatitis and its management.

METHODS

Pubmed searches were conducted by N.J.S. and D.d.C. using the following medical search headings: "Pancreatitis" and "Acute Pancreatitis", "Biliary Tract Diseases", "Endoscopic retrograde cholangiography", "Cholecystectomy" and "Laparoscopic cholecystectomy". These MeSH terms, in combination with title and abstract review, with subheadings such as "diagnosis" and "epidemiology", were employed for the various topics included in this review. A secondary search was performed in Embase, using combinations of the Emtree terms "Acute Pancreatitis", "Biliary Tract Diseases", "Epidemiology", "Endoscopic Retrograde Cholangiopancreatography" and "Cholecystectomy". The search was limited to English language literature and to subtopics 'diagnosis', 'aetiology', 'prevention', 'disease management' and 'surgery'. Articles were selected based on study type, methodological quality and publication date. Where possible, we selected population-based studies for epidemiological data, whereas for treatment recommendations a hierarchical selection strategy was applied based on the level of evidence. Additional articles were explored by cross-referencing the articles found through the literature searches.

The recommendations of the recently revised guidelines from the International Association of Pancreatology / American Pancreatic Association (IAP/APA guidelines) as well as the American College of Gastroenterologists guidelines were incorporated in this review.[10, 11] Regarding the aspects of treatment in which no clear consensus exists or decent quality evidence lacks, recommendations in this article were based on expert opinion and consensus within the Dutch Pancreatitis Study Group.

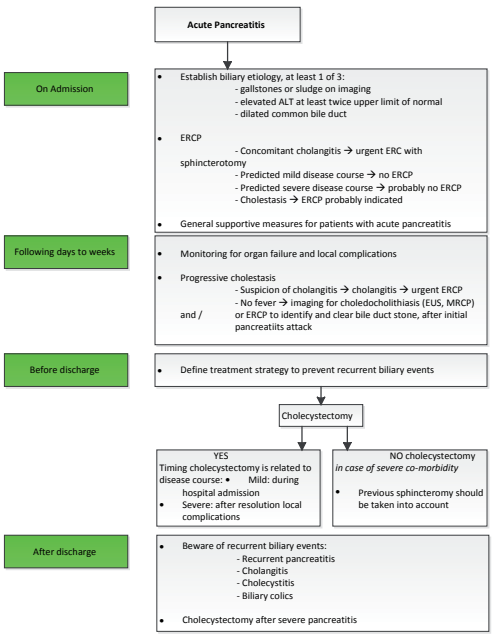
RESULTS

Incidence, classification and diagnosis

Gallstones are listed as the most common cause of pancreatitis, accounting for 27 to 62% of all cases.[12, 13] Either reflux of bile or increased pressure in the pancreatic duct resulting from gallstones or microlithiasis obstructing Vater's ampulla is believed to trigger pancreatic inflammation.[14, 15] Gallstones are more prevalent in women than in men. Consequently, women are twice as likely to develop biliary pancreatitis.[16-18] Population studies have revealed growing incidence numbers for acute pancreatitis over the past few decades, attributed at least in part to the higher prevalence of gallstones associated with obesity. Overall incidence rates of acute pancreatitis increase with age and are between 13 and 50 per 100.000.[19-22] Overall mortality of acute pancreatitis is low (1-4%),[21, 23] but mortality rates increase 5 to 10 fold when organ failure or infected pancreatic necrosis complicate the disease course.[24]

A flow chart with management steps for patients with (suspected) biliary pancreatitis is presented in Figure 1. The diagnosis of acute biliary pancreatitis is made by visualisation of gallstones or sludge in addition to at least two of the following three items: 1) pain in the upper abdomen, 2) serum amylase or lipase at least three times

Figure 1. Management of acute biliary pancreatitis.



ALT: Alanine aminotransferase, ERCP: Endoscopic Retrograde Cholangiopancreatography, EUS: Endoscopic Ultrasound, MRCP: Magnetic Resonance Cholangiopancreatography

the upper limit of normal and 3) characteristics of acute pancreatic inflammation on cross-sectional imaging (if performed).[25] Confirmation of the presence of gallstones is usually done by transabdominal ultrasound of the gallbladder (positive predictive value: 100%), but this is ineffective for detecting microlithiasis.[26] Unless a significant dilatation of the common bile duct is found (i.e. more than 8 mm in patients under 75 years, more than 10 mm in patients aged 75 and over), transabdominal ultrasound cannot be used to reliably assess choledocholithiasis.[27] Aggregate studies have found endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) to be excellent modalities for detection of intraductal gallstones.[28-32] A systematic review comparing EUS and MRCP for choledocholithiasis found positive predictive value scores of 93 and 87% respectively.[31] EUS, while more invasive, has greater potential for finding small gallstones and sludge, especially distally in the common bile duct.[29] Additionally, more recent studies have called into question the ability of MRCP to detect choledocholithiasis in the setting of acute gallstone pancreatitis, as sensitivity dropped to 62%.[33, 34] However, as these are retrospective studies, further investigation is needed for a definitive appraisal of MRCP in this setting.

In addition to imaging, serum liver biochemistry can be highly predictive of a biliary origin. Several studies have identified a strong correlation between the presence of gallstones and raised serum alanine aminotransferase (ALT).[13, 27, 35] ALT levels twice the upper limit of normal have a positive predictive value of 82%, increasing to 92% if raised three times.[13, 27]

Disease severity can be classified into three categories according to the presence or absence of organ failure and pathological features of the pancreas.[25] 'Mild' pancreatitis is characterised by an absence of organ failure and no complications such as extrapancreatic or pancreatic parenchymal necrosis. Patients with organ failure lasting less than 48 hours *or* pancreatic or systemic complications (e.g. exacerbation of previous illness such as chronic heart or lung disease) are classified as 'moderately severe'. Organ failure persisting beyond 48 hours is classified as 'severe' pancreatitis and is frequently accompanied by pancreatic necrosis or fluid collections.[25] Patients with biliary pancreatitis seem to develop organ failure less often compared to alcoholic pancreatitis.[36]

Recurrent biliary events

Literature specifically addressing the incidence of recurrent biliary events is scarce and the few studies available only describe specific subgroups of patients (Table 1). Studies have reported recurrence rates of biliary pancreatitis between 18-61% whilst awaiting cholecystectomy.[9, 37] Readmissions for cholecystitis and simple biliary colics occur less often (around 3% and 7%, respectively).[37] A prospective study including 233 patients with acute biliary pancreatitis reported a 31-fold risk of recurrence in patients in whom the gallbladder was left *in situ*.[38] Severity and mortality rates of the recurrent episodes are similar to those of the primary attack. Nevertheless, some 9% of patients have

Table 1. Studies reporting recurrent pancreatitis and other biliary events.

					Cholecystectomy		Endoscopic sphincterotomy		Neither		Both*	
Author	**Year of publication**	**Type**	**Study period**	**Total No. Of patients**	**Pancrea-titis**	**Biliary events**	**Pancrea-titis**	**Biliary events**	**Pancrea-titis**	**Biliary events**	**Pancrea-titis**	**Note**
Alimoglu[9]	2003	Retrospective cohort	1997-2000	43					61			Single centre study comparing same-admission and interval cholecystectomy
Bakker[40]	2011	Prospective cohort	2004-2007	308			2	7	16	18		Multicenter cohort study including patients with mild biliary pancreatitis
da Costa[89]	2015	Randomised trial	2010-2013	264	3	5	1	17	12	17	3	A randomised multicenter trial in 264 patients with mild biliary pancreatitis
Delorio[89]	1995	Retrospective cohort	1990-1994	113					45			Single centre study including all patients with biliary pancreatitis
El-Dhuwaib[64]	2012	Retrospective cohort	2007-2009	5454		2		5		13		Patients were identified using hospital episode statistics from 2007-2008 and followed through 2009

Hwang[55]	2013	Retrospective cohort	1995-2010	1119	5		8		17		Cohort study using electronic medical records of patients with a first episode of biliary pancreatitis
Ito[90]	2008	Retrospective cohort	1995-2005	281			5	33	18	33	Single centre study on outcomes after same-admission and interval cholecystectomy
Mador[91]	2014	Retrospective cohort	2006-2011	80		0		60			Chart reviews from patients who had all undergone sphincterotomy
Mustafa[59]	2014	Retrospective cohort	2005-2010	5079	4		7	12	23		1	Hospital statistics derived from the National Health Statistics. Patients from 2005 were identified and followed through 2010.
van Baal[37]	2012	Systematic review	1992-2010	998	1			10		24		Pooled data from 8 cohort studies and 1 randomised trial including patients with mild pancreatitis

been reported as having a serious complication during follow-up after an initial mild episode.[38, 39] It should be noted that cholecystectomy does not completely obviate the risk of recurrent disease. Gallstones retained in the biliary tract may cause morbidity in up to 10% of patients who underwent surgery, although their prevalence is unknown.[37, 40-42]

Endoscopic Sphincterotomy

The role of ERCP with sphincterotomy as early intervention in biliary pancreatitis has been the subject of debate for years. The potential benefit of early decompression of the pancreaticobiliary system is weighed against the risks associated with ERCP with sphincterotomy (i.e. bleeding, perforation). In acute biliary pancreatitis, sphincterotomy can be performed; 1) as early intervention to potentially ameliorate the disease course, 2) to extract retrained common bile duct stones or 3) as prophylactic treatment to prevent recurrent biliary events.

ERCP as early intervention

Urgent ERCP is indicated in acute biliary pancreatitis and concomitant cholangitis.[10, 11] A randomized trial of 82 patients with acute cholangitis due to choledocholithiasis showed that early endoscopic biliary drainage decreases mortality compared to surgery.[43] However, these patients did not suffer from concomitant pancreatitis. The undisputed role of ERCP in patients with pancreatitis and cholangitis is based on non-randomized trials and subgroup analysis of randomized trials in biliary pancreatitis.[44, 45] Although consensus exists on performing an ERCP in case of concomitant cholangitis, the definitions for cholangitis vary in the available literature. As such, diagnosing cholangitis is challenging, as signs of inflammation and biliary obstruction are also frequently observed in acute biliary pancreatitis.

Early ERCP is not indicated in patients with mild biliary pancreatitis.[10, 11] As spontaneous stone passage usually occurs, potential benefits do not outweigh the risks for ERCP related complications.[7] Guideline recommendations on ERCP in patients with acute biliary pancreatitis and at high risk for complications are conflicting.[10, 11] In a recent meta-analysis, early ERCP was not beneficial in patients who were at high risk for developing complications.[44] This suggests that either this subgroup may truly not benefit from early decompression, or that this subgroup analysis might lack the statistical power to show an effect. However, several limitations of this meta-analysis should be taken into account. Foremost, it includes randomized trials with widely varying patient selection criteria, resulting in the pooling of patients with cholangitis, non-biliary pancreatitis and patients with low risk of complications. [8, 46-48] Furthermore, endoscopic sphincterotomy was only performed in case of proven common bile duct stones, which resulted in a low percentage of actual sphincterotomy. The beneficial effect of sphincterotomy, however, has been observed regardless of the presence of common

bile duct stones.[46, 47, 49, 50] Additionally, ERCPs were performed during a wide time frame (i.e., within 48 to 72 hours) and no criteria were set to guarantee that ERCPs were performed by experienced endoscopists.[8, 46, 47] A randomized trial investigating the role of early ERCP with sphincterotomy in patients with acute biliary pancreatitis and at high risk for complications is underway (ISRCTN97372133).

Guidelines suggest that early ERCP may be beneficial in patients with ongoing cholestasis due to biliary obstruction.[10, 11] In line, a meta-analysis comprising 519 patients with pancreatitis and biliary obstruction found that a strategy with the routine use of ERCP reduced local complications as defined by authors of the primary study compared to conservative treatment.[44] The indication for ERCP in case of biliary obstruction is not yet fully established due to limitations of available evidence. These include heterogeneous study populations, the use of various definitions and relatively small, pooled sample sizes. A stone detected on imaging may pass spontaneously, in which case an ERCP would probably be redundant. Furthermore, biochemical and radiological signs of biliary obstruction can be unreliable in the acute phase of pancreatitis.[51] The recent guidelines acknowledge these limitations.

Extraction of common bile duct stones

Following an attack of biliary pancreatitis, extraction of retained stones can be scheduled electively by means of ERCP with sphincterotomy. In patients without pancreatitis removal of identified retained stones is generally recommended.[52, 53] Depending on the probability of retained bile duct stones, EUS or MRCP should be performed prior to ERCP in case biochemical tests and dilation of the common bile duct suggest choledocholithiasis.[54] If EUS or MRCP are negative, ERCP and its potential complications can be avoided.

Prevention of recurrent attacks

After the patient has recovered from the initial acute pancreatitis episode, sphincterotomy can be performed to prevent recurrent biliary events. Without endoscopic or surgical intervention, the risk of recurrent biliary events is high (Table 1).[37, 55] Sphincterotomy reduces the risk of recurrent pancreatitis, however not of other biliary events.[37, 40, 56, 57] A large meta-analysis in patients without pancreatitis demonstrated that additional cholecystectomy reduced mortality compared to a wait-and-see-policy.[58] Furthermore, a randomized trial in patients without pancreatitis that successfully underwent sphincterotomy, early cholecystectomy was associated with less recurrent biliary events compared to delayed cholecystectomy.[42] In patients with pancreatitis that have undergone sphincterotomy, no randomized trial has been performed to evaluate the effect of cholecystectomy. Non-randomized studies evaluating the effect of cholecystectomy and additional sphincterotomy in patients with pancreatitis show conflicting results.[57] However, a recent large-scale study using data from over five

thousand patients showed that cholecystectomy and sphincterotomy offers the best long-term results for preventing recurrent biliary pancreatitis.[59] Therefore, guidelines agree that definitive management should include cholecystectomy.[10, 11] Prophylactic sphincterotomy as definitive treatment is currently only recommended in certain subgroups in which cholecystectomy cannot be performed, e.g. patients with severe co-morbidity or in case of necrotising pancreatitis. [10, 11 60-63] However, studies investigating the added benefit of cholecystectomy after sphincterotomy in elderly patients with high risk of anaesthesiological or other perioperative complications are lacking.

Cholecystectomy

Cholecystectomy is the treatment of choice for preventing recurrent biliary events.[10, 11] Despite the recommendations by the guidelines, up to 25 to 50% of patients do not undergo gallbladder removal for various reasons.[55, 64, 65] With similar mortality and complication rates as open cholecystectomy, laparoscopic surgery has become the primary approach in the western world.[66] Iatrogenic injury to the bile duct system is the major surgical complication in cholecystectomy. To avoid bile duct injury, several surgical and technical strategies have been developed. The main goal in gallbladder surgery is acquiring the critical-view-of-safety (CVS), a standardised operative technique for positive identification of the gallbladder, cystic duct and cystic artery. Obtaining CVS considerably reduces the chance of misinterpretation of anatomy, even in case of severe inflammation changes or anatomical anomalies. The CVS technique has been adopted as the standard by most guidelines.[67]

Additionally, several imaging modalities have been developed for intraoperative assessment of bile duct anatomy. The most popular technique in this field is intraoperative cholangiography (IOC). This technique has the added potential of detecting persisting intraductal gallstones. Although some advocate routine use of IOC, evidence for this is lacking to generate international support.[68] A recent systematic review including 8 randomised trials and two large retrospective cohort studies all concluded that routine IOC does not prevent bile duct injury.[69-71] Furthermore, conflicting results have been shown in detecting persisting bile duct stones with routine use of IOC.[69, 72] Moreover, as many of these stones pass spontaneously, the relevance of finding retained stones is debatable.[73, 74] In summary, IOC may be helpful in selected cases, for example when an aberrant anatomy is suspected or with persisting biochemical markers of biliary obstruction. To date there is no solid evidence for the routine use of IOC.

When symptomatic choledocholithiasis is confirmed on IOC (or preoperative EUS or MRCP), some surgeons advocate laparoscopic common bile duct exploration.[75] Two meta-analyses found this one-stage strategy to be as effective and safe as when the bile duct is cleared postoperatively through ERCP.[76, 77] However, laparoscopic bile duct exploration carries the risk of bile duct injury and should only be performed by highly experienced surgeons.[78] Conversely, pre- or postoperative ERCP is not without

risk itself and may be complicated by post-ERCP pancreatitis, haemorrhage or duodenal perforation.[76]

Timing of cholecystectomy

In severe pancreatitis current international guidelines recommend postponing cholecystectomy until after resolution of local or systemic complications. This is usually not before the sixth week after onset of the disease.[10, 11, 79] Performing cholecystectomy earlier is associated with significantly higher complication rates.[81]

Regarding mild pancreatitis, optimal timing of cholecystectomy is a much-discussed topic. International guidelines advise performing cholecystectomy during index admission for mild pancreatitis.[10, 11] However, studies have indicated that adherence to these guidelines in common daily practice is as low as 5%.[37, 40, 41, 55] A recent systematic review including 998 patients indicated that cholecystectomy was performed after a median of 40 days in more than half of all patients.[37] Aside from the logistical challenges that may be encountered with same-admission cholecystectomy,[81, 82] there are two common explanations for this lack of compliance. First, reports from the early laparoscopic era cautioned the use of surgery in the (post)acute phase of pancreatitis, based on the presumption that biliary anatomy is distorted by the inflammation , increasing the risk of surgical complications.[83-85] However, it should be noted that these results were based on findings in patients with *severe* pancreatitis.

Another important reason why the guidelines have not found widespread adoption is that the recommendations are based on low quality evidence.[11] Except for one randomised trial, all available evidence is based on retrospective studies prone to selection and other forms of bias.[37] The only randomised trial concerning the timing of laparoscopy after mild biliary pancreatitis was terminated halfway through and included only 50 patients.[86] Moreover, the patients in the early arm of this trial were randomised for cholecystectomy within 48 hours after onset (i.e. *during* pancreatitis). During this period disease severity may still progress from mild to severe, the latter being considered a contraindication for early surgery.[87]

Recently a multicentre randomised trial conducted by the Dutch Pancreatitis Study Group addressing the timing of cholecystectomy was completed (the PONCHO trial, ISRCTN72764151).[88] In total 264 patients admitted for mild biliary pancreatitis (i.e. no organ failure, no pancreatic necrosis) were randomised to cholecystectomy during the same admission (N=128) or discharge and cholecystectomy after an interval of 25 to 30 days (N=136). The primary outcome consisted of a combined endpoint of mortality or acute readmission for recurrent biliary complications (i.e. pancreatitis, cholecystitis, choledocholithiasis or colics). The primary endpoint occurred significantly less often after same-admission cholecystectomy as compared with interval cholecystectomy (5% vs. 17%, P=0.002). This included a reduction in the onset of recurrent biliary pancreatitis (2% vs. 9%, P=0.03). In addition, more than half of the patients (51%) in the interval

group reported to have suffered gallstone colics at home during the waiting period, compared with only 3% in the same-admission group (P<0.001). Very few surgical complications occurred, indicating that cholecystectomy can and should be performed safely during the same admission.

CONCLUSION

Biliary pancreatitis is a potentially fatal disease and is an increasing cause for major morbidity worldwide. Concomitant cholangitis is an indication to perform urgent biliary decompression by ERCP with sphincterotomy. Early ERCP with sphincterotomy should not be performed in patients with mild pancreatitis. Whether early biliary decompression in patients with predicted severe pancreatitis is indicated is currently under investigation. Current literature is conflicting on the role and timing of ERCP in the setting of biliary obstruction in patients with pancreatitis. To prevent recurrent biliary events, definitive treatment consists of cholecystectomy, or endoscopic sphincterotomy in selected cases. Current consensus is to postpone cholecystectomy in patients with severe pancreatitis until all signs of inflammation have subsided, usually not before six weeks after onset. The question whether sphincterotomy should be performed to avert the risk of recurrence during this period has not been addressed properly. In patients with mild pancreatitis, cholecystectomy before discharge reduces readmissions for recurrent disease. Furthermore, studies are needed to investigate whether those at high risk of surgical or anaesthesiological complications (due to comorbidity) should be subjected to the risk of cholecystectomy, especially if sphincterotomy has already been performed.

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CHAPTER 3

Same-admission *versus* interval cholecystectomy for mild gallstone pancreatitis: a multicentre randomised controlled trial

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Same-admission *versus* interval cholecystectomy for mild gallstone pancreatitis: a multicentre randomised controlled trial

ABSTRACT

Background In patients with mild gallstone pancreatitis, cholecystectomy during the same admission may reduce the risk of recurrent gallstone-related complications, compared with the more common strategy of interval cholecystectomy. However, evidence to support same-admission cholecystectomy is poor and concerns exist about an increased risk of cholecystectomy-related complications with this approach. In this study, we aimed to compare same-admission and interval cholecystectomy, with the hypothesis that same-admission cholecystectomy would reduce the risk of recurrent gallstone-related complications without increasing the difficulty of surgery.

Methods For this multicentre, parallel group, assessor-masked, randomised controlled superiority trial, inpatients recovering from mild gallstone pancreatitis at 23 hospitals in the Netherlands (with hospital discharge foreseen within 48 h) were assessed for eligibility. Adult patients (aged ≥ 18 years) were eligible for randomisation if they had a serum C-reactive protein concentration of less than 100 mg/L, no need for opioid analgesics, and could tolerate a normal oral diet. Patients with an American Society of Anesthesiologists (ASA) class III physical status who were older than 75 years of age, all ASA class IV patients, those with chronic pancreatitis, and those with ongoing alcohol misuse were excluded. A central study coordinator randomly assigned eligible patients (1:1) by computer based randomisation, with varying block sizes of two and four patients, to cholecystectomy within 3 days of randomisation ('same-admission') or to discharge and cholecystectomy after 25 to 30 days after randomisation ('interval'). Randomisation was stratified by centre and by whether or not endoscopic sphincterotomy had been done. Neither investigators nor participants were masked to group assignment. The primary endpoint was a composite of readmission for recurrent gallstone-related complications (pancreatitis, cholangitis, cholecystitis, choledocholithiasis needing endoscopic intervention or gallstone colics) or mortality within 6 months after randomisation, analysed by intention to treat. The trial was designed to reduce the incidence of the primary endpoint from 8% in the interval group to 1% in the same-admission group. Safety endpoints included bile duct leakage and other complications necessitating re-intervention. This trial is registered with Current Controlled Trials, number ISRCTN72764151, and is complete.

Findings Between Dec 22, 2010 and Aug 19, 2013, 266 inpatients from 23 Dutch hospitals were randomly assigned to interval cholecystectomy (N=137) or same-admission cholecystectomy (N=129). One patient from each group was excluded from

the final analyses, because of an incorrect diagnosis of pancreatitis in one patient (interval group) and discontinued follow-up in the other patient (same-admission group). The primary endpoint occurred in 23 (17%) of 136 patients in the interval group and in six (5%) of 128 patients in the same-admission group (risk ratio 0.28; 95% confidence interval [CI] 0.12-0.66; p=0.002). Safety endpoints occurred in four patients: one case of bile duct leakage and one case of postoperative bleeding in each group. All of these were serious adverse events and were judged to be treatment related, but none led to death

Interpretation Compared with interval cholecystectomy, same-admission cholecystectomy, reduced the rate of recurrent gallstone-related complications in patients with mild gallstone pancreatitis, with a very low risk of cholecystectomy-related complications.

INTRODUCTION

Acute pancreatitis is a common gastrointestinal disorder, mostly caused by gallstones or biliary sludge.[1,2] Around 80% of affected patients have mild pancreatitis.[3] Cholecystectomy is indicated in these patients to reduce the risk of recurrent gallstone-related complications such as pancreatitis, cholecystitis, cholangitis or gallstone colics.[4,5]

Several nationwide audits from both Europe and the United States have shown that laparoscopic cholecystectomy is usually done around 6 weeks after discharge from hospital admission for mild gallstone pancreatitis.[6-11] Recent studies from the United Kingdom have reported that up to one third of all patients do not receive any definitive treatment within 1 year after discharge.[9,12] This finding conflicts with the recommendation of cholecystectomy during the same admission or at least within two weeks after discharged, as proposed by the British Society of Gastroenterology.[13] The main reason for this delay in cholecystectomy is a perceived danger of perioperative complications in early cholecystectomy after acute pancreatitis.[7,14] Inflammation and oedema are believed to distort biliary tract anatomy, thereby complicating dissection with an increased risk of conversion and surgical complications such as bile duct injury.[12,15] A delayed approach also helps surgical scheduling, since emergency theatre capacity is often scarce.[14]

The drawback cholecystectomy being postponed until several weeks after discharge is that during this period patients are at risk of developing recurrent gallstone-related complications. For example, recurrent pancreatitis reportedly occurs in up to 33% of patients in observational studies.[16,17] As a result, the recently revised guidelines from both the International Association of Pancreatology / American Pancreatic Association (IAP/APA) and the American Gastroenterology Association (AGA) recommend that cholecystectomy is done during the same hospital admission.[4,5] However, no randomised studies have compared same-admission cholecystectomy to the existing practice of interval cholecystectomy.[16] This absence of high-quality evidence might also contribute to the reported low adherence to guidelines.[7-9,12,18]

We did a nationwide randomised study to investigate whether or not same-admission cholecystectomy, as compared with interval cholecystectomy, reduces recurrent gallstone-related complications in patients with mild gallstone pancreatitis.

METHODS

Study design and participants

The PONCHO (Pancreatitis of biliary origin: Optimal timiNg of CHOlecystectomy) study was designed as a randomised controlled, parallel group, superiority multicenter trial. The rationale and design of the PONCHO trial have been described in detail.[19] The study was done at 23 study sites in the Netherlands, including seven university

medical centres and 16 teaching hospitals (appendix p2). All adult patients (aged ≥ 18 years) admitted to these centres between Dec 7, 2010, and Aug 14, 2013, diagnosed with a first episode of gallstone pancreatitis were assessed for eligibility. The diagnosis of pancreatitis needed at least two of the following three features: epigastric pain, serum amylase or lipase levels at least three times the upper limit of normal, and, if done, characteristic findings of acute pancreatitis on cross-sectional abdominal imaging. 'Mild' pancreatitis was defined by absence of persistent organ failure (ie >48 h), and local complications such as pancreatic necrosis or peripancreatic fluid collections on computed tomography (CT).[20] A biliary cause was defined by gallstones, biliary sludge, or a dilated common bile duct on imaging, or based on biochemical signs of cholestasis (for details, see the Supplementary Appendix Box S1).

Patients were enrolled by the local physicians at each hospital and were randomised to the two treatment groups once discharge from hospital was foreseen within 48 h. Additional eligibility criteria were a serum C-reactive protein (CRP) concentration less than 100 mg/L, no need for opioid analgesics, and tolerance of a normal oral diet, all at the time of randomisation. Patients with American Society of Anaesthesiologists (ASA) class III physical status who were over 75 years of age and all ASA class IV patients (ie irrespective of age) were excluded because of their inherently high risk of complications from anaesthesia or surgery.[21] Other exclusion criteria were chronic pancreatitis and on-going alcohol misuse. After initiation of the trial, pregnancy was added as exclusion criterion in January 2012, both for ethical reasons and because of the paucity of evidence about cholecystectomy in this subgroup.

The study was investigator initiated and was undertaken following the principles of the Declaration of Helsinki (originally adopted in 1964, with the last amendment before this trial in October, 2008) and the Dutch Medical Research Involving Human Subjects Act (1998; last revised in 2006). The central committee for research for research in Nijmegen, the Netherlands (CMO) approved the study protocol. A data safety monitoring committee of four independent, non-participating physicians assessed all serious adverse events after inclusion of every 50 patients in an unmasked fashion. All patients provided written informed consent.

Randomisation and masking

Randomisation was done by the central study coordinator using a web-based randomisation module. Randomisation was stratified according to centre and by whether or not endoscopic sphincterotomy had been done. Computer-generated permutated block randomisation with a 1:1 allocation ratio and concealed varying permuted block sizes of 2 and 4 patients was used. Owing to the invasive nature of the intervention and the logistics involved, neither the trial participants nor the investigators could be masked to group allocation.

Procedures

In the interval cholecystectomy group, patients were discharged and cholecystectomy was electively scheduled 25-30 days after randomisation. This time interval is in line with the maximum waiting period recommended by the American and Dutch treatment guidelines at the time of the design of the trial.[22,23] Same-admission cholecystectomy was done within 3 days after randomisation. All cholecystectomies were done by, or under direct supervision of, a surgeon who had undertaken at least 100 cholecystectomies in the past five years. Intraoperative cholangiography was not mandatory because only about 3% of Dutch surgeons routinely do this procedure.[24] The strategy of preoperative stone extraction through endoscopic retrograde cholangiopancreatography is much more prevalent than intraoperative cholangiography because of the excellent widespread availability of this procedure in the Netherlands.

Data were collected on case record forms by the local physicians in the 23 participating study sites. All data for primary and secondary endpoints were checked for completeness by the study coordinators with source data at each participating centre. Patients were instructed to record all episodes of gallstone colics (ie, irrespective of readmission), that occurred during the six-month follow-up period in the study diary, with reminders via telephone calls from the study research nurse (see Appendix pp 5, 6 and 10 for details). The central study coordinators (SAB and DWdC) drafted reports for all potential primary and safety endpoints, using the primary clinical and biochemical data as collected by the study nurse. An adjudication committee of five gastrointestinal surgeons (DB, MGB, HCvS, HvG and CHD) who were masked to treatment allocation then individually assessed primary and safety endpoints using all available data. Any disagreements were resolved in a consensus meeting.

Outcomes

The primary endpoint was a composite of gallstone-related complications or mortality occurring within six months after randomisation, before or after cholecystectomy, analysed by intention to treat. Gallstone-related complications were defined as acute readmission for recurrent pancreatitis, cholecystitis, cholangitis, obstructive choledocholithiasis needing endoscopic retrograde cholangiopancreatography or gallstone colic.[25,] Secondary endpoints were the individual components of the primary endpoint, difficulty of cholecystectomy as assessed by the most experienced surgeon on a 0-10 visual analogue scale, conversion to open cholecystectomy, health-care use such as total length of hospital stay after randomisation (including readmission), and the number of patient-reported colics irrespective of readmission.

Predefined safety endpoints included cholecystectomy-related complications such as bile duct injury and bleeding; the need for additional surgical, endoscopic or radiological intervention; and other complications such as pneumonia, bacteraemia,

and new-onset organ failure.[26] The Appendix provides definitions for the primary and secondary outcomes.

Statistical Analysis

The sample size calculation was based on an expected reduction of the primary endpoint from 8% within 4 weeks after discharge in the interval cholecystectomy group to 1% in the same-admission cholecystectomy group, as reported in a recent nationwide retrospective study.[6] To show this effect with 80% power, a two-sided α-level of 5% and 0.5% loss to follow up, 266 patients were needed.

An intention-to-treat-analysis was done. We tested differences in dichotomous data between the groups were tested using the χ^2 test or Fisher's exact test (eg, the data for primary outcome, and need for intensive care unit admission), and used the Mann-Whitney *U* test to assess differences in continuous data (eg, length of stay after randomisation, and duration of surgery). Predefined subgroup analyses were done based on age (< 75 years *vs* ≥ 75 years) and endoscopic sphincterotomy (yes *vs* no) before randomisation. We chose these subgroups because we postulated that elderly patients would be more prone to complications (ie both gallstone-related and non-gallstone-related) than younger patients, and to assess a potential protective effect of sphincterotomy on the occurrence of gallstone-related complications.[16] We used logistic regression to test for interactions between subgroups.

An interim analysis of the primary endpoint was performed by an independent statistician after 50% of the patients had completed the six-month follow-up period, which used the Peto approach with symmetric stopping boundaries at a *p* value of less than 0.001.[27] A futility rule was not used, since this study is the first randomised trial on this topic and we felt strongly that, irrespective of the outcome, the results of the trial would be informative. The central study coordinator and steering committee were informed that the Peto criteria were not met and that the trial could continue as planned.

For the final analyses, a two-sided p value of less than 0.05 was judged to be statistically significant. We did not adjust *p* values for multiple testing.

IBM SPSS Statistics version 22 was used for statistical analyses.

This trial is register with Current Controlled Trials number ISRCTN72764151.

Role of the funding source

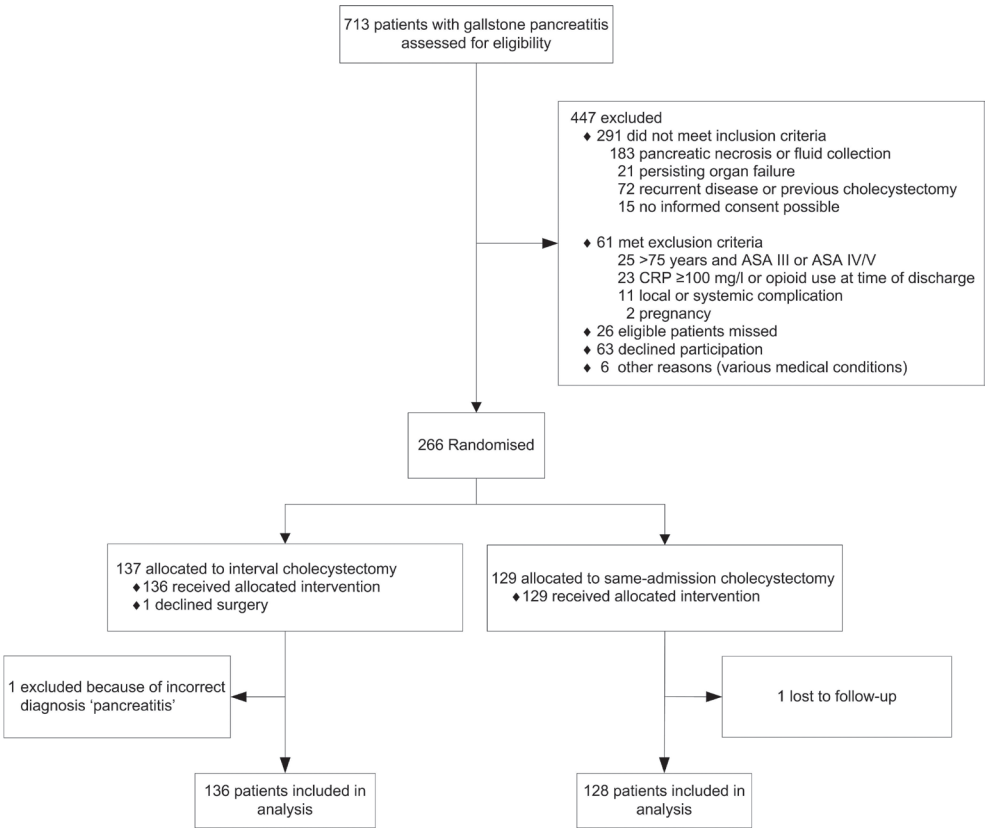
The funder of the study had no role in the study design, execution, data analysis or publication. The joint first authors (DdC and SAB), second author (NJS), statistical and methodological expert (MGD) and last author (DB) had full access to all the data. DB had final responsibility for the decision to submit for publication.

RESULTS

Enrolment and randomisation

Between December 2010 and August 2013, 713 patients with gallstone pancreatitis were assessed for eligibility (Figure 1). After 447 patients were excluded, 266 patients were enrolled and randomly assigned: 137 in the interval cholecystectomy group and 129 patients in the same-admission cholecystectomy group. The masked adjudication committee excluded one patient in the interval group from the final analysis because of an incorrect diagnosis of acute pancreatitis, since the serum amylase level did not exceed three times the upper limit of normal. One patient in the same-admission group was lost to follow up at three months after randomisation. Before randomisation 42 patients in the interval group (31%) and 36 patients in the same-admission group (28%) had undergone endoscopic sphincterotomy (p=0.6). In both groups sphincterotomy was done a median of one day (IQR 0-2 days in the interval group and 0-1 day in the same

Figure 1. Enrolment, allocation and follow-up of patients



admission group) after admission. The baseline characteristics of the participants did not differ significantly between the two treatment groups (Table 1).

In the interval group, median time to cholecystectomy after randomisation was 27 days (interquartile range [IQR] 26 to 29 days) and 100 of the patients (74%) underwent surgery within the designated 25 to 30 days. Recurrent gallstone-related complications required emergency or earlier cholecystectomy in 13 patients (10%). One patient in the interval group ultimately refused cholecystectomy. In the same-admission group, median time to cholecystectomy following randomisation was 1 day (IQR 1 to 2 days), and 119 of the patients (93%) underwent surgery within the designated 3

Table 1. Baseline characteristics.

Characteristic	Interval cholecystectomy (N=136)	Same admission cholecystectomy (N=128)
Age in years; median (IQR)	54 (41-68)	53 (38-66)
Female sex; No. (%)	84 (62)	76 (59)
Body Mass Index (kg/m^2); median (IQR)	28 (25-31)	27 (24-32)
Medical History; No. (%)		
Upper abdominal surgery	6 (4)	8(6)
History of gallstone colics	35 (26)	38 (30)
History of cholecystitis	2 (1)	3 (2)
Diabetes	7 (5)	11 (9)
American Society of Anaesthesiologists class; No. (%)		
I: healthy status	51 (38)	43 (34)
II: mild systemic disease	74 (54)	72 (56)
III: severe systemic disease	11 (8)	13 (10)
Endoscopic sphincterotomy prior to randomisation; No. (%)	42 (31)	35 (27)
CRP (mg/l) on the day of randomisation; median (IQR)	36 (15-69)	31 (11-66)
Days of admission prior to randomisation; median (IQR)	5 (3-9)	5 (3-8)
Days between randomisation and cholecystectomy; median (IQR)	27 (26-29)	1 (1-2)

IQR: Inter Quartile Range. CRP: C-Reactive Protein.

days. The experience of the surgeons performing cholecystectomy did not differ between groups (further details are found in the Supplementary Appendix).

Outcomes

Primary and secondary endpoints

The composite primary endpoint of acute readmission for a gallstone-related complication or mortality occurred in 23 of 136 patients (17%) in the interval group, as compared with 6 of 128 patients (5%) in the same-admission group (risk ratio 0.28; 95% confidence interval [CI] 0.12 to 0.66; p=0.002) (Table 2). In the interval group, 21 of the 23 primary endpoints (91%) occurred before cholecystectomy, with a median time from discharge to readmission of 15 days (IQR 8 to 21 days). In the same-admission group all primary endpoints occurred after cholecystectomy and within the first 3 weeks after discharge (median 12 days, IQR 5 to 18).

Recurrent gallstone pancreatitis occurred in 12 patients in the interval group (9%) versus 3 patients in the same-admission group (2%; risk ratio 0.27; 95% CI 0.08 to 0.92; p=0.03). These 15 patients were readmitted for a median of 6 days (IQR 4 to 10) and did not develop pancreatic necrosis or organ failure. In the same admission group, a 75-year-old patient with a recent carotid endarterectomy died at home one week after cholecystectomy because of ischemic stroke.

In the interval group, 62 patients (51%) of 121 responding patients reported gallstone colics before cholecystectomy, irrespective of the need for readmission, versus 3 patients (3%) of 93 responding patients in the same-admission group (risk ratio 0.06; 95% CI 0.02 to 0.19; p<0.0001). In the interval group this was reported as “severe pain” by 39 out of 62 patients (63%). (Table S2 in the Supplementary Appendix).

Length of hospital stay after randomisation did not differ between groups (Table 2). Difficulty of cholecystectomy, the number of conversions, or healthcare use did not differ between the groups (details on the secondary endpoints and cholecystectomies are provided in the Supplementary Appendix).

Safety endpoints

In each group one patient developed a cystic duct leakage. This was treated by endoscopic sphincterotomy in one patient and by percutaneous catheter drainage in the other. A hematoma was evacuated by percutaneous drainage in one patient in the interval group, and by laparoscopic drainage in another patient in the same-admission group. No differences in the number of other complications that needed treatment were seen (Table 2).

Table 2. Primary, secondary and safety endpoints

	Interval cholecystectomy (N=136)	Same-admission cholecystectomy (N=128)	Risk Ratio (95% CI)	p Value
Primary Endpoint; No. (%)				
Mortality or readmission for gallstone-related complications	23 (17)	6 (5)	0.28 (0.12-0.66)	0.002
Secondary Endpoints				
Readmission for gallstone-related complications; No. (%)				
Recurrent pancreatitis	12 (9)	3 (2)	0.27 (0.08-0.92)	0.03
Cholecystitis	2 (1)	0		0.50
Choledocholithiasis needing ERCP	2 (1)	1 (1)	0.53 (0.05-5.79)	1.00
Gallstone colics	7 (5)	2 (1)	0.30 (0.06-1.43)	0.17
Mortality	0	1 (1)		0.48
Patients reporting colics during waiting period; No. (%)*	62 (51)	3 (3)	0.06 (0.02-0.19)	<0.0001
Difficulty of cholecystectomy; median (IQR)	6 (4-7)	6 (4-7)		0.70
Conversion to open cholecystectomy; No (%)¶	4 (3)	5 (4)	1.31 (0.36-4.77)	0.74
Operating time; median (IQR)	60 (44-78)	58 (44-70)		0.47
Total length of stay after randomisation; median (IQR)	3 (2-5)	3 (2-4)		0.94
Need for ICU admission; No. (%)	1 (1)	1 (1)		1.00
Safety Endpoints; No. (%)				
Cystic duct leakage	1 (1)	1 (1)		1.00
Bleeding needing reoperation or transfusion; No. (%)	1 (1)	1 (1)		1.00
Need for additional intervention				
Surgical	0	1 (1)		0.48
Endoscopic	0	1 (1)		0.48
Radiological	2 (1)	0		0.50
Pneumonia	0	2 (1)		0.23
Pulmonary embolism§	1 (1)	0		1.00

CI: Confidence Interval. N/A: Not applicable. ICU: Intensive Care Unit. SD: standard deviation. IQR: Interquartile range. ERCP: Endoscopic Retrograde Cholangiopancreatography.
* Interval cholecystectomy N=121, same-admission cholecystectomy N=93
¶ 4 patients in interval and 2 in same-admission group not included in analysis due to primary open cholecystectomy.
§Endpoint not previously defined in the protocol

Subgroup analysis

In a subgroup analysis, formal statistical tests showed no interaction between the different subgroups and the effect of same-admission cholecystectomy in the occurrence of the primary endpoint ($p>0.05$ for all). In the subgroup of patients who had undergone endoscopic sphincterotomy, the primary endpoint occurred in seven of 42 patients (17%) compared with one of 35 in the same-admission group (3%; $p=0.07$; Table S4 in the Supplementary Appendix). In the interval group, one patient developed recurrent pancreatitis, two cholecystitis, one choledocholithiasis, and three were readmitted for gallstone colic. One patient in the same-admission group was readmitted for choledocholithiasis.

DISCUSSION

This study demonstrates that in patients with mild gallstone pancreatitis, same-admission cholecystectomy reduces the risk of recurrent gallstone-related complications, including pancreatitis. The very low incidence of cholecystectomy-related complications suggests that cholecystectomy can be done safely during the same hospital admission.

Several observational and mostly retrospective studies also showed a reduced risk of gallstone-related complications following same-admission cholecystectomy in mild gallstone pancreatitis.[12,16,18] However, because of their non-randomised design, these studies are prone to selection bias. For example, elderly patients, patients with considerable co-morbidity, or patients with a more severe course of pancreatitis may have undergone interval cholecystectomy. Only one small, randomised study has been done on timing of cholecystectomy in patients with mild gallstone pancreatitis.[28] In this trial patients were randomised between cholecystectomy within 48 hours and cholecystectomy after 48 hours after admission. The study was designed with length of hospital stay as primary endpoint and was not powered to detect differences in clinically relevant outcomes such as recurrent gallstone-related complications. Moreover, cholecystectomy within 48 hours after admission in gallstone pancreatitis is controversial because patients may still develop pancreatic necrosis or organ failure during this phase of the disease, which both are considered contraindications for early surgery.[15,29,30] Conversely, the randomisation criteria as applied in this study (most notably a C-reactive protein concentration of <100 mg/l) may have unnecessarily increased length of stay in some patients. Therefore, although our study has demonstrated the benefit of performing cholecystectomy before discharge, future studies should be directed at exploring the optimal timing of cholecystectomy during a hospital stay.

Although current guidelines recommend conservative management in case of mild gallstone pancreatitis without cholangitis, quite a large percentage of patients in our study population underwent endoscopic sphincterotomy. However, these rates are similar to those reported in large, nationwide studies from the United Kingdom and

United States.[7,12,18] In view of the protective effect of sphincterotomy on the recurrence of pancreatitis, this may have moderated the contrast in primary endpoints between the groups in favour of interval cholecystectomy.[18] More importantly, our results showed that these patients remained at risk for recurrent gallstone-related complications even after sphincterotomy. This finding differs from previous retrospective studies that suggested that patients after sphincterotomy do not need to undergo early cholecystectomy.[31] Although sphincterotomy may reduce the risk of recurrent pancreatitis, it evidently does not provide adequate protection from other events such as cholecystitis and colics to warrant interval cholecystectomy.[10,17,18] The findings of our study are in line with a recent meta-analysis on prophylactic cholecystectomy after sphincterotomy for gallstone-related complications other than pancreatitis.[32] Some have advocated the use of endoscopic sphincterotomy as a bridge to cholecystectomy in patients with more severe pancreatitis, complicated by local complications such as parenchymal necrosis or peripancreatic fluid collections.[31,33] This issue has not been addressed in prospective trials and needs further study.

Although our study was not powered to detect significant differences in cholecystectomy-related complications (e.g. bile duct leakage), the overall low incidence of these complications challenges the notion that cholecystectomy in the early phase after recovery from acute pancreatitis is not safe.[15,30] This hypothesis is supported by the similar scores of surgical difficulty obtained between the same-admission and interval group. Studies on patients with other gallstone-related diseases such as cholecystitis or choledocholithiasis also showed no differences in technical difficulty between early and delayed cholecystectomy.[34,35] Nevertheless, large, population based studies may provide more comprehensive data for a definitive appraisal of the relative risk of surgical complications between same-admission and interval cholecystectomy.

Same-admission cholecystectomy has several benefits for both patients and healthcare providers.

Foremost, the risk of readmission for recurrent pancreatitis and other gallstone-related complications is minimised. Furthermore, same admission cholecystectomy prevents disabling colics that would otherwise have occurred in more than half of those patients awaiting elective surgery. An additional advantage is that both treatment and prevention of future gallstone-related complications for acute pancreatitis is provided during a single hospital stay. From a healthcare utilisation perspective, however, widespread implementation of this strategy may be challenging, since it demands a shift from elective to acute-care surgery, which will necessitate a change in both the mindset towards the urgency of cholecystectomy in this particular patient group and in logistics and infrastructure. In the setting of a randomised trial, same-admission cholecystectomy did not prove an obstacle for the 23 participating Dutch centres, but

this obviously does not guarantee worldwide implementation. However, several recent international studies have shown that quite straightforward organisational adjustments, such as direct admission to the surgical ward, can lead to improved efficiency in care for gallstone pancreatitis patients.[7,14,36] With respect to external validity, we should note that our results can not be extrapolated to patients over 75 years of age and ASA class III or any patients with a higher ASA classification. These patients are poor surgical candidates in whom the risk of perioperative complications can outweigh the long-term protective effect of cholecystectomy, especially if endoscopic sphincterotomy has already been done. The optimum strategy in this vulnerable patient group needs further investigation.

In conclusion, the results of this multicentre trial show that same-admission cholecystectomy in patients with mild gallstone pancreatitis was safe and reduced the risk of recurrent gallstone-related complications, as compared with interval cholecystectomy.

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Supplementary Appendix to manuscript:

Same-admission *versus* interval cholecystectomy for mild gallstone pancreatitis: a multi-centre randomised controlled trial

Additional information:

Additional information: definitions

In absence of gallstones or sludge on imaging, and not other cause for pancreatitis, gallstone pancreatitis was defined by a serum alanine aminotransferase (ALT) at least twice the level of normal *and* exceeding the aspartate aminotransferase (AST) level.[1,2] Bile duct injuries were classified according to the Amsterdam criteria (see Box S1).[3] Organ failure was defined according to the modified Marshall score, as proposed in the revised Atlanta classification.[4] Concerning the secondary end points, for recurrent pancreatitis the same criteria as for regular pancreatitis were used. The diagnosis of cholecystitis and cholangitis was made using the 2007 Tokyo guidelines (with modifications to the cholangitis criteria).[2,5] For the diagnosis of gallstone colics the Rome criteria were used.[6] In patients in whom chronic pancreatitis was suspected, the diagnostic criteria from the M-ANNHEIM classification system were applied.[7]

Additional information: treatment allocation

The median number of days between admission and cholecystectomy was 32 in the interval group (interquartile range [IQR] 29-37) and 7 in the same-admission group (IQR 5-10; $p<0.0001$). The median number of days between sphincterotomy and randomisation was 4 days in the interval group (IQR 2-6) and 5 days in the same-admission group (IQR 2-8; $p=0.38$).

In 22 patients in the interval group, the time-window was not met due to various reasons: in 17 patients because of logistical issues. In 5 patients cholecystectomy was postponed due to medical issues: in 1 patient cholecystectomy was suspended in order to recuperate from severe colics, 1 patient underwent elective ERCP for choledocholithiasis and 1 experienced a psychosis. In the remaining 2 patients other medical conditions were treated before cholecystectomy.

Nine patients in the same-admission group underwent cholecystectomy outside the 72-hour time window: 3 patients were operated on the fourth day after randomization day due to scheduling difficulties and 1 after 17 days for personal reasons. In 3 others the surgeon postponed cholecystectomy, deeming surgery unsafe after palpating extensive infiltration of the tissue surrounding the gallbladder. In the remaining 2 patients the operation was suspended due to medical reasons; 1 patient had high risk of bleeding due to the use of multiple platelet aggregation inhibitors. The second patient developed symptoms of carotid artery occlusion on the day of randomization for which he first underwent carotid endarterectomy.

Additional information: imaging studies and gallstone aetiology

Abdominal ultrasound was performed prior to randomisation in 241 out of the 264 patients (91%), 45 underwent abdominal CT (17%), endoscopic ultrasound in 20 (8%) and magnetic resonance cholangiopancreatography in 35 patients (13%) (Table S1). Gallstones or sludge were found in 260 patients (98%), a dilated common bile duct

in 2 (diameter of 9 and 11mm on ultrasound and computed tomography, respectively; 1%) and elevated ALT levels in 2 patients (1%). In these last 2 patients, imaging studies were inconclusive for gallstones or sludge, but they were clinically suspected of gallstone disease and had exceedingly high alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serum levels (ALT 945 IU/l with AST 474 IU/l and ALT 453 IU/l with AST 171 IU/l, respectively).

Additional information: assessment of the probability of choledocholithiasis

A risk assessment of the presence of common bile duct stones was performed in which patients have a high probability (>50%) of choledocholithiasis and should undergo preoperative evaluation of the bile duct when:[9]

1. an intraductal gallstone is present on imaging *or*
2. serum bilirubin levels exceed 70 µmol/l *or*
3. imaging reveals a common bile duct diameter exceeding 6mm *and* a serum bilirubin level between 30 and 70 µmol *or*
4. the patient exhibits signs of ascending cholangitis.

The central study coordinator encouraged a proactive bile duct evaluation strategy whenever the suspicion of choledocholithiasis arose. However, the final decision for performing ERCP with or without sphincterotomy was left to the discretion of the treating physician.

Of the 264 patients, 29 patients had high risk of choledocholithiasis due to bile duct stones on imaging, 28 of whom underwent ERCP prior to cholecystectomy (24 with stone extraction). The last patient was managed conservatively, as the gallstone seen previously on abdominal ultrasound was not detected on MRCP 5 days later and the bilirubin declined spontaneously to under 30 µmol/l. The patient underwent an uncomplicated cholecystectomy and had an uneventful recovery.

An additional 50 patients had bilirubin levels exceeding 70 µmol/l without intraductal stones on imaging. Of these, 20 were treated with ERCP (13 with stone extraction) while in the remaining 30 patients, 28 showed normal bilirubin levels (i.e. <30 µmol/l) or receding bile duct diameters on new imaging over the next few days, indicative of spontaneous bile duct clearance. One of these patients was nonetheless readmitted postoperatively due to gallstone colics and ERCP was performed. Of the other two conservatively treated patients, one had asymptomatic but persisting high bilirubin levels until the day of randomisation (110 µmol /l) while the other had a common bile duct of 7mm on MRCP along with a declining serum bilirubin level of 35 µmol/l on the day of randomisation. These two patients had uneventful recoveries.

Furthermore, 25 patients had common bile duct dilatation on imaging with bilirubin levels between 30 and 70 µmol/l, without intraductal stones. In 11 ERCP

was performed (6 with stone extraction), while the remaining 14 recovered with conservative treatment, with normalised bilirubin levels at the time of randomisation (i.e. <30 μmol/l). All had uneventful recoveries.

No patients in the study developed cholangitis.

In summary, 104 patients (39%) were at high risk of choledocholithiasis at some point before randomisation. Of these, 59 underwent bile duct evaluation through ERCP while 43 out of the remaining 45 patients had spontaneous resolution of radiologic or biochemical signs of choledocholithiasis and therefore did not need bile duct evaluation. The two patients who were at risk of choledocholithiasis at the time of randomisation, according to the Maple criteria, recovered without any signs of potentially retained common bile duct stones.

Additional information: gallstone colic questionnaires and patient reported outcomes

After randomization, all patients received a diary with instructions to document colics they experienced in the following three months. A second diary was provided during follow up to document the next three months. Patients were instructed to rate the pain on a 0 to 10 numeric rating scale (NRS). Responses in the gallstone diaries were categorized as 'no pain' (NRS: 0), 'mild pain' (NRS: 1 to 3), 'moderate pain' (NRS: 4 to 6) and 'severe pain' (NRS: 7 to 10).[10]

Gallstone diaries were received from 103 patients in the interval group, with another 18 patients reporting no complaints at follow-up by telephone before cholecystectomy (total response rate 89%). In the same-admission group diaries were received from 93 patients, with an additional 13 in the following 3 months (total response rate 91%). No differences in post-procedural pain scores were found (data not shown). The responses are presented in Table S1 using the χ^2 test for categorical data.

Additional information: surgeon reported outcomes

Surgeons with at least 100 laparoscopic interventions in the past 5 years carried out or supervised 236 of the 265 operations (89% in both groups; p=0.96). Difficulty of cholecystectomy was rated similar between groups, although more cholecystectomies were scored 8 or higher in the interval group (15% versus 19%, p=0.73). Difficult dissection (both 37%), conversion (3% interval versus 4% same-admission) and operating time (60 minutes interval versus median 58 minutes same-admission) were similar between groups.

In 17 patients, an intraoperative cholangiography (IOC) was performed: 9 in the interval and 8 in the same-admission group. Median duration of IOC was similar (13 and 14 minutes, respectively, p=0.28) No stone extractions were performed and no bile duct injuries exposed. In 1 patient in the interval group a filling defect was seen on IOC that was managed conservatively. The post-hoc analysis did not reveal significant

differences in the primary end point between patients in who underwent the procedure was performed and in those who did not. The primary endpoint occurred in 26 of 246 patients (11%) who did not undergo IOC versus in 3 of 17 patients who did (18%; risk ratio 1.67; 95% confidence interval 0.56 to 4.96; p=0.4).

Additional information: timing of readmissions

In the interval group, 18 of the 21 readmissions (78%) occurred within 3 weeks after the first discharge. In the same-admission group all primary end points occurred within 3 weeks after cholecystectomy. Previous endoscopic sphincterotomy (ES) had no influence on the median number of days to readmission (ES; 9 days versus No ES; 15 days, p=0.11).

Additional information: length of stay

The median number of days between admission and randomisation was 5 in both groups (interquartile range [IQR] same-admission group 3-8, IQR interval 3-9). The median number of days between randomisation and discharge in the same-admission group was 2 (IQR 2-3). As mentioned in Table 1 in the manuscript, cholecystectomy was performed after a median of 1 day in this group (IQR 1-2). Almost all patients in the interval group were discharged on the day of randomisation (median 0, IQR 0-1). The median length of stay for elective cholecystectomy was 2 days (IQR 1-2). Furthermore, in the same-admission group, there were a few patients with lengthy admission periods due to various complications (e.g. bleeding, pneumonia, see the figure below). Median length of stay after randomisation was 2 days in both groups if readmissions were left out, but this increased to 3 when readmission days were included.

Additional information: Costs

Costs were based on the number of admission days, costs of surgery, radiological and endoscopic procedures, emergency room and outpatient visits and indirect costs through missed hours of work. Table S3 contains an overview of consumption of these healthcare resources.

We found that total mean costs for patients in the same-admission group were €4993, compared with €5226 in the interval group (cost difference -€234, 95% confidence interval -€1249 to €738). The mean direct medical costs were slightly higher in the same-admission group due to the number of days of admission (€3389 same admission versus €3224 interval; cost difference €144, 95% CI -€393 to €722). Indirect costs on account of missed hours of work were lower in the same-admission group: €1604 versus €1982 in the interval group (cost difference -€378, 95%CI -€1045 to €251).

Box S1: List of definitions

Gallstone aetiology	Gallstones or sludge on imaging
	Bile duct dilatation (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old)
	ALT levels raised >2 times upper level of normal *and* higher than ALT
Bile duct injury	Type A: cystic duct leaks or leakage from aberrant or peripheral hepatic radicals;
	Type B: major bile duct leaks with or without concomitant biliary strictures;
	Type C: bile duct strictures without bile leakage;
	Type D: complete transection of the duct with or without excision of some portion of the bile duct.
Gallstone related complications	
Cholecystitis	Local signs of inflammation: positive Murphy's sign or right upper quadrant mass, pain or tenderness
	Systemic signs of inflammation: fever, elevated C-reactive protein or elevated white blood cell count
	Signs of local and systemic inflammation with characteristics of cholecystitis on imaging
Cholangitis	Serum total bilirubin level >40 µmol/l (>2.3 mg/dl) or dilated common bile duct (>8 mm) on imaging *and*
	Temperature >38.5°C
Symptomatic choledocholithiasis	Biochemical signs of cholestasis with bile duct dilatation or intraductal gallstones on imaging
Gallstone colic	Upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30 minutes

Table S1. *Data on imaging studies prior to randomisation.*

Characteristic	Interval cholecystectomy (N=136)	Same admission cholecystectomy (N=128)
Imaging studies prior to randomisation; No. (%)		
Abdominal ultrasound	126 (93)	115 (90)
Endoscopic ultrasound	11 (8)	9 (7)
Computed tomography	26 (19)	18 (14)
Magnetic resonance cholangiopancreatography	18 (13)	17 (13)
Biliary aetiology; No. (%)		
Gallstones or sludge	134 (98)	126 (98)
Dilated common bile duct on imaging*	1 (1)	1 (1)
Biochemical data§	1 (1)	1 (1)

*Diameter of the common bile duct of >8 mm in patients ≤75 years old or >10 mm in patients >75 years old.
§ Serum alanine aminotransferase of at least 2 times the upper limit of normal *and* higher than serum aspartate aminotransferase level

Table S2. Gallstone colics before cholecystectomy as reported in the gallstone questionnaire

	Interval cholecystectomy (N=121)	Same-admission cholecystectomy (N=93)	p value
Pain before cholecystectomy*; N (%)			<0.0001
Mild pain	10 (8)	1 (1)	
Moderate pain	13 (11)	0	
Severe pain	39 (32)	2 (2)	

*Mild pain: NRS 1 to 3; Moderate pain: NRS 4 to 6; Severe pain: NRS 7 to 10.

Table S3. Healthcare utilization after randomization

Healthcare utilization	Interval cholecystectomy (N=136)	Same-admission cholecystectomy (N=128)	p value^
Endoscopic procedures			
Gastroscopy	4 (0-1)	5 (0-1)	0.67
EUS	3 (0-1)	0	0.09
ERCP	7 (0-1)	3 (0-1)	0.23
Colonoscopy	3 (0-1)	1 (0-1)	0.60
Radiology			
Ultrasound	34 (0-4)	23 (0-3)	0.34
X-ray (chest and abdominal)	10 (0-2)	22 (0-4)	0.20
CT scans	11 (0-2)	16 (0-3)	0.53
MRCP	1 (0-1)	4 (0-1)	0.20
Other			
ER visits	10 (0-3)	5 (0-1)	0.81

^ p value calculated with Mann-Whitney U test
Continuous data are total number per study group and range per patient.
EUS denotes endoscopic ultrasound; ERCP endoscopic retrograde cholangiopancreatography; CT computed tomography; MRCP magnetic resonance cholangiopancreatography; ER emergency room.

Table S4. Distribution of endpoints in predefined subgroups.

		Interval cholecystectomy (N=42)	Same-admission cholecystectomy (N=35)	Risk ratio (95% CI)	p Value
ES	Primary end point; No. (%)	7 (17)	1 (3)	0.17 (0.02-1.33)	0.07
	Recurrent pancreatitis	1 (2)	0		
	Cholecystitis	2 (5)	0		
	Choledocholithiasis requiring ERCP	1 (2)	1 (3)	1.20 (0.08-18.50)	
	Colics	3 (7)	0		
	Mortality	0	0		

		Interval cholecystectomy (N=94)	Same-admission cholecystectomy (N=93)	Risk ratio (95% CI)	p Value
No ES	Primary end point; No. (%)	16 (17)	5 (5)	0.32 (0.12-0.83)	0.02
	Recurrent pancreatitis	11 (12)	3 (3)	0.28 (0.08-0.96)	
	Cholecystitis	0	0		
	Choledocholithiasis requiring ERCP	1 (1)	0		
	Colics	4 (4)	2 (2)	0.51 (0.09-2.69)	
	Mortality	0	1 (1)		

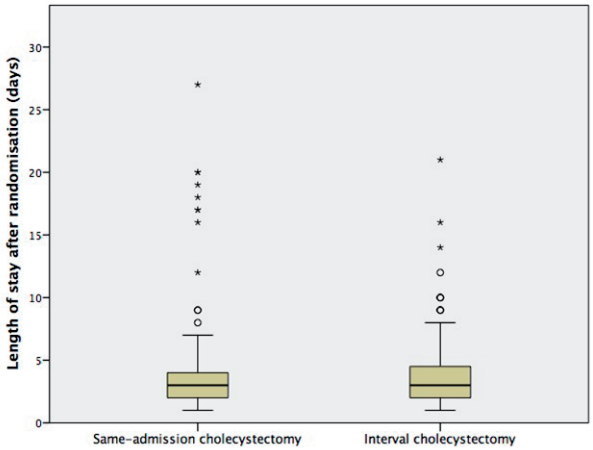
Table S4 (continued)

		Interval cholecystectomy (N=16)	Same-admission cholecystectomy (N=15)	Risk ratio (95% CI)	p Value
Age 75 or older	Primary end point; No. (%)	2 (13)	1 (7)	0.53 (0.05-5.29)	1.00
	Recurrent pancreatitis	1 (6)	0		
	Cholecystitis	1 (6)	0		
	Choledocholithiasis requiring ERCP	0	0		
	Colics	0	0		
	Mortality	0	1 (7)		

		Interval cholecystectomy (N=120)	Same-admission cholecystectomy (N=113)	Risk ratio (95% CI)	p Value
Age under 75	Primary end point; No. (%)	21 (18)	5 (4)	0.25 (0.10-0.65)	0.002
	Recurrent pancreatitis	11 (9)	3 (3)	0.29 (0.08-1.01)	
	Cholecystitis	1 (1)	0		
	Choledocholithiasis requiring ERCP	2 (2)	1 (1)	0.53 (0.05-5.78)	
	Colics	7 (6)	2 (2)	0.30 (0.06-1.43)	
	Mortality	0	0		

*ES denotes endoscopic sphincterotomy of sphincter of Oddi; ERCP: endoscopic retrograde cholangiopancreatography. Tests for interaction were not significant (p=0.60 for endoscopic sphincterotomy, p=0.55 for age over 75).

Figure S1. Length of stay after randomisation per treatment group**.**



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CHAPTER 4

Cost-effectiveness of same-admission *versus* interval cholecystectomy after mild gallstone pancreatitis in a multicentre, randomised controlled trial

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Cost-effectiveness of same-admission *versus* interval cholecystectomy after mild gallstone pancreatitis in a multicentre, randomised controlled trial

ABSTRACT

Background: Same-admission cholecystectomy is indicated after gallstone pancreatitis to reduce the risk of recurrent disease or other gallstone-related complications but its impact on overall costs are unclear. This study analysed cost-effectiveness of same-admission versus interval cholecystectomy after mild gallstone pancreatitis.

Methods: In a multicentre RCT (Pancreatitis of biliary Origin: optimal timiNg of CHOlecystectomy; PONCHO) patients with mild gallstone pancreatitis were randomized before discharge to either cholecystectomy within 72h ('same-admission cholecystectomy') or cholecystectomy after 25 to 30 days ('interval cholecystectomy'). Healthcare use of all patients was recorded prospectively with clinical report forms. Unit costs of used resources were determined and patients completed multiple Health and Labour Questionnaires to record pancreatitis-related absence from work. Cost-effectiveness analyses were performed from societal and health care perspectives with the costs per readmission prevented as primary outcome with a time horizon of 6 months.

Results: All 264 trial participants were included in the present analysis, 128 randomized to same-admission cholecystectomy and 136 to interval cholecystectomy. Same-admission cholecystectomy reduced the risk of acute readmission for recurrent gallstone-related complications from 17 to 5% (p=0.002). Mean costs from a societal perspective were €234 less per patient in the same-admission cholecystectomy group (95% confidence interval [CI] -1249 to 738). Same-admission cholecystectomy was superior to interval cholecystectomy with a societal incremental cost-effectiveness ratio of -€1918 to prevent one readmission for gallstone-related complications.

Conclusion: From a societal perspective same-admission cholecystectomy was both more effective and less costly than interval cholecystectomy.

INTRODUCTION

With its growing incidence, acute pancreatitis is becoming an increasingly large burden on healthcare services and their resources worldwide[1-3]. The disease leads to 26 000 annual hospital admissions in England and 270 000 in the United States (US), where it has become the most common gastrointestinal reason for emergency admission[4, 5]. Epidemiological studies are increasingly being published worldwide, and report growing incidence of acute pancreatitis ranging between 13 and 45 cases per 100 000 persons per year[6]. The majority of patients with pancreatitis need only supportive care and recover within 1 week[7]. The remainder, approximately 15%, develop more severe disease, characterised by (peri)pancreatic necrosis, fluid collections and organ failure. Long hospital stays, intensive care unit admission and various diagnostic and therapeutic procedures often result in high treatment costs in these patients[8]. The volume of patients with mild disease and the expensive care of patients with severe disease means that acute pancreatitis generates vast financial costs, amounting to over $2 billion in the US in 2010[9].

In up to 62% of patients, migrating gallstones or sludge obstructing the pancreatic duct are the cause of pancreatic inflammation[10]. Cholecystectomy is indicated in these patients to reduce the risk of recurrence or other gallstone related complications (biliary events). Several studies have shown that cholecystectomy should be performed before discharge to minimise this risk[11-14]. However, reports from several international audits have shown that cholecystectomy is often not carried out until 6 weeks after discharge, and not at all in many patients[15-17]. Delaying surgery exposes the patient to a higher risk of readmission for recurrent biliary events. For this reason, cholecystectomy is recommended during the same admission by the international guidelines, or at least within two weeks after discharge according to the British Society of Gastroenterology[18-20]. Same-admission cholecystectomy may reduce the number of readmissions but its impact on healthcare costs is unclear. Two recent model-based studies from the United Kingdom found that early cholecystectomy could be cost-effective, but substantial adjustments of logistics and resource allocation would be needed[21, 22].

The aim of this study was to carry out a cost-effectiveness analysis on the two strategies using actual resource data from a Dutch randomised trial.

METHODS

Patients and treatment protocol

The rationale and design for the clinical trial[23] and the primary endpoint results[11] have been described previously. In brief, patients with a first episode of mild biliary pancreatitis were eligible for inclusion[7]. Among the 23 participating medical centres were seven university hospitals and 16 teaching hospitals. Randomization took place

when the treating physician foresaw discharge within 24 to 48 hours. Additional criteria for randomization included cessation of opioid analgesics, a normal oral diet and a maximal C-reactive protein serum level of 100 mg/l. Patients randomized to same-admission cholecystectomy underwent surgery within 72 hours after randomization, whereas patients in the interval group were discharged and planned for cholecystectomy 25 to 30 days later. The primary outcome was a combined endpoint of mortality *or* acute readmission for a biliary complication, defined as recurrent pancreatitis, cholecystitis, symptomatic choledocholithiasis requiring endoscopic retrograde cholangiopancreatography (ERCP) and biliary colic.

Design of the cost-effectiveness analysis

Cost-effectiveness analyses from societal and health care perspectives were performed with the costs per prevented acute readmission as primary outcome. Mortality was not included in this outcome, as only one elderly patient in the same-admission group died due to an unrelated cause. Costs until the moment of death were included for this patient. Direct medical and indirect medical and non-medical, pancreatitis-related costs during a follow-up period of six months after randomization were taken into account. For the reporting of this study, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines were adhered[24].

The following health care resources consumed after randomization were prospectively registered for each patient: the number of days of admission (on the general ward and intensive care unit [ICU]), surgical procedures, radiography (ultrasound, computed tomography [CT], plain X-rays, magnetic resonance imaging [MRI], radiological drainage procedures), endoscopic procedures (gastroscopy, enteral feeding tube placement, endoscopic retrograde cholangiopancreatography [ERCP], endoscopic ultrasound, colonoscopy), and the use of other medical services (outpatient clinic visits, telephonic consultations and emergency room visits). Volumes of haematological, biochemical or microbiological blood tests were not taken into account, as no differences were expected based on their low unit costs. For patients without any record of a visit in the outpatient clinic was found, the mean volume of the treatment group was imputed.

Unit costs for admission days (general ward and ICU), outpatient and emergency room visits were based on the 2010 Dutch manual for costing in health care research.[25] Unit costs of radiologic and endoscopic procedures were derived from the St. Antonius Hospital tariffs ledger, which included personnel, material and overhead costs. Unit costs for cholecystectomy were calculated from specialists' fees for surgeon and anaesthesiologist, personnel costs, purchase prices of materials used and overhead costs. As in the Netherlands personnel is entitled to overtime pay between 19.00 and 22.00 hours on weekdays and during the weekend, adjusted unit costs were calculated for surgery done during off hours. A correction was made for differences in overtime rate

between university and general hospitals. Unit costs were (general) price-indexed for the year 2013 and are presented in Table 1 in euros.

Costs were calculated as the product of the volumes of resources used and their respective unit costs. The main analysis includes costs made after occurrence of the primary outcome (*i.e.* the costs of readmission), but these downstream costs are also reported separately. No discounting was applied as follow-up consisted of 6 months.

Indirect non-medical costs

To enable calculation of indirect costs of sick leave from work, all patients were sent a Health and Labour Questionnaire (HLQ; Institute for Medical Technology Assessment, Erasmus University, Rotterdam, the Netherlands) at one and three months after randomization on which employment status and number of missed hours at work from that month were registered[26, 27]. Data from the second questionnaire were doubled to account for the number of missed hours in the second month after discharge. As no further cholecystectomy- or pancreatitis-related sick leave was expected from a clinical perspective, no questionnaires were issued for the last three months of follow up.

Missing questionnaires from non-responders over the age of 65 years were assessed as non-informative given the legal retirement age at the time of the study period of 65. For the non-responders under 66 years of age, missing data were handled by

Table 1. Baseline characteristics.

	Same-admission cholecystectomy (N=128)	**Interval cholecystectomy (N=136)**
Age in years; median (IQR)	53 (38-66)	54 (41-68)
Female sex; No. (%)	76 (59)	84 (62)
Body Mass Index (kg/m2); median (IQR)	27 (24-32)	28 (25-31)
Medical History; No. (%)		
Cardiovascular disease	23 (18)	21 (15)
Pulmonary disease	16 (12)	8 (6)
Chronic renal insufficiency	2 (2)	2 (2)
Diabetes	12 (9)	7 (5)
Endoscopic sphincterotomy prior to randomisation; No. (%)	37 (29)	42 (31)

IQR, interquartile range

imputing the mean of each group per questionnaire. The friction cost approach was used to value the total number of missed hours. Productivity loss was valued by multiplying the number of missed hours by the average wage per hour in 2013 (€32.68)[25].

Statistical analysis

Analyses were performed on the intention to treat principle. Group contrasts were assessed by calculating 95 % confidence intervals (CI) for the mean differences after bias-corrected, accelerated non-parametric bootstrapping, drawing 1000 samples of the same size as the original sample for each group. The incremental cost-effectiveness ratio for the two strategies was calculated by dividing the difference in mean costs per patient by the treatment effect (i.e. the difference in event rates of the primary end point). The results were visualized by means of a cost-effectiveness plane in which each of the quadrants represents one of the following four possible scenarios: same-admission strategy is more costly and more effective (upper right quadrant, Q1), same-admission strategy is costlier and less effective (upper left, Q2) same-admission strategy is cheaper and less effective (lower left, Q3), same-admission strategy is cheaper and more effective (lower right, Q4). A cost-effectiveness acceptability curve was drawn, showing the probability of same-admission cholecystectomy being cost-effective for various levels of willingness to pay per prevented acute readmission. The willingness-to-pay level at which about 95% of the decisions for same-admission cholecystectomy would be cost-effective was reported separately. Both societal and healthcare perspective curves are reported, the former including the costs of production loss. A sensitivity analysis was using gender and age-specific wages per lost working hour rather than a general average. An exploratory subgroup analysis was performed for patients below and at or above 66 years of age as the age of retirement.

RESULTS

Between December 2010 and August 2013, 266 patients in 23 Dutch hospitals were randomly assigned to same-admission (N=129) or interval (N=137) cholecystectomy. In the same-admission group one patient was lost to follow up. In the interval group, one patient was excluded due to an incorrect diagnosis of pancreatitis. Baseline characteristics were similar between the two groups (Table 1). Patients randomized to same-admission cholecystectomy underwent surgery a median of 1 day (interquartile range [IQR] 1 to 2 days) after randomization, compared with 27 days (IQR 26 to 29 days) in the interval group. In the latter group, one patient ultimately refused cholecystectomy.

The total and mean volumes per healthcare item were calculated for each group (Table 2). In the same-admission cholecystectomy group, mean societal costs per patient were €4993, compared with €5226 in the interval group (mean difference of -€234, 95%

Table 2. Mean volume and costs per patient.

	Same admission cholecystectomy (N=128)			Interval cholecystectomy (N=136)			Mean cost difference (€)	95 % CI
	N	Mean volume	Mean €	N	Mean volume	Mean €		
Hospital stay			1 929			1 784	144	(-319, 648)
General ward (days)	523	4.09	1 910	514	3.78	1 767	143	
Intensive care unit (days)	1	0.01	18	1	0.01	17	1	
Surgery			1 248			1 220	28	(9, 55)
Laparoscopic cholecystectomy	128	1.00	1 239	135	0.99	1 220	19	
Office hours	101	0.79	969	132	0.97	1 192	-223	
Off hours	27	0.21	271	3	0.02	28	242	
Diagnostic laparoscopy	1	0.01	9	0	0.00	0	9	
Radiology			58			49	9	(-28, 49)
Abdominal ultrasound	23	0.18	14	34	0.25	19	-5	
X-ray thorax	19	0.15	8	5	0.04	2	6	
X-ray abdomen	3	0.02	1	5	0.04	2	-1	
CT scan	16	0.13	27	10	0.07	17	10	
MRCP	4	0.03	8	1	0.01	2	6	
Ultrasound guided drainage	0	0.00	0	1	0.01	3	-3	
CT guided drainage	0	0.00	0	1	0.01	3	-3	

Endoscopy			47			73	-26	(-85, 32)
Gastroscopy	5	0.04	16	4	0.03	12	4	
Enteral feeding tube	2	0.02	7	1	0.01	3	4	
ERCP	3	0.02	21	7	0.05	45	-25	
Endoscopic ultrasound	0	0.00	0	3	0.02	3	-3	
Colonoscopy	1	0.01	4	3	0.02	10	-7	
Other medical consumption			107			118	-11	(-34, 14)
Outpatient visits	178	1.39	97	200	1.47	102	-5	
Telephonic consultations	34	0.27	4	41	0.30	5	-1	
Emergency room visits	5	0.04	6	10	0.07	11	-5	
Health care costs per patient			3 389			3 244	144	(-393, 722)
Indirect non-medical costs								
Productivity loss (hours)	6283	49.08	1 604	8249	60.65	1 982	-378	(-1045, 251)
Societal costs per patient			4 993			5 226	-234	(-1249, 738)

confidence interval [CI] -1294 to 738; Table 2). The number of days of admission following randomization was slightly higher in the same-admission group (mean of 4.1 versus 3.8 days, see also Figure S1 in the supplementary appendix). Because of the 72-hour time limit for same-admission cholecystectomy, more patients in this group underwent cholecystectomy out of hours. A diagnostic laparoscopy was performed post cholecystectomy in one patient in the same-admission group for suspected bleeding. Overall, health care costs were marginally higher (mean difference of €144, 95% CI -393 to 722) in the same-admission group, mainly due to the difference in hospital length of stay. The mean (downstream) costs of readmission per randomised patient were €271 in the same-admission group versus €471 in the interval group, again mostly as a result of admission days (mean of 14 days in the same-admission group versus 6 in the interval group). The relative impact of each cost component on the total costs for each treatment group can be found in the Supplementary Appendix.

Health and Labour Questionnaires

The response rates of the two Health and Labour Questionnaires were 82.5% and 73.4%, respectively. There were no differences between groups in response rates or baseline characteristics, including employment status and educational level (data not shown). Patients in the same-admission group reported fewer missed hours of work, and so lower indirect costs of productivity loss (-€378, 95% CI -1045 to 251).

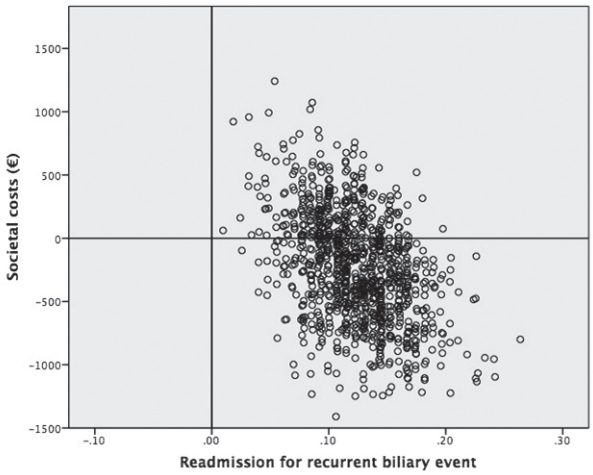
Clinical outcome and cost difference

The primary clinical endpoint of mortality or acute readmission for biliary events occurred in 6 out of 128 patients (4.7%) in the same-admission group, compared with 23 out of 136 patients (16.9%) randomized to interval cholecystectomy (absolute risk reduction of 12.2%; $p<0.002$). The incremental societal costs per prevented readmission was -€1918 (-€234/0.122). Figure 1a shows the cost-effectiveness plane from the societal perspective. Most bootstrap results (69.8%) are in Q4, signifying both superior treatment effect and lower costs. A superior treatment effect (right half of the plane) was seen in all bootstraps. If society would be willing to pay a maximum of €5000 to prevent the next case of acute readmission for recurrence of a biliary event, the probability of same-admission cholecystectomy being cost-effective was 94.5% (Figure 1b).

Scenario analysis

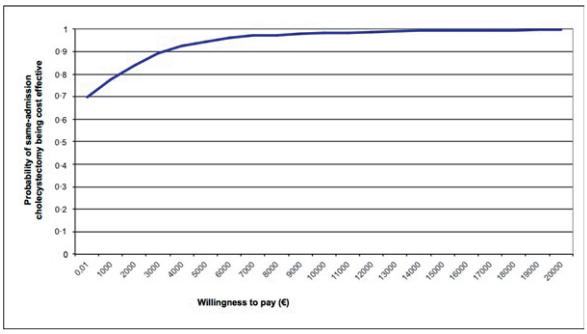
When only the health care costs were considered, the incremental cost-effectiveness ratio increased to €1180 per acute readmission prevented (€144/0.122). In the cost-effectiveness plane all bootstrap results again were in the right half of the plane, but with 70.3% of the cases in Q1, signifying higher costs (Figure 2a). To achieve a 95% probability of same-admission cholecystectomy being cost-effective in this scenario would now require a willingness-to-pay of €7000 (Figure 2b).

Figure 1a. Cost-effectiveness plane from a societal perspective.



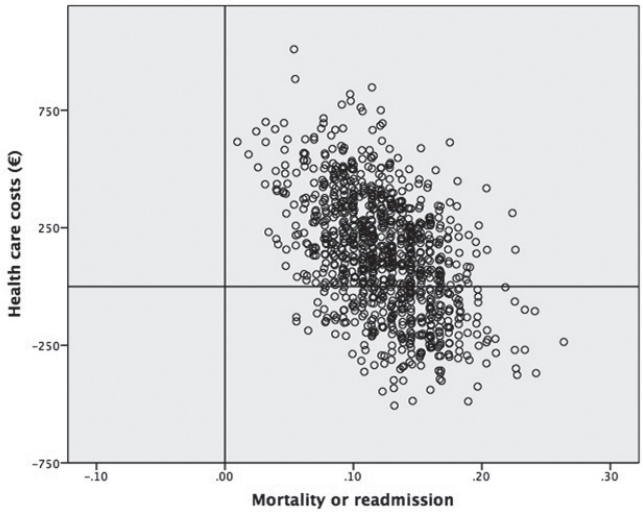
Cost effectiveness plane from a societal perspective at 6 months. Y-axis: difference in costs (i.e. positive costs denote more costs for same-admission cholecystectomy. X-axis: difference in effect (i.e. positive effect denotes readmissions prevented). The majority of bootstrap results (69.8 %) are in Q4, signifying both superior treatment effect and lower costs.

Figure 1b. Cost-effectiveness acceptability curve from a societal perspective.



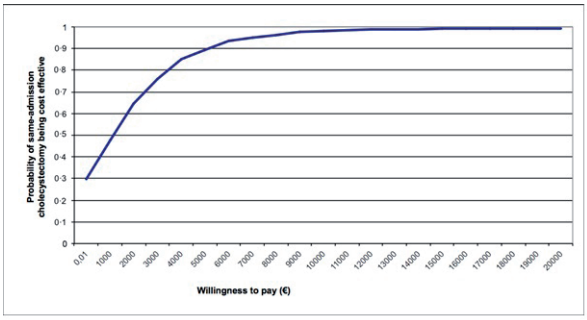
Cost-effectiveness acceptability curve, showing the probability that same-admission cholecystectomy is cost-effective for different values of the societal willingness to pay per readmission prevented.

Figure 2a. Cost-effectiveness plane from a health care perspective.



Cost effectiveness plane from a healthcare perspective at 6 months. Y-axis: difference in costs (i.e. positive costs denote more costs for same-admission cholecystectomy. X-axis: difference in effect (i.e. positive effect denotes readmissions prevented). The majority of the bootstrap results (70.3 %) are in Q1, signifying still a superior treatment effect but higher medical costs for same-admission cholecystectomy

Figure 2b. Cost-effectiveness acceptability curve from a health care perspective.



Cost-effectiveness acceptability curve, showing the probability that same-admission cholecystectomy is cost-effective for different values of the societal willingness to pay per readmission prevented. Costs of production losses are not taken into account.

Sensitivity analysis

Cost differences between treatment groups decreased if gender and age-specific wages rather than average wages per lost working hour were applied. The wages for males ranged from €19.33 for the 20-24 age group via €42.88 for the 55-59 age group to €42.60 for the 60-65 age group, whereas the wages for females ranged from €18.70 via €32.12 to €31.23 respectively (Table S2). The difference of -€378 (95% CI -1045 to 251) per patient for costs of productivity loss in favour of same admission cholecystectomy decreased to -€299 (95% CI -1039 to 513). The difference in societal costs per patient decreased from -€234 (95% CI -1249 to 738) to -€154 (95% CI -1202 to 879), resulting in an incremental societal costs per prevented readmission of -€1262 (-€154/0.122).

Subgroup analysis

Among patients under the age of 66, 5.2% (95% CI 1.1 to 10.6) of patients in the same-admission group and 20% (95% CI 13 to 27.3) of patients in the interval group were readmitted, with a difference in prevented readmissions of 14.8% (95% CI 5.6 to 24) in favour of the same-admission group. The incremental societal costs per prevented readmission were -€2311 (-€342/0.148; see also Table S3).

Among patients aged 66 or more, 3.1% (95% CI 0 to 9.4) and 8.3% (95% CI 0 to 18.3) patients in the same-admission and interval groups were readmitted respectively, with a difference in prevented readmissions of 5.2% (95% CI -6.3 to 16.7) tending in favour of the same-admission group. The incremental societal costs per prevented readmission were -€577 (-€30/0.052; Table S4).

DISCUSSION

In this cost-effectiveness analysis within a randomized controlled multicentre trial, same-admission cholecystectomy was more effective and overall less costly per patient by a mean of €234 than interval cholecystectomy in patients with mild gallstone pancreatitis. Health care costs were marginally higher in the same-admission group, but this difference was reversed by lower indirect costs on account of reduced missed hours at work. These results build substantial confidence in same-admission cholecystectomy not only being an effective, but also efficient treatment modality.

The economic effects of timing of cholecystectomy after mild gallstone pancreatitis have been explored in two previous studies. In a retrospective study from 2009, readmission costs of 21 patients were determined based on bed occupancy, radiology and other diagnostic testing[21]. These costs were compared with the theoretical costs of reserving a half-day operating list every fortnight, which would be needed to comply with the recommendations from the British Society of Gastroenterology. The authors concluded

that instigating such an operating list would both be cost neutral and facilitate surgery within the recommendations. In a model-based cost-utility analysis was performed comparing cholecystectomy within 3 days of admission, beyond 3 days but before discharge or elective cholecystectomy[22], both cholecystectomy within 3 days of admission and cholecystectomy before discharge generated less costs than elective cholecystectomy as a result of shorter length of stay and readmission costs.

The clinical results from the PONCHO trial have demonstrated that same-admission cholecystectomy reduces morbidity from recurrent gallstone-related complications, thereby decreasing the number of readmissions from 17 to 5 %[11]. In contrast with previous research, we did not find that same-admission cholecystectomy leads to a reduction in length of stay[12, 13, 28]. This may be the result of two factors. First, mean length of stay in this group was increased substantially by 7 patients with long admission periods, resulting from various types of complications (gallstone-related, cholecystectomy-related and others). Second, patients were eligible for randomization after normalization of biochemical signs of inflammation (*i.e.* a C-reactive protein level below 100 mg/l) and when discharge was expected within 24 to 48 hours. Furthermore, to assist surgical planning, a time window of 72 hours within randomisation was set for same-admission cholecystectomy. This resulted in 1 or 2 in-hospital waiting days in many patients in this group. Combined, these aspects of the trial design may have inadvertently led to admission periods longer than strictly necessary. If same-admission cholecystectomy is successfully implemented in daily practice, patients can be scheduled for cholecystectomy as soon as it becomes apparent that pancreatitis severity will remain mild. It is therefore likely that actual healthcare costs for same-admission cholecystectomy may be lower than we found in our study. Yet, we still observed an economic advantage in this group, as patients reported less days of sick leave. It is the author's belief that efficiency of care for these patients can improve substantially by creating clear pathways from admission to surgery. For example, admitting patients directly to a surgical ward has already been shown to decrease the time to surgery and overall healthcare costs[29]. By placing the patients under the direct care of a surgeon, fitness for surgery can be assessed on a daily basis. Likewise, hospitals in which high volumes of cholecystectomies are performed have been shown to adhere to the guidelines to a higher degree than low volume centres, signifying the importance of hospital infrastructure[30]. For lower volume centres, a possible solution would be to create fortnightly surgery lists, as described above[21].

Several limitations of the study should be addressed. A full economic evaluation from the societal perspective generally includes a cost-utility analysis with the costs per quality adjusted life year (QALY) as the primary outcome. No data were gathered with health utility instruments such as the EQ-5D, so a calculation of QALYs could not be derived empirically. The economic evaluation was therefore restricted to a cost-effectiveness

analysis with the costs per readmission as primary outcome. As a result, the presented data are valuable for assessment and comparisons of treatments for acute pancreatitis in particular and other areas in gastroenterology (or even in medicine as a whole) where the same outcome measures might apply.

Furthermore, for practical reasons, unit costs of in-hospital procedures were determined in a single Dutch hospital. Although this may only have a marginal negative impact on the external validity for the Netherlands is marginal, it may limit the applicability of the results to other countries. However, the similar proportions of the individual components of the health care costs suggest that same-admission cholecystectomy would be roughly cost neutral in any setting.

A third limitation is that no direct information from the second month after discharge was available because only two questionnaires were sent out. However, the moments of measurement were chosen based on discussions with clinicians about the process of patients' recovery and periods of relative stability, allowing for extrapolation of observed data.

Cost effectiveness analyses may not always translate well into different settings and should always be interpreted with caution. However, the treatment of patients with mild acute biliary pancreatitis is quite universal. Furthermore, as evident from Table 1, healthcare consumption after randomisation was similar between the two groups. The authors believe that these volumes can be used globally for comparative purposes. In the same-admission group, these costs were accrued primarily by a small number of patients with various complications. As such, the results can be seen as something of a worst-case scenario for same-admission cholecystectomy. Still, the strategy was more effective and approximately cost neutral in terms of direct medical costs. Regarding sick days, this aspect of the present analysis may be most susceptible to differences in other healthcare systems. However, it seems reasonable to assume that, from the employer perspective, same-admission cholecystectomy should be as effective, if not more, than interval cholecystectomy. It should further be noted that the applied friction cost method to productivity losses following the Dutch costing guideline coincides with the internationally more common human capital approach to productivity losses, because the durations of production losses were smaller than the current Dutch friction cost period of 85 days at maximum. Hence, no truncation of costs of productivity losses took place.

In conclusion, the present study is the first to compare actual instead of hypothetical costs for different strategies in patients with gallstone pancreatitis. We found same-admission cholecystectomy to be the superior treatment for patients with mild gallstone pancreatitis, both from clinical and economic perspectives. The economic benefits are potentially even higher when same-admission cholecystectomy is fully incorporated in the treatment protocol for gallstone pancreatitis.

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Supplementary Appendix to the manuscript

Cost-effectiveness of same-admission *versus* interval cholecystectomy after mild gallstone pancreatitis in a multicentre, randomised controlled trial"

Available on the website of the *British Journal of Surgery*

Additional information:

Table S1. Mean costs per unit.

	Cost per unit (€, adjusted for 2013)	**Source**
Hospital stay		
General ward (per day)	435	Dutch manual for costing (2010)
Intensive care unit (per day)	2183	Dutch manual for costing (2010)
Surgery		
Cholecystectomy (office hours)	1 228	Top down cost calculation
Cholecystectomy (irregular hours)	1 283	Top down cost calculation
Diagnostic laparoscopy	1114	Top down cost calculation
Radiology		
Abdominal ultrasound	76	Hospital ledger
X-ray thorax	52	Hospital ledger
X-ray abdomen	52	Hospital ledger
CT scan	216	Hospital ledger
MRI scan	279	Hospital ledger
Ultrasound guided drainage	437	Hospital ledger
CT guided drainage	437	Hospital ledger
Endoscopy		
Gastroscopy	405	Hospital ledger
Enteral feeding tube placement	459	Hospital ledger
ERCP	876	Hospital ledger
Endoscopic ultrasound	125	Hospital ledger
Colonoscopy	459	Hospital ledger
Other		
Outpatient clinic	69	Dutch manual for costing (2010)
Telephonic outpatient consultation	15	Dutch manual for costing (2010)
Emergency room visit	152	Dutch manual for costing (2010)
Indirect non-medical costs		
Productivity loss (per hour)	33	Dutch manual for costing (2010)

Table S2. Gender and age group specific productivity costs.

Age group	Male (€)	Female (€)
15-19	10.51	9.54
20-24	19.33	18.70
25-29	26.34	25.72
30-34	32.28	29.98
35-39	37.05	31.85
40-44	39.92	31.64
45-49	41.72	31.48
50-54	42.53	31.85
55-59	42.88	32.12
60-65	42.60	31.23

Figures are based on the 2009 gender and age group specific productivity costs published in the Dutch costing manual (Hakkaart et al, 2010), corrected for 2013.

Table S3. Mean volumes and costs per patient under 66 years old.

	Same admission cholecystectomy (N=96)			Interval cholecystectomy (N=100)				
	N	mean volume	mean €	N	mean volume	mean €	Cost difference (€)	95% CI
Hospital stay			1831			1650	181	(-317, 679)
General ward (days)	371	3.86	1807	353	3.53	1650	157	
Intensive care unit (days)	1	0.01	24	0	0.00	0	24	
Surgery			1240			1217	23	(-2, 48)
Laparoscopic cholecystectomy	96	1.00	1240	99	0.99	1217	23	
Office hours	75	0.78	958	97	0.97	1191	-223	
Off hours	21	0.22	282	2	0.02	26	256	
Diagnostic laparoscopy	0	0.00	0	0	0.00	0	0	
Radiology			52			38	14	(-25, 55)
Abdominal ultrasound	17	0.18	13	23	0.23	17	-4	
X-ray thorax	10	0.10	5	2	0.02	1	4	
X-ray abdomen	2	0.02	1	2	0.02	1	0	
CT scan	10	0.10	22	7	0.07	15	7	
MRCP	4	0.04	11	0	0.00	0	11	
Ultrasound guided drainage	0	0.00	0	0	0.00	0	0	
CT guided drainage	0	0.00	0	1	0.01	4	-4	

Endoscopy			59			57	2	(-66, 71)
Gastroscopy	4	0.04	17	2	0.02	8	9	
Enteral feeding tube	2	0.02	10	1	0.01	5	5	
ERCP	3	0.03	27	4	0.04	35	-8	
Endoscopic ultrasound	0	0.00	0	3	0.03	4	-4	
Colonoscopy	1	0.01	5	1	0.01	5	0	
Other medical costs			113			119	-6	(-38, 25)
Outpatient visits	142	1.54	103	145	1.53	101	2	
Telephonic consultations	29	0.30	5	26	0.26	4	1	
Emergency room visits	3	0.03	5	9	0.09	14	-9	
Health care costs per patient			3295			3081	214	(-361, 790)
Indirect non-medical costs								
Productivity loss (hours)	6283	65.54	2139	8249	82.47	2695	-557	(-1372, 258)
Societal costs per patient					5776		-342	(-1455, 771)

Table S4. Mean volumes and costs per patient of 66 years or older.

	Same admission cholecystectomy (N=32)			Interval cholecystectomy (N=36)				
	N	mean volume	mean €	N	mean volume	mean €	Cost difference (€)	95% CI
Hospital stay			2221			2156	65	(-830, 959)
General ward (days)	152	4.75	2221	161	4.47	2091	130	
Intensive care unit (days)	0	0.00	0	1	0.03	65	-65	
Surgery			1272			1229	43	(-22, 109)
Laparoscopic cholecystectomy	32	1.00	1239	36	0.99	1229	10	
Office hours	26	0.81	995	35	0.97	1191	-196	
Off hours	6	0.19	244	1	0.03	38	206	
Diagnostic laparoscopy	1	0.03	33	0	0.00	0	33	
Radiology			71			74	-3	(-89, 80)
Abdominal ultrasound	6	0.19	14	11	0.31	23	-9	
X-ray thorax	9	0.28	15	3	0.08	4	11	
X-ray abdomen	1	0.03	2	3	0.08	4	-2	
CT scan	6	0.19	40	4	0.11	24	16	
MRCP	0	0.00	0	1	0.03	7	-7	
Ultrasound guided drainage	0	0.00	0	1	0.03	12	-12	
CT guided drainage	0	0.00	0	0	0.00	0	0	

Endoscopy			13			122	-109	(-225, 8)
Gastroscopy	1	0.03	13	2	0.06	23	-10	
Enteral feeding tube	2	0.02	0	0	0.00	0	0	
ERCP	0	0.00	0	3	0.08	73	-73	
Endoscopic ultrasound	0	0.00	0	0	0.00	0	0	
Colonoscopy	0	0.00	0	2	0.06	26	-26	
Other medical costs			89			115	-26	(-54, 3)
Outpatient visits	36	1.16	78	55	1.53	105	-27	
Telephonic consultations	5	0.16	2	15	0.42	6	-4	
Emergency room visits	2	0.06	9	1	0.03	4	5	
Health care costs per patient			3666			3696	-30	(-1050, 991)
Indirect non-medical costs								
Productivity loss (hours)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Societal costs per patient			N/A			N/A	N/A	N/A

Figure S1. Box plot of length of stay after randomisation per treatment group.

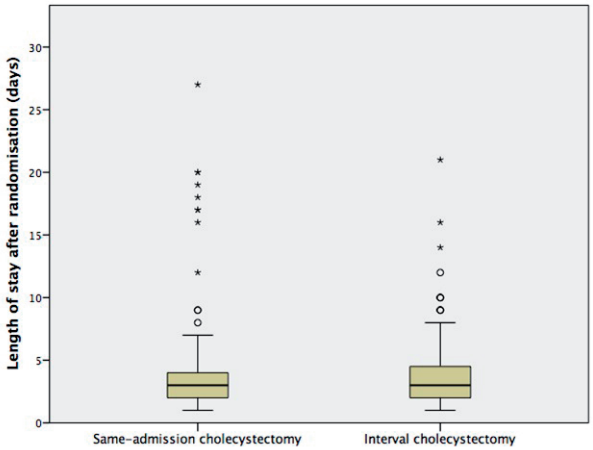


Figure S2. Costs of same-admission cholecystectomy per item.

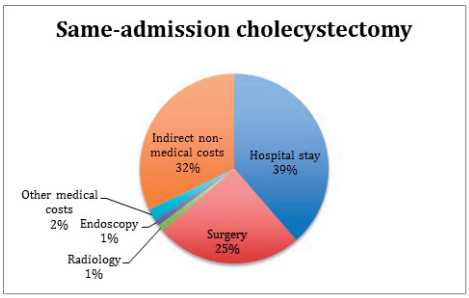
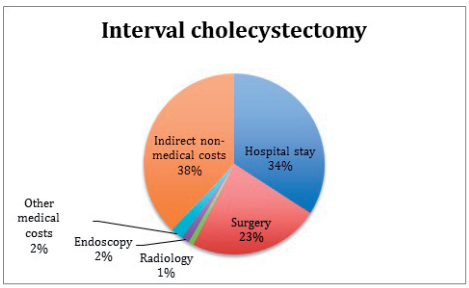


Figure S3. Costs of interval cholecystectomy per item.



CHAPTER 5

Recurrent gallstone colics and related complications after cholecystectomy for mild gallstone pancreatitis

Submitted

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Recurrent gallstone colics and related complications after cholecystectomy for mild gallstone pancreatitis

ABSTRACT

Background: Same-admission cholecystectomy is advised after mild gallstone pancreatitis to prevent recurrence. Data on recurrent gallstone colics and related complications after cholecystectomy for gallstone pancreatitis are lacking.

Methods: Patients participating in a previously published randomized controlled multicenter trial (PONCHO) on the timing of cholecystectomy after mild gallstone pancreatitis were included. Data on healthcare consumption for recurrent biliary events and questionnaires regarding gallstone related symptoms were obtained during 6 months follow up after cholecystectomy. Risk factors for recurrent biliary events were analyzed through regression analysis.

Results: In 25 of 262 patients (10%) postoperative abdominal symptoms necessitated biochemical testing or imaging for persisting common bile duct stones. Acute readmission for recurrent biliary events was required in 7 of these patients (3%); pancreatitis in 4 (2%), biliary colics in 2 (1%) and choledocholithiasis in 1 (<1%). Endoscopic retrograde cholangiopancreatography was performed in 2 patients, with stone extraction in 1 patient. In the remaining 18 patients, tests failed to confirm a biliary cause. Questionnaires were obtained from 191 patients (73%). Postoperative gallstone colics were reported by 28 of 191 patients (15%); 16 (57%) experienced these colics in the first month after cholecystectomy and 6 (21%) in the second month. Only 4 patients (2%) reported gallstone colics during the sixth month of follow-up. Most of these were single events and self-limiting. No predictors for the development of postoperative colics were identified.

Conclusion: While the risk of readmission for recurrent biliary events after cholecystectomy was low (3%), a substantial portion of patients (15%) reported postoperative colics.

INTRODUCTION

Cholecystectomy is among the most common surgical procedures in the Western World.[1] A recent systematic review reported that up to one third of patients who undergo this procedure for symptomatic gallbladder stones have persisting or new abdominal symptoms, such as upper abdominal pain.[2] These findings have raised concerns about the appropriateness of cholecystectomy in uncomplicated symptomatic gallstone disease.[3,4]

In patients with complicated gallstone disease such as gallstone pancreatitis or acute cholecystitis, the general consensus is that the risk of recurrence of these gallstone related complications outweighs the risk of surgery or postoperative symptoms.[5-7] Several studies have demonstrated that cholecystectomy following gallstone pancreatitis does not completely eliminate the risk of recurrent disease, as this may occur in 5% of patients.[8-12] Detailed data on the frequency and natural history of these recurrent symptoms after cholecystectomy for gallstone pancreatitis are lacking.[13] One study reported persisting pain in 10 out of 34 patients who underwent cholecystectomy for acute cholecystitis.[14] In daily practice cholecystectomy is often presented to patients with gallstone pancreatitis as a means to completely prevent recurrent biliary colics or related complications. In business terms, we may be overpromising and under-delivering, and if this is true, we would consequently need to inform our patients better of the risks of recurrent biliary colics or related complications.

To this end, we prospectively investigated the risk of recurrent gallstone colics and related complications after cholecystectomy for mild gallstone pancreatitis, both from a patient and healthcare perspective. Furthermore, we explored potential risk factors for postoperative colics in these patients.

METHODS

Study design

This was a prospective analysis in patients enrolled in the randomized controlled multicenter PONCHO trial on timing of cholecystectomy after mild gallstone pancreatitis.[11,15] Patients were enrolled between December 2010 and August 2013 in 23 Dutch hospitals, including 7 university medical centers and 16 teaching hospitals. Adult patients admitted with a first episode of gallstone pancreatitis were screened for eligibility, excluding those with severe gallstone pancreatitis (i.e. organ failure for more than 48 hours, pancreatic necrosis or peripancreatic fluid collections on imaging), chronic pancreatitis, pregnancy or *a priori* high risk of perioperative complications (American Society of Anesthesiologists [ASA] class III and age over 75, all those with ASA class IV or V).[16,17] Once discharge was foreseen within 48 hours, participants were randomized to cholecystectomy within 3 days (i.e. same-admission) or interval cholecystectomy after 25 to 30 days. The primary analysis of the trial was performed on

the occurrence of death or acute readmission for gallstone-related complications during a 6-month follow-up period. In the present study, outcomes after cholecystectomy with a time horizon of 6 months were investigated from a healthcare and patient perspective.

Healthcare based outcomes

Health care utilization of all participants was prospectively registered during the 6-month follow-up period. The following healthcare components were included in this study: hospital visits for gallstone-related disease (e.g. recurrent gallstone pancreatitis), diagnostics for suspected persisting common bile duct stones (e.g. ultrasound, endoscopic retrograde cholangiopancreatography). Hospital visits for surgical complications (such as wound infections) or diagnostics revealing an unrelated cause of symptoms were excluded, as the focus of this study was on postoperative gallstone-related complications.

Patient-reported symptoms

Upon inclusion in the PONCHO trial, all patients were given questionnaires with instructions to prospectively document what they considered to be gallstone colics during a 6-month period. Events were rated on a 0 to 10 numeric rating scale (NRS), with 0 representing 'no pain' and 10 'the worst pain imaginable'. Duration of the event was documented dichotomously as either shorter or longer than 30 minutes. We defined postoperative gallstone colics as 1) persisting pain of at least 30 minutes, corresponding with the Rome criteria, and 2) pain with an NRS score of 5 or higher, which we considered a reasonable cut-off value for colicky pain.[18] The trial study nurse contacted all participants by telephone approximately every 2 months and at the end of the 6-month follow-up period.

Risk factors for recurrent gallstone colics

The following variables were examined for a potential effect on the development of postoperative colics or other symptoms: age, sex, body mass index (BMI), overall health status based on ASA classification, a history of gallstone colics, endoscopic sphincterotomy prior to surgery, the number of days between onset of pancreatitis and cholecystectomy, conversion to open cholecystectomy and difficulty of cholecystectomy according to the surgeon. This last variable was included because difficult cholecystectomy, with much manipulation of the gallbladder, could theoretically increase the risk of gallbladder stones being forced into the common bile duct. Difficulty of cholecystectomy was assessed by the surgeon on a 0 to 10 NRS (10 being most difficult). Additionally, risk factors for common bile duct stones were assessed using the guidelines of the American Society for Gastrointestinal Endoscopy (ASGE).[19] According to this stratification system, factors associated with high risk (*i.e.* >50%) for choledocholithiasis are 1) gallstones in the common bile duct on imaging, 2) serum bilirubin levels exceeding 70 μmol/l, 3) dilatation of the common bile duct ≥7mm AND serum bilirubin levels between 30 and

70 μmol/l. or 4) signs of cholangitis. Finally, the findings of patients who underwent intraoperative cholangiography (IOC) were evaluated.

Statistical analysis

Only investigations or hospital visits for (suspected) recurrent gallstone colics and related complications were included in this study. Patients were dichotomized based on post-cholecystectomy healthcare resource utilization. Patients who made a completely uneventful recovery were grouped as 'no additional care'; those with postoperative symptoms needing additional medical care through diagnostics or treatment as 'additional care'. In the latter category, all diagnostics and treatment for direct surgical complications such as bleeding or wound infections were excluded.

All continuous data were non-normally distributed and therefore reported as median with interquartile range (IQR). For differences in distribution of categorical variables the χ^2 was used. Relationships between the variables of interest and outcomes were tested through univariable logistic regression. Results from these analyses were reported as odds ratios (ORs) with 95% confidence intervals (CI) and p value. Regarding the patient-reported outcomes, the analyses included all patients who had returned the questionnaires. All analyses were performed in SPSS version 22 (Chicago, IL).

RESULTS

Patients

Of the 266 participants in the PONCHO trial, 4 patients were excluded, due to incorrect diagnosis of pancreatitis, declined cholecystectomy, withdrawn informed consent and death due to ischemic stroke. Baseline characteristics of the included patients are listed in Table 1.

Healthcare based outcomes

Twenty-five out of the 262 patients (10%) needed postoperative hospital care for gallstone colics or related complications. Table 2 presents an overview of the type and total number of diagnostic procedures and emergency room visits. Gallstone-related complications led to acute readmissions in 7 of these patients (3%); 4 with recurrent pancreatitis (2%), 2 with gallstone colics (1%) and 1 with choledocholithiasis (<1%). Two of these 7 patients underwent post-operative ERCP for suspected choledocholithiasis, which was found in one. All other patients were treated conservatively. Recurrent pancreatitis was mild in all patients. All re-admissions occurred within one month after cholecystectomy.

In the remaining 18 patients, biochemical testing and imaging failed to confirm remnant common bile duct stones as the cause of the complaints.

Table 1. Baseline characteristics.

	Total cohort (N=262)	Questionnaire Respondents (N=191)
Age; median (IQR)	53 (40-66)	54 (42-68)
Sex (male); N (%)	103 (39)	76 (40)
Body mass index; median (IQR)	28 (24-31)	27 (24-30)
ASA class; N (%)		
1	94 (36)	68 (36)
2	145 (55)	108 (57)
3	23 (9)	15 (8)
History of gallstone colics; N (%)	77 (29)	54 (28)
Endoscopic sphincterotomy prior to cholecystectomy; N (%)	80 (31)	49 (26)
Days from onset of pancreatitis to cholecystectomy; median (IQR)	22 (7-33)	20 (7-33)
Difficulty of cholecystectomy; NRS score median (IQR)	6 (4-7)	6 (4-7)
Conversion[§]; N (%)	9 (3)	6 (3)

[§] excluding 4 patients in whom primary open cholecystectomy was performed
IQR, interquartile range; ASA, American Society of Anesthesiologists; NRS, numeric rating scale

Table 2. Health care consumption during 6 months follow up after cholecystectomy for mild gallstone pancreatitis.

Procedure	Total no.	Range per patient
Ultrasound	24	1-3
CT	8	1
ERCP	2	1
MRCP	4	1
Endoscopic ultrasound	1	1
Emergency room visit	7	1-2

CT Computed Tomography; MRCP Magnetic Resonance Cholangiopancreatography; ERCP Endoscopic Retrograde Cholangiopancreatography
Note: This table does not include diagnostics performed postoperatively for (suspected) surgical complications or other, unrelated causes of symptoms.

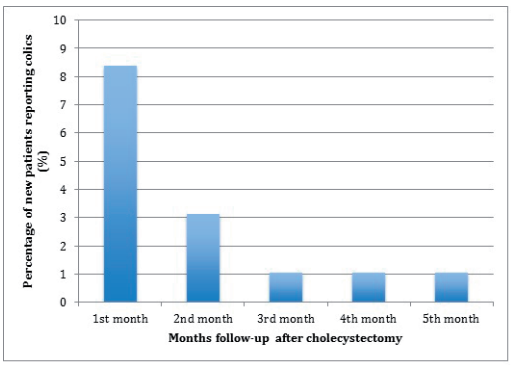
Patient reported symptoms

Questionnaires were returned by 191 of the 262 patients (73%). Baseline characteristics of these 191 patients are shown in Table 1. During the 6-month follow-up period, 28 patients (15%) reported postoperative gallstone colics. This was one event in 14 patients, two events in 5 patients and the other 9 patients reported three or more events (range 1-12 events). Seven patients (25%) had a history of gallstone colics prior to admission for pancreatitis. Of the 28 patients, 16 (57%) developed colics during the first month after cholecystectomy, 6 (21%) in the second month and 2 (7%) in the third, fourth and fifth months (Figure 1). One patient (4%) reported colics in four consecutive months, 6 patients (21%) over the course of 2 months and the remaining 21 patients (75%) had colics during 1 month. Only 4 (2%) of the 191 responding patients reported colics during the final month of follow-up.

Common bile duct stones

Excluding the 80 patients who had undergone preoperative biliary tract clearance with endoscopic sphincterotomy prior to surgery, only one patient had documented common bile duct stones on imaging prior to cholecystectomy. Endoscopic retrograde cholangiopancreatography was unsuccessful in this patient due to previous bariatric surgery and the patient was managed conservatively. This patient had an uneventful recovery without additional care or colics. Likewise, only one patient had a preoperative serum bilirubin level exceeding 70 µmol/l. This patient was not re-admitted and did not report colics in the questionnaire. One patient had a common bile duct of 7 mm on magnetic resonance cholangiopancreatography with slightly elevated serum bilirubin of 35 µmol/l prior to surgery. As the bilirubin level decreased spontaneously, the patient was managed conservatively and recovered without needing additional care or reporting colics. There were no patients with signs of cholangitis.

Figure 1. Timing of patient-reported recurrent gallstone colics per month after cholecystectomy for mild gallstone pancreatitis.



Intraoperative cholangiography was attempted in 17 patients (6%). Cannulation of the cystic duct was unsuccessful in 2 patients. In 1 of the 15 remaining patients (7%) a filling defect was seen during IOC, which was managed conservatively. The patient made an uneventful recovery without reporting colics.

Predictors of recurrent gallstone colics or related complications.

No predictors of gallstone colics could be identified through univariable regression analysis (Table 3). An additional analysis was performed including only those patients who underwent cholecystectomy according to the treatment protocol of the PONCHO trial (i.e. same-admission cholecystectomy (n=91) vs. interval cholecystectomy, (n=70)). No effect of treatment strategy was found, with 14 patients (15%) reporting colics after same-admission cholecystectomy and 13 (18%) in the interval group (odds ratio [OR] for interval cholecystectomy of 1.25, 95% confidence interval [CI] 0.55-2.87; p=0.59).

Table 3. Univariable logistic regression analysis of factors predicting postoperative symptoms.

	Postoperative medical treatment (N=262)		**Postoperative gallstone colics (N=191)**	
Predictor	OR (95% CI)	p	OR (95% CI)	p
Age	0.98 (0.96-1.01)	0.15	0.99 (0.96-1.01)	0.33
Male Sex	0.70 (0.29-1.70)	0.43	0.68 (0.29-1.59)	0.37
Body Mass Index	1.02 (0.96-1.09)	0.50	0.95 (0.88-1.04)	0.27
ASA class 1*	0.83 (0.34-1.99)	0.67	1.01 (0.44-2.32)	0.99
History of gallstone colics	1.15 (0.47-2.78)	0.76	0.82 (0.33-2.07)	0.68
Endoscopic sphincterotomy prior to cholecystectomy	1.32 (0.56-3.12)	0.53	0.44 (0.14-1.33)	0.15
Days from admission to cholecystectomy	0.98 (0.96-1.01)	0.22	1.00 (0.97-1.03)	0.90
Difficulty of cholecystectomy	1.04 (0.85-1.27)	0.68	1.07 (0.87-1.32)	0.51
Conversion	1.16 (0.14-9.69)	0.89	1.14 (0.13-10.15)	0.91

ASA American Society for Anesthesiologists
* compared with ASA class 2 and 3 patients

DISCUSSION

This analysis performed within a randomized controlled multicenter trial found that 10% of patients after cholecystectomy for mild gallstone pancreatitis required medical treatment for gallstone colics or complications, and 15% of patients reported gallstone colics during 6 months follow-up after cholecystectomy. Recurrent pancreatitis after cholecystectomy occurred in 2% of patients and was mild in all cases. Postoperative colics were self-limiting and of short duration. No risk factors for the occurrence of either variable could be identified.

Previous studies in unselected cohorts have indicated that up to 33% of patients experience persisting upper abdominal pain after cholecystectomy.[2,14] Along with cholecystitis, gallstone pancreatitis is generally considered an absolute indication for cholecystectomy. While this strategy reduces the risk of recurrent gallstone related complications, there is little data available on the incidence of colics or related complications after cholecystectomy for this indication.[20,21] Although several studies have described postoperative symptoms in unselected cohorts *including* patients with pancreatitis or cholecystitis, the present study is the first to investigate this subgroup specifically.[22,23] We found that a substantial proportion of patients experienced recurrent gallstone colics serious enough to warrant additional medical treatment. Obviously, these findings do not question the indication for cholecystectomy after gallstone pancreatitis: in the patients awaiting cholecystectomy in the interval group of the PONCHO trial, 51% reported gallstone colics and 17% required re-admission for recurrent biliary events.[11] Other studies have reported recurrent gallstone-related morbidity in 16 to 61% of patients in whom cholecystectomy was delayed.[24,25] Furthermore, a recurrent attack of pancreatitis may be more severe in up to 9% of patients and mortality rates of relapses are similar to those of the first attack.[26,27]

There are several potential explanations for recurrent gallstone colics or related complications after cholecystectomy. Although sphincter of Oddi dysfunction and neuropathic pain have been reported as causes of post-cholecystectomy pain[28] the most obvious cause is persisting common bile duct stones. These stones may already be present before operation or forced into the common bile duct by manipulation of the gallbladder during surgery. The latter mechanism may explain why preoperative risk factors were not capable of predicting recurrent colics. Therefore, the most appropriate moment for evaluating the presence of common bile duct stones is during or immediately following cholecystectomy. Intraoperative cholangiography allows for confirming suspected choledocholithiasis, after which the stones can be dealt with through transcystic stone extraction, laparoscopic bile duct exploration or postoperative ERCP with stone extraction. Notably, there is no consensus on managing asymptomatic

common bile duct stones since most of these stones will pass spontaneously.[29] Whether all patients undergoing cholecystectomy for gallstone pancreatitis should be subjected to the procedural risks of laparoscopic bile duct exploration (*i.e.* bile leak) or ERCP (*i.e.* perforation, bleeding, post-ERCP pancreatitis) remains subject to debate. Moreover, multiple studies have found similar rates of recurrent gallstone-related complications in patients who had undergone IOC compared to patients who had not.[30-32] Therefore, many have argued that since stones can be missed or patients may develop symptoms regardless of the procedure, IOC should be reserved for clinically or biochemically 'high-risk' patients.[30,31,33] The question remains how to prevent postoperative gallstone complications. Despite all proposed strategies a small proportion of patients continue to develop symptomatic common bile duct stones or recurrent gallstone pancreatitis. Resolving this issue requires prospective studies documenting the presence of common bile duct stones shortly after surgery, using highly accurate imaging modalities such as endoscopic ultrasound or magnetic resonance cholangiopancreatography. Combined with biochemical investigations, these patients can then be followed to study which features are predictive of developing symptoms.

This study has several strengths and limitations. We present a large, prospective cohort of patients with clear, uniform definitions of pancreatitis and other gallstone-related complications collected within the context of a randomized controlled trial. For all patients comprehensive pre- and postoperative clinical and healthcare usage information was available. Additionally, we had relatively high response rates for the questionnaires describing the postoperative events in great detail. Some limitations also have to be addressed. First, since no validated questionnaire for gallstone colics is available, such a questionnaire was designed by our study group. As trial participants already received two questionnaires to document pancreatitis-related sick leave in addition to 6 months worth of gallstone symptoms, no gastrointestinal quality of life form was included in the study. However, based on the postoperative healthcare use and patterns of colics, only a very small proportion of patients had persisting postoperative symptoms and we expect the impact on quality of life to have been only minor. Finally, it is possible that patients developed symptoms outside of the 6-month follow up period, although this seems unlikely as the majority of readmissions and postoperative colics occurred very shortly after cholecystectomy.

In conclusion, in this multicenter cohort of patients followed after cholecystectomy for mild gallstone pancreatitis, the risk of readmission for recurrent biliary events after cholecystectomy was very low (3%), although a substantial subset of patients (15%) reported one or more postoperative gallstone colics. While these risks do not outweigh the benefit of cholecystectomy, they should be discussed during preoperative counseling.

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CHAPTER 6

Predicting a difficult cholecystectomy after mild gallstone pancreatitis

Submitted

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ABSTRACT

Background: Cholecystectomy after gallstone pancreatitis may be technically challenging. Preoperative identification of patients at high risk of surgery difficult cholecystectomy may improve surgical planning but data are lacking. We investigated potential risk factors for a difficult cholecystectomy after mild gallstone pancreatitis.

Methods: This was a side-study during a previously published trial on timing of cholecystectomy after mild gallstone pancreatitis (the PONCHO trial). Difficulty of cholecystectomy was scored prospectively on a 0 to 10 visual analogue scale (VAS) after the cholecystectomy by the most senior attending surgeon. The primary outcome 'difficult cholecystectomy' was defined by presence of at least one of the following features: a VAS-difficulty beyond the 75th percentile, conversion, subtotal cholecystectomy or duration of the procedure beyond the 75th percentile. The relationship between risk factors and the primary outcome was investigated through multivariate analyses. Results are presented as odds ratios with 95% confidence intervals. Sensitivity analysis was performed by excluding patients operated by less experienced teams (defined as <100 laparoscopic cholecystectomies performed).

Results: Of the 264 participants, 249 (93%) could be included in the current analysis. A difficult cholecystectomy occurred in 82 patients (33%). A bile duct injury was observed in .2 patients (1%; both cystic duct leakage). Laparoscopy was converted in 9 patients (3%), 2 of which were completed as subtotal cholecystectomies. After multivariate analysis male sex (OR 1.80, 95% CI 1.04-3.13; p=0.037), prior sphincterotomy (OR 1.79, 95% CI 1.01-3.16; p=0.046), and delaying cholecystectomy until after 2 weeks after admission (OR 1.81, 95% CI 1.04-3.16; p=0.036) were independent predictors of a difficult cholecystectomy. The risk for a difficult cholecystectomy in women, operated within two weeks after onset of pancreatitis, without sphincterotomy was 16%. When including only surgeons with more than 100 laparoscopic operations, no predictive factors could be identified through uni- or multivariable analysis

Conclusion: Risk factors for a difficult cholecystectomy after mild gallstone pancreatitis are male sex, prior sphincterotomy and delaying cholecystectomy until after 2 weeks after admission although the overall risk of conversion and bile duct injury was low.

INTRODUCTION

Cholecystectomy is the treatment of choice in complicated gallstone disease such as cholecystitis or gallstone pancreatitis.[1-3] As most cholecystectomies are performed electively for symptomatic cholelithiasis, the procedure is one of the cornerstones of surgical trainee progrxams.[4] In recent years a shift in treatment strategies for complicated gallstone disease has taken place. Current guidelines now advocate early cholecystectomy in acute cholecystitis and mild gallstone pancreatitis.[1-3,5,6] In coming years, increasing numbers of cholecystectomies will be performed as acute or semi-acute care procedures. Accordingly, it is vital to recognize in which patients cholecystectomy is anticipated to be difficult.[7] Cholecystectomy in patients at high risk for surgical complications can then be assigned or supervised by specialized gastrointestinal surgeons, instead of to general surgeons or surgical trainees.[8]

Studies in cohorts of unselected patients have identified several risk factors that may increase the technical difficulty of cholecystectomy. Among these are male sex, previous endoscopic sphincterotomy, high age and inflammation of the gallbladder or pancreas.[9-17] Very few studies have focused on the difficulty of cholecystectomy after mild gallstone pancreatitis. Only three studies specifically report the surgeon's intraoperative assessment of technical difficulty in patients after gallstone pancreatitis, two of which are small case series including less than 25 patients.[9,18,19] Other studies that describe outcome of cholecystectomy after pancreatitis have not described the difficulty and complications of these procedures.[20,21] This lack of research is especially surprising, as the concern for increased complexity with ensuing surgical complications after pancreatic inflammation has traditionally been the most important argument for delaying cholecystectomy after mild gallstone pancreatitis.[22]

In this study we investigated which factors increase technical complexity of cholecystectomy after gallstone pancreatitis.

METHODS

Study design

This was a prospective side-study during the previously published multicenter PONCHO trial.[6] In brief, 266 adult patients with mild gallstone pancreatitis from 23 Dutch centers were randomized 24-48 hours before anticipated discharge. Patients with documented organ failure (persisting for more than 48 hours), pancreatic necrosis with peripancreatic fluid collections, chronic pancreatitis or alcohol abuse were not eligible for participation. Patients were randomized to either cholecystectomy within 3 days ('same-admission cholecystectomy') or discharge and cholecystectomy after 25-30 days ('interval cholecystectomy'). Patients were followed up for 6 months after surgery for the occurrence of the primary endpoint; *i.e.* a combination of acute readmission for

gallstone related complications (recurrent pancreatitis, cholangitis, choledocholithiasis requiring endoscopic retrograde cholangiopancreatography or simple gallstone colic) or mortality. Clinical, radiological and surgical data were prospectively collected on case record forms and source material and entered into the trial database. Surgical data included the experience with laparoscopic surgery of the team, operating time, difficulty of cholecystectomy according to the most experienced attending surgeon on a 0 to 10 visual analogue scale (10 being most difficult; VAS), the presence of adhesions and the reason for conversion or subtotal cholecystectomy. Additionally, the forms included questions regarding the difficulty of dissection, dichotomized as 'easy' or 'difficult', and the presence or absence of dense adhesions in the dissection area. As this study focuses on the intraoperative findings as described by the surgeon and the subjective difficulty of dissection, postoperative complications were not part of this analysis.

Variables, data sources and measurements

The primary outcome of this study was a difficult cholecystectomy, as defined by a VAS score beyond the 75th percentile, conversion, subtotal cholecystectomy or duration of surgery beyond the 75th percentile. In a secondary analysis, the individual components of this combined outcome measure were investigated. Predictive factors were sex, age, body mass index (BMI), significant comorbidity (defined as ASA class III), a history of gallstone colics, a history of upper abdominal surgery, endoscopic sphincterotomy before surgery, the number of days between sphincterotomy and cholecystectomy and the interval between pancreatitis onset and cholecystectomy. For practical applicability, the latter was both tested as a continuous variable and dichotomized in 'cholecystectomy within or after 2 weeks of admission'. This arbitrary cut-off value was chosen, as cholecystectomy within this period should be possible for virtually all patients with mild pancreatitis. Furthermore, all computed tomography imaging (CT) performed before cholecystectomy was retrieved and scored according to the CT Severity Index (CTSI) by an experienced radiologist (T.L.B.).[23]

Statistical analysis

Analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk NY). The relationship between the predictive factors and difficult cholecystectomy (the combined endpoint) was first explored through univariable logistic regression analysis. Factors with a p-value less than 0.2 were then selected for a multivariable logistic regression model. The final multivariable model was internally validated using 5000 bootstrap resamples and a nomogram of the model was designed. Risks are presented as odds ratios (OR) with 95% confidence interval (CI). Additionally, the predictive value of the variables on the individual components of the combined endpoint was explored. A sensitivity analysis was performed, excluding cases in which the most experienced member of the surgical team had performed 100 or less laparoscopic cholecystectomies.

Differences in the dichotomous outcomes 'difficult dissection' and the presence or absence of adhesions were tested through the χ^2 or Mann-Whitney U test, as appropriate.

RESULTS

Of the 266 patients originally randomized in the PONCHO trial, two were excluded from the present study. In one patient the amylase levels on admission did not exceed three times the upper limit of normal required for the diagnosis acute pancreatitis, leading to exclusion by the adjudication committee; the other patient ultimately refused cholecystectomy. Baseline characteristics of the 264 included patients can be found in Table 1. Overall difficulty of surgery was recorded in 259 patients (98%), with a median VAS of 6 (interquartile range [IQR] 4 to 7). In 44 of these patients (17%), the surgeon scored a VAS of 8 or higher. A primary open cholecystectomy was performed in 6 patients (2%); these patients were not included in the analysis predicting conversion or subtotal cholecystectomy. Laparoscopy was converted in 9 patients (3%), 2 of which were completed as subtotal cholecystectomies. A third subtotal cholecystectomy was completed laparoscopically. Duration of surgery was recorded in 250 patients (95%) with a median of 60 minutes (IQR 43 to 75 minutes). In 60 patients the duration of surgery exceeded 75 minutes (24%). When taking missing data and overlap into account, cholecystectomy was difficult in 82 out of 249 patients (33%). In 238 cases (90%) the experience of the surgeons with laparoscopic surgery exceeded 100 cholecystectomies.

Table 1. Baseline characteristics.

	Patients (N=264)
Demographics and history	
Age; median (IQR)	53 (40-66)
Male sex; N (%)	104 (39)
Body mass index; median (IQR)	28 (25-31)
Morbidly obese (BMI ≥40); N (%)	13 (5)
ASA class; N (%)	
Class 1	94 (36)
Class 2	149 (55)
Class 3	25 (10)
History of gallstone colics; N (%)	74 (28)

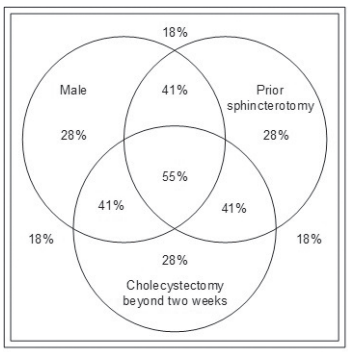
History of upper abdominal surgery	15 (6)
Preoperative features	
Endoscopic sphincterotomy prior to cholecystectomy; N (%)	81 (31)
Complications during ERCP*	8 (9)
Number of days between sphincterotomy and cholecystectomy; median (IQR)	21 (7-32)
Peripancreatic fluid on CT (N=39)[§]	
CTSI 0	9 (23)
CTSI 2	9 (23)
CTSI 3	12 (31)
CTSI 4	9 (23)
Days of pancreatitis[#]; median (IQR)	5 (3-8)
Days from pancreatitis onset to cholecystectomy; median (IQR)	22 (7-33)
Cholecystectomy delayed until 2 weeks after admission; N (%)	145 (55)
Surgical characteristics	
Difficulty of cholecystectomy^; median (IQR)	6 (4-7)
VAS ≥8; N (%)	44 (17)
Conversion[±]; N (%)	9 (3)
Subtotal cholecystectomy	3 (1)
Duration of surgery in minutes[$]; median (IQR)	60 (43-75)
>75 minutes	60 (24)

* 5 bleedings and 3 perforations in 88 patients who underwent ERCP
[§] scans were performed prior to cholecystectomy in 42 patients, 39 were retrieved for review. CTSI scores 3 and 4 involve acute peripancreatic fluid collections.
[#] Calculated as the number of days between admission and randomization in the PONCHO trial.
^ Case record forms were received from 259 patients.
[±] Excluding 6 patients in whom a primary open cholecystectomy was performed.
[$] Duration of surgery was reported in 250 patients.
IQR denotes interquartile range; ASA, American Society for Anesthesiology; ERCP, Endoscopic Retrograde CholangioPancreatography; CT, computed tomography; CTSI, Computed Tomography Severity Index; VAS, Visual Analogue Scale.

Excluding 11 patients with missing variables, 69 out of 227 patients (30%) had difficult cholecystectomies.

At univariable analysis, male sex (OR 1.75, 95% CI 1.02-3.00; p=0.042), previous sphincterotomy (OR 1.77, 95% CI 1.02-3.09; p=0.044) and cholecystectomy after 2 weeks of admission (OR 1.81, 95% CI 1.05-3.11; p=0.034) were strong predictors of a difficult cholecystectomy (Table 2). As a continuous variable, the number of days between admission and cholecystectomy was significantly predictive of a difficult cholecystectomy with an OR of 1.02 per day (95% CI 1.00-1.04; p=0.022). However, this effect diminished when adjusting the cut-off value to cholecystectomy after 1 or 3 weeks (both p>0.05). The presence of peripancreatic fluid on CT had no impact on difficulty of surgery. In the multivariable model, these three factors remained statistically significant; male sex (OR 1.88, 95% CI 1.08-3.27; p=0.025), sphincterotomy (OR 1.77, 95% CI 1.00-3.13; p=0.046), delayed cholecystectomy (OR 1.81, 95% CI 1.04-3.16; p=0.036). The internal validation of the model with 5000 bootstrap resamples yielded no new insights. A visualization of the constructed nomogram is presented in Figure 1. Presence of all risk factors (i.e. a male patient who had undergone sphincterotomy and delayed cholecystectomy) resulted in an overall chance of a difficult cholecystectomy of 55%; this chance was 18% in absence of these factors. When including only surgeons with more than 100 laparoscopic operations for the sensitivity analysis, no predictive factors could be identified through uni- or multivariable analysis (Table 2).

Figure 1. Nomogram for the prediction of a difficult cholecystectomy*.



*The nomogram is based on a multivariable logistic regression model including male sex, prior sphincterotomy and cholecystectomy performed beyond two weeks after initial admission. Depending on the presence or absence of these factors, the chance of a difficult procedure is between 18 and 55%.

Table 2. Univariable and multivariable analysis with sensitivity analysis.

	All cases (N=249)				Surgical experience >100 laparoscopic cholecystectomies (N=227)	
	Univariable analysis		Multivariable analysis		Univariable analysis	
Predictor	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	1.01 (0.99-1.03)	0.32			1.01 (0.99-1.03)	0.42
Male Sex	1.75 (1.02-3.00)	0.042	1.88 (1.08-3.27)	0.025	1.52 (0.85-2.72)	0.15
Morbidly obese (BMI ≥40)	1.81 (0.59-5.55)	0.30			2.05 (0.66-6.36)	0.22
ASA class 3	1.52 (0.64-3.58)	0.34			1.26 (0.48-3.31)	0.64
History of gallstone colics	1.06 (0.58-1.93)	0.86			1.17 (0.62-2.19)	0.64
History of upper abdominal surgery	1.39 (0.48-4.04)	0.55			1.69 (0.52-5.51)	0.39
Endoscopic sphincterotomy prior to cholecystectomy	1.77 (1.02-3.09)	0.044	1.77 (1.00-3.13)	0.05	1.61 (0.89-2.92)	0.11
Days between sphincterotomy and cholecystectomy	1.02 (0.99-1.05)	0.27			1.01 (0.97-1.04)	0.68
Cholecystectomy after 2 weeks of admission	1.81 (1.05-3.11)	0.034	1.81 (1.04-3.16)	0.036	1.16 (0.90-2.88)	0.11
Peripancreatic fluid on preoperative CT	1.40 (0.55-3.57)	0.48			1.76 (0.67-4.59)	0.25

Analysis of the individual components of the combined endpoint

Male sex (OR 2.31, 95% CI 1.16-4.59; p=0.018), morbid obesity (OR 4.49, 95% CI 1.32-15.30; p=0.017) and previous sphincterotomy (OR 2.60, 95% CI 1.32-5.15; p=0.006) were individually associated through multivariable analysis with a VAS of 8 or higher (Table 3). No multivariable models could be created for the other two endpoints. Age (OR 1.08, 95% CI 1.02-1.13; p=0.008) and male sex (OR 5.77, 95% CI 1.17-28.36; p=0.031) were significantly associated with conversion or subtotal cholecystectomy and number of days of pancreatitis (OR 1.17, 95% CI 1.02-1.19; p=0.017) with a long procedure in through univariable analysis.

Difficult dissection and adhesions

Information on difficulty of dissection and the presence of adhesions was returned in 254 patients (96%). Dissection was difficult in a significantly larger proportion of men (p=0.009). Dense adhesions were also found in a significantly higher proportion of men (p<0.001). Otherwise, no uneven distributions were found (Table 4).

DISCUSSION

In this prospective side-study within a randomized controlled multicenter trial, gallstone pancreatitis male sex, previous endoscopic sphincterotomy and delaying cholecystectomy until two weeks after admission predicted a difficult cholecystectomy after mild gallstone pancreatitis. When only analyzing procedures performed by experienced surgeons no risk factors were identified.

Several studies demonstrated the superiority of early cholecystectomy over interval cholecystectomy for mild gallstone pancreatitis in terms of disease recurrence.[6,19-21,24] These studies were mainly performed to convince the surgical community to abandon interval cholecystectomy, which has been the approach preferred by many according to international reports.[25,26] This strategy was advocated in the early 90's, when early cholecystectomy after acute pancreatitis was associated with high conversion rates. Moreover, as a result of concerns of bile duct injury, mild gallstone pancreatitis and acute cholecystitis were generally considered a contraindication for early laparoscopic surgery.[21,27,28] As experience and proficiency with laparoscopic surgery increased, indications have shifted.[29] More progressive surgeons found that while severe pancreatitis did affect technical difficulty and risk of conversion, mild disease did not.[21] Cholecystectomy during the same admission for mild pancreatitis became standard in some centers, but the majority of the surgical community continued to delay cholecystectomy.[30,31] This can be explained in part because interval surgery has distinct logistical advantages, but also due to the lingering doubt regarding the safety of early surgery. Studies addressing the safety of cholecystectomy have largely refrained to conversion and general surgical

Table 3. Uni- and multivariable analysis of individual components of the combined endpoint.

	VAS Difficulty ≥8 (N=259)				Conversion or subtotal cholecystectomy (N=258)		Duration of surgery >75 minutes (N=250)	
	Univariable		Multivariable		Univariable		Univariable	
Predictor	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	1.02 (1.00-1.04)	0.15			1.08 (1.02-1.13)	0.008	1.00 (0.99-1.02)	0.68
Male Sex	1.89 (0.98-3.62)	0.057	2.31 (1.16-4.59)	0.018	5.77 (1.17-28.36)	0.031	1.44 (0.80-2.58)	0.23
Morbidly obese (BMI ≥40)	3.03 (1.03-10.62)	0.045	4.49 (1.32-15.30)	0.017	1.00 (0.99-1.00)	0.99	2.07 (0.65-6.58)	0.22
ASA class 3	1.25 (0.44-3.53)	0.67			1.23 (0.15-10.26)	0.85	2.06 (0.85-4.98)	0.11
History of gallstone colics	0.99 (0.48-2.05)	0.98			0.73 (0.15-3.60)	0.70	1.27 (0.67-2.41)	0.47
History of upper abdominal surgery	1.24 (0.33-4.58)	0.75			2.27 (0.26-19.53)	0.46	1.16 (0.36-3.79)	0.80
Endoscopic sphincterotomy prior to cholecystectomy	2.36 (1.22-4.57)	0.011	2.60 (1.32-5.15)	0.0060	0.26 (0.03-2.15)	0.21	1.42 (0.77-2,62)	0.26
Days between sphincterotomy and cholecystectomy	1.01 (0.97-1.04)	0.68			1.04 (0.93-1.16)	0.47	1.01 (0.98-1.05)	0.43
Cholecystectomy after 2 weeks of admission	1.68 (0.85-3.31)	0.13			1.04 (0.27-3.96)	0.96	1.59 (0.87-2.89)	0.13
Peripancreatic fluid on preoperative CT	1.62 (0.56-4.69)	0.37			3.41 (0.66-17.59)	0.14	2.24 (0.87-5.87)	0.094

Table 4. Distribution of difficult dissections and presence of adhesions.

	Difficult dissection			Dense adhesions		
	Easy (N=161)	**Difficult (N=93)**	**p**	**Absent (N=162)**	**Present (N=92)**	**p**
Age	53 (38-66)	54 (41-68)	0.23*	53 (37-66)	54 (43-69)	0.15*
Male Sex	53 (33)	46 (49)	0.009	49 (30)	57 (52)	<0.001
Morbidly obese (BMI ≥40)	6 (4)	7 (8)	0.19	8 (5)	5 (5)	0.87
ASA class 3	16 (10)	8 (9)	0.73	17 (10)	8 (9)	0.64
History of gallstone colics	45 (28)	24 (26)	0.71	46 (28)	24 (26)	0.69
History of upper abdominal surgery	10 (6)	5 (5)	0.79	10 (6)	5 (5)	0.81
Endoscopic sphincterotomy prior to cholecystectomy	45 (28)	34 (37)	0.15	47 (29)	32 (35)	0.34
Days between sphincterotomy and cholecystectomy	14 (6-31)	22 (8-33)	0.53*	19 (6-31)	23 (8-32)	0.60*
Complication during ERCP	5 (3)	2 (2)	0.49	4 (2)	3 (3)	0.71
Cholecystectomy after 2 weeks of admission	87 (54)	54 (58)	0.53	88 (54)	52 (57)	0.74
Peripancreatic fluid on preoperative CT	12 (8)	9 (8)	0.99	11 (7)	9 (10)	0.40

Data are N (%) or median (interquartile range)
* Mann-Whitney U test

complications such as wound infections, as more specific complications like bile duct injury are relatively rare.[32]. Neither conversion nor complication rates differed between the two strategies in any of these studies.[18,20,21,24,26,33,34]

The present study is the largest cohort so far focusing on technical difficulty of cholecystectomy. The finding of male sex as a risk factor for difficult cholecystectomy is in line with data from several reports on cholecystectomy in unselected cohorts, among which a systematic review including 109 studies, in which male patients were at a significantly higher risk of conversion.[10,16,17,35] An anatomical explanation for this phenomenon could be a narrower costal margin in males, resulting in a more difficult angle for the surgeon to operate in. Likewise, previous endoscopic sphincterotomy has been shown to increase difficulty of laparoscopic cholecystectomy.[11,14,36-38] It is difficult to understand why this is an independent risk factor because it raises the question why an uncomplicated sphincterotomy has an effect of Calot's triangle and any impact on the critical view of safety. It has been hypothesized that this is the result of scarring of the hepatoduodenal ligament due to bacterial colonization and low-grade inflammation of the common bile duct, which can be seen after sphincterotomy.[39,40] In our cohort however, the ERCP's were performed relatively short before cholecystectomy in most patients. This raises the question how this scarring can occur on such short notice. Perhaps a reaction of the bile duct wall to the habitual presence of intraductal gallstones for which the ERCP is performed offers a more logical pathophysiological explanation. Furthermore, in contrast with the belief that cholecystectomy in the early post-acute phase of pancreatitis would be technically more demanding, our results rather indicate the opposite.[41] Although we were unable to determine what the exact mechanism behind this effect is in our study, previous investigators found more dense adhesions and difficult dissection of Calot's triangle in delayed cholecystectomy.[18,19]

This study provides a twofold argument for performing cholecystectomy during the same admission following mild gallstone pancreatitis. Firstly, because of the positive correlation we found between increasing delay to cholecystectomy and difficult surgery. Second, from our results it follows that the same risk factors apply for cholecystectomy after mild pancreatitis as for the general population needing cholecystectomy. Even in the small subgroup of patients with peripancreatic fluid (but not necrosis) within this study of mild biliary pancreatitis, which would theoretically lead to upgrading the pancreatitis severity status to 'moderately severe' according to the revised Atlanta grading system[42], no extra difficulties were encountered. Together with the results from other studies on the subject, we believe this to be further evidence against the theory of mild pancreatitis distorting the biliary anatomy in the early post-acute phase. From a clinical point of view, this means that these patients do not have to be assigned to specialized surgeons but can be operated on by trainees, provided an experienced surgeon is present for supervision.[14,31]

This study has some limitations. Technical 'difficulty' is, by definition, a subjective term. Quantifying and dichotomizing these outcomes is therefore inherently arbitrary. We believe that by combining the perceived difficulty, conversion, need for subtotal cholecystectomy and duration of the procedure that we have succeeded in providing a reasonable representation of the most difficult cholecystectomies.

In conclusion, risk factors for a difficult cholecystectomy after mild gallstone pancreatitis are male sex, prior sphincterotomy and delaying cholecystectomy until after 2 weeks after admission, although the overall risk of conversion and bile duct injury is low. Cholecystectomy should be performed during the same admission and, especially when risk factors are present, by gastrointestinal surgeons.

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CHAPTER 7

Laparoscopic partial cholecystectomy for the difficult gallbladder: a systematic review

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Laparoscopic partial cholecystectomy for the difficult gallbladder: a systematic review

ABSTRACT

Introduction In the setting of difficult dissection of Calot's triangle during laparoscopic cholecystectomy, conversion is commonly advocated. An alternative approach aiming at preventing bile duct injury, is laparoscopic partial cholecystectomy (LPC). Safety and efficacy of this procedure are unclear.

Methods A systematic review of the literature was performed independently by three researchers. Outcomes were conversion rate, hospital length-of stay (LOS), bile duct injury (BDI), bile leak, symptomatic gallstones in remnant gallbladder, the need for reoperation, postoperative endoscopic retrograde cholangiopancreaticography (ERCP), percutaneous intervention and mortality.

Results The review included 15 publications, which reported on 625 patients. Four different operative techniques could be distinguished. Conversion to open (partial) cholecystectomy was performed in 10.4%. Median length of stay (LOS) was 4.5 days, ranging from 0-48 days. The most common complication was postoperative bile leak, which occurred in 66 patients (10.6%). There was one case of bile duct injury. During the follow-up period, 2.2% of patients experienced recurrent symptoms of gallstones. Eight patients (2.7%) underwent reoperation. Postoperative ERCP was performed for 26 of 349 (7.5%) patients. A percutaneous intervention was performed in 5 of 353 (1.4%) patients. Three deaths were described in the reviewed series (one of pulmonary sepsis and two of myocardial infarctions). A rough comparison showed that fewer bile leaks, less need for ERCP and less recurrent symptoms of gallstones seemed to occur when the cystic duct and the gallbladder remnant were closed.

Conclusions Literature concerning LPC is scarce. Four different LPC techniques can be distinguished. LPC seems a safe and feasible alternative to conversion when encountering a difficult gallbladder during LC. Closing the cystic duct, gallbladder remnant or both seems to be preferable.

INTRODUCTION

After the introduction of laparoscopic cholecystectomy (LC) in the mid-1980s[1] the laparoscopic approach quickly became the standard treatment for gallstone disease. Currently, it is performed by most surgeons because it is standard of care in international guidelines[2]. The LC procedure was initially considered unsafe and harmful in the setting of acute gallbladder inflammation, but it is now the most common procedure performed for gallstone disease and acute cholecystitis. When the 'critical view of safety' (positive identification of biliary anatomy) cannot be obtained during dissection of Calot's triangle, conversion to open surgery is advocated to prevent bile duct injury[3]. However, experienced laparoscopic surgeons may feel comfortable by proceeding laparoscopically using alternative approaches and techniques. Moreover, the newer generations of surgeons and surgical residents currently have little or no experience with the open procedure, and as a consequence converting may potentially pose an even more significant risk. Conversion *per se* does not always provide a better view of the anatomy and for those without experience using the open approach it may be even harder to continue safely. This eventually may lead to even more severe bile duct injury, such as transection or resection of the common bile duct (CBD)[4]. In the case of a difficult LC (eg in acute cholecystitis where dissection of Calot's triangle is challenging due to severe adhesions or inflammation), a change of surgical strategy, such as antegrade or partial cholecystectomy (PC) or even drainage, may be more practical than conversion *per se*[5]. Because surgical skill and experience play an important role, an alternative surgical strategy may be especially valuable for less experienced surgical teams. A PC can be efficiently performed. In 1985, Bornman and Terblanche first described open PC[6] and since 1993, laparoscopic partial cholecystectomy (LPC) has been performed as well[7].

The LPC procedure may be an alternative for conversion to open cholecystectomy in situations with increased risk of injury to Calot's components. Many different techniques have been described such as whether to leave the posterior gallbladder wall in situ or not and whether to close the remnant gallbladder stump with or without drainage. Theoretically, leaving the cystic duct open would avoid further risk of bile duct injury. However, it may have some disadvantages; it could lead to higher postoperative bile leak rates, prolonged drainage and more frequent necessity of percutaneous drainage. Unfortunately, evidence is limited and no randomized trials on this subject have been published. Available literature consists mainly of small consecutive series. Although each situation may ask for a customized approach, it remains unclear what the morbidity, mortality, and long-term sequelae of LPC are. The current study aims to systematically review the available evidence on morbidity, mortality and long-term results of LPC.

METHODS

Literature search

The Cochrane Database of systematic reviews, the Cochrane central register of controlled trials, and MEDLINE databases were searched by using the keywords (partial OR incomplete OR subtotal) AND (cholecystitis OR cholecystectomy) to identify studies published up to January 2012. Free text words were used instead of MeSH terms to avoid missing recent articles that had not been given a MeSH label. Three investigators (DH, DdC, SML) independently performed the literature search. Electronic links to related articles and references of selected articles were hand-searched as well. References were snowballed. A hand search of relevant journals and conference proceedings was not performed. The search was not restricted to any language, but in the systematic review only studies published in English were taken into account.

Study selection and data extraction. From the potentially eligible inclusions, only studies were included if they reported on partial (or incomplete) cholecystectomy in patients with cholecystitis. Studies were included if they formulated a clear definition of PC. The definition needed to include "some portion of the gallbladder left in continuity with the cystic duct and not resected"[8].

The same three investigators independently searched the list of abstracts according to the search results and selected articles for closer reading. Subsequently, two investigators (DH, DdC) extracted the following outcomes, if reported, from the original articles using a preformatted sheet: conversion rate, hospital length-of stay (LOS), bile duct injury (BDI), bile leak, symptomatic gallstones in the remnant gallbladder, the need for reoperation, the need for postoperative endoscopic retrograde cholangiopancreaticography (ERCP), the need for percutaneous intervention and mortality.

Duplicate publications and papers that reported on (parts of) the same study population were excluded. In that situation only the largest, most recent or most relevant publication was included. Each of the selected studies was critically appraised by the two investigators (DH, DdC), using a modified form as proposed by the Dutch Cochrane Collaboration. They assessed whether a study was 1. randomized, consecutive, prospective or retrospective; 2. whether it had similar groups and 3. whether there was an adequate follow up. In the case of retrospective analysis of data collected prospectively, a study was defined as prospective. Final inclusion was done after consensus was reached. Discrepancies in judgment, if any, were resolved by discussion between the investigators in a consensus meeting.

RESULTS

Included studies

Using the aforementioned search terms, 925 publications were identified. Eight-hundred and forty-three articles the words "subtotal/partial/incomplete" and "cholecystectomy" were contained in a different context and were therefore deemed irrelevant. In total, 102 articles were selected for closer reading. Of the 102 remaining articles 18 were not written in English and 67 concerned PC either as case reports or as treatment only for other conditions than AC (e.g. Mirizzi syndrome, xanthogranulomatous cholecystitis), or addressed open PC, and were therefore discarded.

The remaining 17 articles were scrutinized and mined for data. One article was excluded in this phase because the indication for LPC was liver cirrhosis in all patients[9]. A paper by the same author[10] was also excluded because it seemed to include mostly the same patients as the earlier article. Finally, 15 articles remained (Figure 1)[7,8,11-23]. The included studies had several limitations (Table 1). Most were retrospective single-centre studies with generally small or moderate sample sizes.

Indication for LPC

The 15 papers included 625 patients. In 13 papers that mentioned it, 352 patients (56%) had acute cholecystitis. Eight articles reported the incidence of Mirizzi syndrome, which was the indication for LPC in 28/371 patients (7.5%).

Figure 1. Flowchart of included papers.

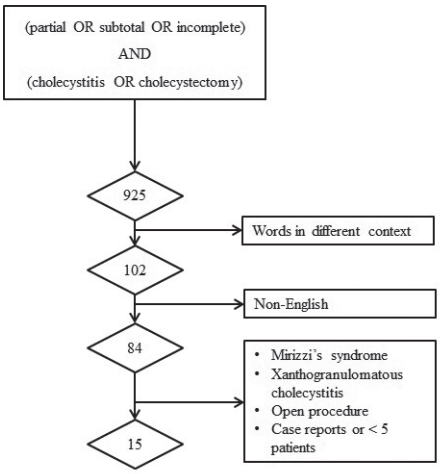

Table 1. Quality of included studies.

Publication	Description of Study	Median Follow-up months (range)	Quality Points										Total
			1	2	3	4	5	6	7	8	9	10	
Beldi 2003	Prospective consecutive series Comparison LPC with nationwide LC database	19 (6-54)	1	1	0	0	1	0	1	1	1	1	7
Bickel 1993	Retrospective consecutive series	-	0	0	0	0	0	0	0	1	0	0	1
Bonavina 2007	Retrospective consecutive series (letter to editor)	-	0	0	0	0	0	0	0	0	0	0	0
Chowbey 2000	Retrospective consecutive series	-	1	0	0	0	1	0	1	0	0	1	4
Horiuchi 2008	Retrospective study Comparison of early and late group	-	1	1	0	0	0	1	0	1	0	1	5
Hubert 2010	Prospective consecutive series	4 (2-16)	1	0	0	0	1	0	1	1	1	1	6
Ji 2006	Retrospective consecutive series Comparison of LPC and LC.	-	1	0	0	0	1	0	0	1	0	1	4
Michalowski 1998	Retrospective consecutive series	-	1	0	0	0	0	0	0	0	0	1	2
Nakajima 2009	Retrospective consecutive series Comparison of LC in early and late (after introduction of LPC) group.	42(1-100)	1	1	0	0	0	0	1	0	0	1	4
Philips 2008	Restrospective consecutive series	-	1	0	0	0	1	0	1	0	0	1	4
Ransom 1998	Retrospective consecutive series	-	0	0	0	0	1	0	0	1	0	0	2
Singal 2009	Prospective consecutive series	10	1	0	0	0	1	0	1	1	1	1	6
Sinha 2007	Prospective consecutive series	-	1	1	0	0	1	0	1	1	1	1	7
Sharp 2009	Retrospective consecutive series. Telephonic follow-up.	-	1	0	0	0	1	0	1	1	0	1	5
Tian 2009	Retrospective consecutive series	-	1	0	0	0	0	0	1	1	0	1	4

1. Definition of study objectives	Clear:1 unclear/no: 0 points
2. Statistical method described	Yes: 1 no: 0 points
3. Possible bias in inclusion/exclusion.	Not present:1, present/unclear: 0 points
4. Different types of treatment besides the evaluated one	Not present: 1, present/unclear: 0 points
5. Different technique in patients from same series	No: 1 Yes/not defined: 0 points
6. Differences in population of compared groups	No: 1 Yes/not defined: 0 points
7. Measures of outcomes	Defined: 1, had to be calculated: 0 pts
Commercial interest cited to used devices	Devices not cited: 1, cited: 0

LC= laparoscopic cholecystectomy LPC= laparoscopic partial cholecystectomy

Operative techniques

The described operative techniques vary per author. The differences in operative steps among the authors are displayed in Table 2. Four different techniques can be distinguished. The first method basically involves excision of most of the anterior wall of the gallbladder, leaving a part of the posterior wall attached to the liver. The risk of dangerous dissection of the posterior wall is thus avoided. When the remaining gallbladder stump is not closed, we categorised this method as method A. Seven of 15 authors used this technique. All of them describe the routine use of a drain. Method B is similar to A but the gallbladder stump is closed. One author uses this method, and another author used the method in 33% of the patients. Then, the third method is different from A and B because it includes resection of both the anterior and posterior

Table 2. Different operative techniques.

Author	Excision anterior wall	Excision anterior and posterior wall	Routine drain	Coagulation of mucosa	Closure of gallbladder stump	Closure of cystic duct	Method
Beldi	+	-	+	+	-	-	A
Bickel	+	-	+	+	-	+ (100%)	A
Bonavina	?	?	?	?	+	?	
Chowbey	-	+	-	-	+	+ (100%)	C
Horiuchi	+	-	+	+	-	+ (90%)	A
Hubert	-	+	+	+ (laser)	-	+ (100%)	D
Ji	+	-	+	+/-	-	+ (93%)	A
Michalowski	+	-	+	+/-	-	+(93%)	A
Nakajima	-	+	-	+	+	-	C
Philips	+	-	+	-	-	-	A
Ransom	+	-	-	-	+	+ (62.5%)	B
Singal	-	+ *	-	- *	+	- (10%)	C
Sinha	+	-	+	-	-	-	A
Sharp	+(12%)	+(88%)	+	-	-	-	D
Tian							
method 1	-	+(67%)	-	+	+	-	C
method 2	+ (33%)	-	+	-	+	-	B

A; excision anterior wall, no gallbladder stump closure, leaving a drain in situ. +/- coagulation of remnant gallbladder mucosa

B; excision of anterior wall with gallbladder stump closure, with or without a drain.

C; dissection of posterior wall from liver, leaving a closed gallbladder stump without drain

D; dissection of posterior wall from liver, leaving an open gallbladder stump with a drain

*: Dissection of posterior wall when possible. If not, coagulation of mucosa of remnant posterior wall.

gallbladder wall. It mainly differs from a conventional cholecystectomy in its the location of transection: at the gallbladder neck or Hartmann's pouch, leaving a remnant gallbladder pouch behind. We categorised it as method C when this pouch was closed. The four authors advocating this technique did not use drains routinely. Method D resembles method C but the pouch is left open with a drain close to it. Two authors used this method. Finally, the technique was not described in one paper [12]. Irrespective of the used technique, authors chose to coagulate or not to coagulate the mucosa of the remnant gallbladder, or to either close the cystic duct or to leave it open. The cystic duct was reported to be clipped, sutured or sutured from inside. The cystic duct was closed in 330 of 625 patients (53%). The median operative time for LPC was 81.1 minutes (range 50-180 minutes).

Outcomes

Main outcomes concerning several items of morbidity and mortality are displayed in Table 3. Outcomes sorted per operative method and cystic duct closure are displayed in Table 4.

Conversion rate

Conversion to open partial cholecystectomy was performed in 54 of 520 patients (10.4%). With method D, conversion was done in 30 of 60 patients (50%), mainly because one author described a very high conversion rate.

Length of stay

Median length of stay (LOS) was reported in 13 studies and varied from 0-48 days with a median of 4.5 days.

Bile duct injury

One case of iatrogenic bile duct injury was reported [18], all other studies had none.

Bile Leak

The most common complication was postoperative bile leak, which occurred in 66 patients (10.6%). Three authors report a median duration of the leak of 7 days, one author had a median of 17 days of leakage. Ranges were not given.

Patients in which the cystic duct was closed had a leak in 18 of 321 cases (5,6%), whereas with an open cystic duct, leakage occurred in 48 of 295 patients (16%). Method A lead to a bile leak in 54 of 332 patients (16.2%) and method B (one article, 0 out of 8 patients) lead to no leaks. Method C showed a leak rate of 6/168 patients (3.5%) and method D saw a bile leak in 3 of 60 patients (5%).

Table 3. Overall outcomes.

Author	N	AC (%)	Conversion	Median LOS (days)	Bile leak	Duration of leak (mean days)	Symptomatic gallstones	Reoperation	Postop ERCP	PCI	mortality
Beldi	46		9	12	33	7		3	7	1	1
Bickel	6	2 (33%)	0		0			0	0	0	0
Bonavina	9	9 (100%)	0	2	0		1	0	1		0
Chowbey	56	35 (62,5%)	3	2,5	3	7		0	1		0
Horiuchi	29			11	1	7			0	0	0
Hubert	39	3 (8%)	10	4	0		2	0	2	0	0
Ji	168	135 (80,3%)	5	4,2	8					1	0
Michalowski	29	23 (79,3%)	5	5	3		0	0	0	2	1
Nakajima	60	60 (100%)	1	5	0		0				0
Philips	26	9 (34,6%)	0	5	4		1	2	5		1
Ransom	8	8 (100%)	0	2,7	0			0	0	0	0
Sharp	21	19 (90,5%)	20	6	3		0	1	4		0
Singhal	52	24 (46,2%)	1	2	3			2	3		0
Sinha	28	14 (50%)		3	5	17			3	1	0
Tian	48	11 (22,9%)	5	5,2	3						0
Total	625	352 (56,3%)	59 (9,4%)	5,1	66 (10.5)	9,5	4 (2.2%)	8 (2,7%)	26 (7.5%)	5 (1,4%)	3 (0.5%)

AC: Acute Cholecystititis, LOS: Length Of Stay, ERCP: Endoscopic Retrograde Cholangiopancreatography, PCI: Percutaneous Intervention,

Table 4. Outcomes per operative method.

Method	N	No of papers	Conversion rate	Bile leak	Symptomatic gallstones	Reoperation	Postop ERCP	PCI
A	332	7	19/275 (6.9%)	54/332 (16%)	1/55 (1.8%)	5/107 (4.7%)	15/164 (9.1%)	7/164 (4.3%)
B	24	2	0/8 (0%)	0/8 (0%)	-	0/8 (0%)	0/8 (0%)	0/8 (0%)
C	200	4	5/168 (3%)	6/168 (3.6%)	0/60 (0%)-	2/108 (1.9%)	4/108 (3.7%)	0/60 (0%)-
D	60	2	30/60 (50%)	3/60 (5%)	1/60 (1.7%)	1/60 (1.7%)	6/60 (10%)	2/39 (5%)
Cystic duct closure								
yes >90%	321	7	24/321 (7.4%)	18/321 (5.6%)	2/98 (2%)	2/190 (1%)	6/219 (2.7%)	3/279 (1%)
No	295	8	35/295 (11.9%)	48/295 (16.3%)	1/159 (0,6%)	6/93 (6.4%)	19/121 (16%)	2/74 (3%)

A excision anterior wall, no gallbladder stump closure, leaving a drain in situ, +/- coagulation of remnant gallbladder mucosa;
B excision of anterior wall with gallbladder stump closure, with or without a drain;
C dissection of posterior wall from liver, leaving a closed gallbladder stump without a drain;
D dissection of posterior wall from liver, leaving an open gallbladder stump with a drain

ERCP endoscopic retrograde cholangiopancreaticography; PCI percutaneous intervention;

Recurrent symptomatic gallstones

In the papers that describe some follow-up, 4 (2.2%) patients experienced recurrence of symptomatic cholelithiasis despite the LPC. Three of these patients, all presenting within 6 months after the LPC, were successfully managed with endoscopic papillotomy [12, 15]. One patient required completion laparoscopic cholecystectomy for recurrent right upper quadrant pain[19]. The authors did not state at what time interval after the LPC this procedure took place.

Reoperation

Eight of 292 (2.7%) patients had a reoperation. Three reoperations were done for intra-abdominal abscess, two for persistent bile leak, one for removal of an infected residual stone and one patient had a reoperation for bleeding from the liver bed.

Postoperative ERCP

Postoperative ERCP was not uncommon in the described patient group and was performed in 26 of 349 (7.5%) patients. Indications for ERCP were retained CBD stones (n=9) and stenting in case of biliary leakage of the cystic stump (n=8). Two patients underwent postoperative ERCP for elevated liver enzymes, with no abnormalities found. Beldi et al [11] described 7 patients undergoing postoperative ERCP, all for either CBD stones or biliary leakage, without stating how many patients had each indication. ERCP was needed in 6 of 219 patients (2.7%) when the cystic duct was closed, as opposed to 19 of 121(16%) when the cystic duct was not closed.

Percutaneous intervention

Apart from postoperative drainage, a percutaneous (radiological) intervention was necessary in a few patients. In 5 cases a percutaneous intervention was described because of subhepatic or subphrenic abcess or hematoma. All of these patients had been treated by using method A (5 of 332 patients, 1.5%).

Mortality

Three deaths were described in the entire series (one of pulmonary sepsis and two of myocardial infarctions).

DISCUSSION

The present review shows that the laparoscopic approach at partial cholecystectomy is feasible in approximately 90% of patients undergoing difficult resection and only 10.4% of cases was converted to open procedure. In the majority of patients, the indication for laparoscopic partial cholecystectomy (LPC) was acute cholecystitis. Overall, LPC seems to be safe and effective in avoiding major bile duct injury (BDI) as only one case

of major BDI was reported in all reviewed papers. Also, no procedure related deaths occurred. Not surprisingly, the most frequent complication after LPC was not further specified bile leakage from an inadequate or not closed cystic duct. As part of the surgical strategy, ERCP and subsequent stenting can be added as elegant therapy for bile leakage after leaving the cystic duct or gallbladder remnant open on purpose. LPC therefore is associated with a relatively high number of postoperative ERCPs (7.5%). The risk of BDI, however, is minimized by this approach. Moreover, the majority of bile leaks resolved spontaneously after a mean of 9.5 days.

Another important issue is the formation of gallstones and/or residual gallstones in the remnant gallbladder. Symptomatic gallstone disease recurred in 4 of 184 (2.2%) patients during a maximum follow-up of 100 months; with all papers reporting a maximum of 5% recurrent symptomatic gallstones at follow-up. Three of these patients were successfully treated with endoscopic papillotomy and only one patient required completion laparoscopic cholecystectomy. The experience of this completion procedure was not discussed in detail, however. It should be noted that recurrent symptoms after conventional cholecystectomy, the so-called post-cholecystectomy syndrome, occur in 10 to 40% of patients and is often related to recurrent or residual gallstones[24]. With those numbers in mind, the results of LPC seem acceptable (recurrent gallstone formation does not seem to be a major issue). It should be kept in mind that follow-up was limited in most series, possibly underestimating the need for completion cholecystectomy on the longer term, as a remnant gallbladder has the potential to develop recurrent stones. Evidence of the safety and feasibility of (laparoscopic) completion cholecystectomy following LPC is even scarcer and is beyond the scope of this study.

The current review has its weaknesses. The selected papers include mainly retrospective consecutive series with small to moderate sample sizes, and poor quality. Follow-up is lacking in most series. Another problem that makes it hard to draw firm conclusions is the variety of techniques described in the reviewed series. Every author published his or her own interpretation of LPC, differing in part of gallbladder excised, closure of the stump or cystic duct, coagulation of mucosa and use of drains. Some authors even used different techniques in the same series. This makes it hard to pool data and compare the different methods statistically. For rough comparison, however, the authors of the current review distinguished four techniques of LPC and identified closure of the gallbladder remnant and/or cystic duct an important step that seems to influence outcome favorable. Method D (leaving the transsected gallbladder neck open) showed a conversion rate of 50%, but this is due to a single series with an extraordinarily high conversion rate. Postoperative bile leak seems to be appearing most when method A was used, being the minimal variant in which only the anterior gallbladder wall is excised, and the stump is not closed. Also, the need for ERCP seemed higher when the gallbladder stump was left open as with methods A or D. Therefore, closure of the cystic

duct seems advantageous and it minimizes the need for ERCP, reduces the amount of leaks, seems to reduce the associated length of hospital stay and lowers the rate of recurrent symptoms of gallstone disease. Whether to dissect the posterior wall (methods C and D) or to leave a drain is hard to conclude from the current data.

In conclusion, laparoscopic partial cholecystectomy (LPC) seems feasible and may be a good alternative to conversion for a difficult gallbladder at laparoscopic cholecystectomy. This permits the surgeon to continue the procedure laparoscopically without increasing the risk of BDI. There could not be dawn firm conclusions about the preferred method at LPC, but closure of the remnant gallbladder pouch and/or cystic duct seems favorable. Of course, expertise of the surgical team plays an important role.

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CHAPTER 8

Staged, multidisciplinary, step-up management strategies for necrotizing pancreatitis

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Staged, multidisciplinary, step-up management strategies for necrotizing pancreatitis

ABSTRACT

Background: Some 15 % of all patients with acute pancreatitis develop necrotizing pancreatitis, with potentially significant consequences for both patients and healthcare services.

Methods: This review summarizes the latest insights into the surgical and medical management of necrotizing pancreatitis. General management strategies for the treatment of complications are discussed in relation to the stage of the disease.

Results: Frequent clinical evaluation of the patient's condition remains paramount in the first 24–72 h of the disease. Liberal goal-directed fluid resuscitation and early enteral nutrition should be provided. Urgent endoscopic retrograde cholangiopancreatography is indicated when cholangitis is suspected, but it is unclear whether this is appropriate in patients with predicted severe biliary pancreatitis without cholangitis. Antibiotic prophylaxis does not prevent infection of necrosis and antibiotics are not indicated as part of initial management. Bacteriologically confirmed infections should receive targeted antibiotics. With the more conservative approach to necrotizing pancreatitis currently advocated, fine-needle aspiration culture of pancreatic or extrapancreatic necrosis will less often lead to a change in management and is therefore indicated less frequently. Optimal treatment of infected necrotizing pancreatitis consists of a staged multidisciplinary 'step-up' approach. The initial step is drainage, either percutaneous or transluminal, followed by surgical or endoscopic transluminal debridement only if needed. Debridement is delayed until the acute necrotic collection has become 'walled-off'.

Conclusion: Outcome following necrotizing pancreatitis has improved substantially in recent years as a result of a shift from early surgical debridement to a staged, minimally invasive, multidisciplinary, step-up approach.

INTRODUCTION

In recent decades the incidence of acute pancreatitis has increased globally and the burden of acute pancreatitis on worldwide healthcare services is expected to increase even further[1–6]. Some 85% of patients with acute pancreatitis make a quick and uneventful recovery, requiring little more than analgesia with or without minor supportive measures (fluid therapy). However, around 15% develop necrosis of the pancreatic parenchyma or extrapancreatic tissue. Failure of one or more organ systems will ensue in approximately 40% of these patients. Only a minority of patients without pancreatic necrosis develop organ failure, but it can sometimes occur[7]. Both complications are independently associated with prolonged hospital admission, and high morbidity and mortality rates. Should pancreatic or extrapancreatic necrosis become infected, mortality rates increase up to 20%[8].

In necrotizing pancreatitis, the type of complication that may develop is closely related to the time from symptom onset, and specific complications may be managed differently at different time points. Therefore, this review addresses staged multidisciplinary 'step-up' strategies for necrotizing pancreatitis according to time from onset of symptoms. The complications and subsequent management strategies are described in each phase of necrotizing pancreatitis.

METHODS

The recommendations in this review are based on the recently revised guidelines[9,10] of the International Association of Pancreatology (IAP)/American Pancreatic Association (APA) and the American Gastroenterological Association. To construct the revised IAP/APA guideline multiple systematic reviews were performed by different groups of experts covering the most important areas of necrotizing pancreatitis. Recommendations for areas of necrotizing pancreatitis that lack solid evidence are based on expert opinion from international experts and consensus within the Dutch Pancreatitis Study Group.

The different events following the time after symptom onset are described in accordance with the most likely chronological presentation to the treating physician. Starting with diagnosis and management on admission, the treatment suggestions for the first week are described followed by those for weeks 2 and 3, weeks 4–6 and after week 6.

Definition

The 2012 revised classification of acute pancreatitis[11,12] is now considered the new standard for defining acute pancreatitis and its complications (*Table 1*). In the revised classification, mild acute pancreatitis is defined by the absence of organ failure and local complications. Symptoms usually resolve within the first few days after admission

Table 1. Overview of the revised classification of acute pancreatitis.

Category	Characteristics
Mild	No organ failure No local or systemic complications
Moderate	Organ failure for < 48 h *or* Local* or other systemic† complications
Severe	Organ failure for more than 48 h Local or systemic complications usually present

*Such as pancreatic necrosis, extrapancreatic fluid collection, splenic vein thrombosis; †exacerbation of pre-existing co-morbidity, for example chronic lung disease.

and most patients are discharged from hospital within a week. If performed, contrast-enhanced computed tomography (CECT) may reveal interstitial pancreatic oedema occasionally accompanied by extrapancreatic fatty tissue inflammation. Most often the result of gallstones or alcohol abuse, definitive treatment consists of cholecystectomy or alcohol avoidance[1]. Although less common, several types of drug may cause pancreatitis and accordingly changes in medication should be queried on admission[13]. Any possible provoking agent should be discontinued immediately. Acute pancreatitis affects men and women in equal proportions, although alcoholic pancreatitis seems more prevalent in men whereas women are more likely to develop gallstone pancreatitis. The overall mortality rate of acute pancreatitis does not exceed 5 % and 75 % of patients do not suffer a recurrence[14,15]. In moderately severe acute pancreatitis, patients develop either transient organ failure (lasting less than 48 h) or local complications, such as pancreatic or extrapancreatic necrosis or pancreatic fluid collections. Severe pancreatitis is marked by persisting organ failure (lasting more than 48 h) and is usually accompanied by local complications. The rationale for this cut-off value of 48 h is that organ failure persisting beyond this point is associated with a much higher risk of death[16–19].

Evaluation and diagnosis on admission

Acute pancreatitis is diagnosed when two of the following three criteria are present: pain in the upper abdominal region, raised levels of lipase or amylase at least three times the upper limit of normal, and characteristic findings on cross-sectional abdominal imaging. In most patients the first two criteria suffice for the diagnosis and no imaging is needed. CECT should be carried out only if there is diagnostic uncertainty. The aetiology of pancreatitis should be determined, because it has implications for both short- and long-term management[20].

Laboratory testing

On admission, the serum level of amylase or lipase is merely diagnostic and is not associated with an increased risk of developing complications[21]. Both parameters reach their peak and decrease back to normal in 2–4 days (amylase) and 8–14 days (lipase)[22]. Repeated measurements after admission are not indicated. Increased alanine aminotransferase levels on admission of over 60 units/l show a high probability of a biliary aetiology (positive predictive value 80–90%)[23,24]. Additional blood tests on admission should be carried out to rule out less common aetiologies such as hypertriglyceridaemia and hypercalcaemia.

Radiology

Ultrasonography is indicated in all patients with suspected gallstone disease. It is useful for diagnosing cholecystolithiasis, but less accurate for detecting common bile duct stones (*Table 2*)[24–26]. However, significant dilatation of the common bile duct (diameter over 8 mm in patients aged 75 or younger, and more than 10 mm in patients over 75 years of age) is considered positive for a biliary aetiology. Both magnetic resonance cholangiopancreatography and endoscopic ultrasonography have excellent accuracy for detecting choledocholithiasis. Endoscopic ultrasonography is superior in detecting sludge and small stones, especially in non-dilated bile ducts[24,27–29]. Early CECT or magnetic resonance imaging (MRI) might be used to confirm the diagnosis of acute pancreatitis in those rare instances when the diagnosis cannot be established by clinical signs and biochemical parameters, for example if there clinical signs of an acute abdomen.

Table 2. Radiological accuracy for determining biliary origin.

	Sensitivity	Specificity	Positive predictive value	Overall
Cholecystolithiasis				
Ultrasonography	High	Moderate	Excellent	High
Choledocholithiasis				
Ultrasonography	Poor	High	Moderate	Moderate
EUS	Excellent	Excellent	Excellent	Excellent
MRCP	Excellent	Excellent	High	Excellent
CECT	High	High	High	High

Poor, below 60 %; moderate, 60–74 %; high, 75–90 %; excellent, 91–100 %. EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; CECT, contrast-enhanced computed tomography.

Severity prediction

Several predictive scoring systems have been proposed for identification of patients at risk of developing organ failure or pancreatic complications[30–33]. Identification of these patients is important for institution of early supportive measures and for inclusion in clinical trials. Unfortunately, because the discriminatory power of most traditional scoring systems is moderate at best, their clinical applicability is limited[34–36]. More recent endeavours have aimed at identifying single serum markers to predict severity as opposed to the older, more complex systems that use multiple clinical and biochemical features (such as the modified Glasgow score, Ranson score and the Acute Physiology And Chronic Health Evaluation (APACHE) II)[37]. For example, serum creatinine concentration correlates strongly with the development of pancreatic necrosis, with a positive predictive value of 93 %, if blood levels rise to above 1.8 mg/dl (or 159 μmol/l) within 48 h of admission[38]. Blood urea nitrogen levels are a strong predictor of death[32]. A blood urea nitrogen level of 20 mg/l (7.14 μmol/l) or higher on admission, or any rise within 24 h after admission, is associated with an odds ratio for death of 4.6 and 4.3 respectively.

In the first 72 h after symptom onset, necrosis of the pancreatic parenchyma cannot be assessed reliably on CECT[34]. Consequently, CECT has no role in assessing or predicting the severity of disease on admission in the first few days after admission[30,34,39–43].

Management during the first week

Management of necrotizing pancreatitis during the first week of admission mainly consists of frequent clinical evaluation, analgesia and supportive measures (*Fig. 1*). In the first few days after admission, patients should be evaluated for the presence of the systemic inflammatory response syndrome (SIRS). Patients with persisting SIRS have a significantly worse outcome[18,44,45]. Monitoring SIRS is an effective bedside tool for assessment of disease progression because measurement of its components can be done easily and repeated[9].

In the event of deterioration or absence of clinical improvement at the end of the first week, CECT or MRI is indicated to assess the presence and extent of pancreatic or extrapancreatic necrosis, or extrapancreatic fluid collections[46,47]. Clinical deterioration during the first week is most often caused by progression of SIRS and seldom because of early infection of pancreatic necrosis[48]. As such, surgical intervention is not indicated during this phase unless an ischaemic or perforated viscus is the cause. If emergency surgery is deemed necessary, it is associated with mortality rates of 40–78 %[7,49,50]. Early emergency surgery potentially aggravates multiple organ failure, as shown by an increase in APACHE II scores after operation[51,52]. Additionally, complications (such as bleeding, intestinal fistula) are more prone to occur if surgery is performed before the acute necrotic collection has had time to progress to 'walled-off' necrosis (*Fig. 2*). Although there is no compelling evidence to support either of these arguments, the unfavourable

Figure 1. Suggested treatment algorithm for necrotizing pancreatitis according to the time after onset of symptoms. CECT, contrast-enhanced computed tomography; SIRS, systemic inflammatory response syndrome; ERCP, endoscopic retrograde cholangiopancreatography; MRI, magnetic resonance imaging; FNA, fine-needle aspiration

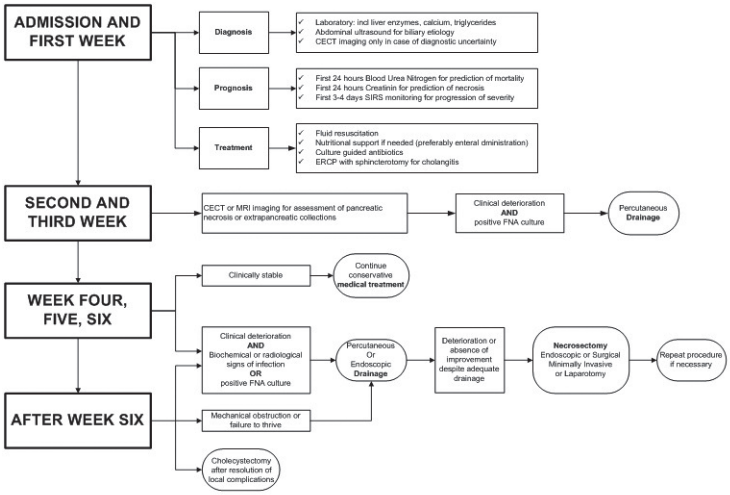
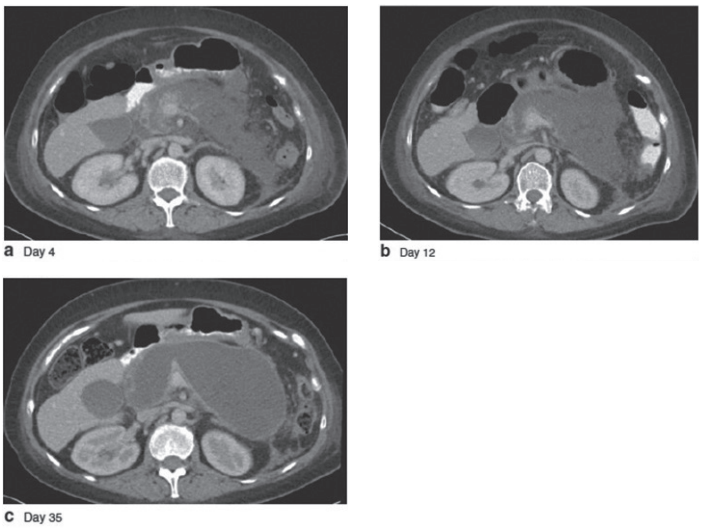


Figure 2. Example of contrast-enhanced computed tomography in a patient with necrotizing pancreatitis.



a Acute necrotic collection on day 4 after the onset of symptoms. Note the heterogeneous non-liquid pancreatic and extrapancreatic components in the retroperitoneum.
b On day 12 after symptom onset the acute necrotic collection is not yet fully encapsulated.
c On day 35 after symptom onset note the enhancing wall of reactive tissue or encapsulation; this is an example of walled-off necrosis

outcomes following early debridement have driven clinicians towards more conservative policies in the early phase of the disease[7,50,53–55].

Fluid resuscitation

Fluid resuscitation aims at counteracting the effects of hypovolaemia due to 'third spacing', and is directed at restoring the microcirculation and thereby oxygenation of the pancreas and other organ systems[56]. Adequate fluid resuscitation may prevent further local injury to the pancreas and so might inhibit the systemic inflammatory response[57–59]. Traditionally, liberal intravenous fluid infusion has been advocated. The patient's vital signs (heart rate, blood pressure, oxygen saturation) and urinary output (accepted urinary output over 0.5 ml per kg per h) are monitored, taking into account pre-existing conditions contraindicating high-volume fluid infusion[14,20,40]. Fluid resuscitation is especially important in the first 12–24 h after admission. Thereafter, the amount of fluid administered can be decreased[10]. It is unclear what type of fluid should be used. A recent systematic review[57] found no clinically significant differences between the use of isotonic crystalloid or colloid fluid.

Role of endoscopic retrograde cholangiopancreatography

In gallstone pancreatitis, obstructing stones or biliary sludge usually pass through the biliary tract spontaneously[60]. Obstruction persists in some patients, increasing the risk of developing cholangitis. If progressive cholestasis and dilatation of the common bile duct is accompanied by fever, the patient should be suspected of cholangitis and urgent endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy is indicated[61,62].

The benefit of ERCP in patients with pancreatitis without cholangitis, however, is unclear. A recent meta-analysis[63] with pooled data from seven randomized trials, including 757 patients with gallstone pancreatitis, found no significant reduction in morbidity or mortality by routine use of early ERCP (within 72 h after admission) compared with conservative treatment. Unfortunately, the subgroup of patients with predicted severe pancreatitis was relatively small, raising the possibility of a type II error. Further research is needed in this group of patients. Recently, a new randomized multicentre trial has been started in the Netherlands investigating routine early ERCP with sphincterotomy in patients with predicted severe biliary pancreatitis (APEC trial; ISRCTN97372133).

Nutrition

In necrotizing pancreatitis, adequate nutritional intake can be obtained through an oral diet or enteral nutrition. Several meta-analyses[64–66] of randomized trials comparing enteral with parenteral nutrition showed that enteral nutrition significantly reduces organ failure, infections and mortality. Two small randomized studies[67,68], with 31 and

50 patients with severe pancreatitis, concluded that nasogastric feeding was just as well tolerated as nasojejunal feeding. No differences were found between different types of enteral nutrition formulations[69].

Enteral feeding is hypothesized to maintain the integrity of the gastrointestinal mucosal barrier, thus inhibiting bacterial translocation and reducing infectious complications[70–73]. Several non-randomized studies[74,75] concluded that very early enteral feeding (within 24–48 h after onset) reduces pancreatic infections and multiple organ failure even further. The results are awaited from a multicentre trial[76] investigating the effect of very early enteral feeding in patients with predicted severe pancreatitis. In this trial, 208 patients were assigned randomly to very early nasojejunal feeding (within 24 h after onset) or standard practice (oral diet after 72 h after admission or, if needed, enteral feeding after 72 h).

Antibiotic prophylaxis

Secondary infection of pancreatic or extrapancreatic necrosis occurs in approximately one-third of patients with necrotizing pancreatitis[7,77,78]. Many efforts have been made to test antibiotic prophylaxis in prevention of infected pancreatic necrosis. Early small randomized trials[79,80] showed promising results, reporting lower rates of mortality and infected necrosis. More recent placebo-controlled studies[81–83], however, failed to confirm these results. In the past 5 years, ten meta-analyses[78,84–92] have been published on the subject. Eight of these did not find a reduction in infected pancreatic necrosis and none showed a reduction in mortality. These clinical studies have been critiqued for their low methodological quality[93]. So far, three double-blinded and placebo-controlled studies[81–83] have been performed, showing no positive effects of antibiotic prophylaxis.

In the first week after admission, there is no role for routine antibiotic prophylaxis in the treatment of necrotizing pancreatitis. Antibiotics should be withheld until infection is proven with positive cultures. In most patients, infection of pancreatic or extrapancreatic necrosis does not occur until week 3 or 4. Antimicrobial agents with favourable pancreatic tissue penetration, such as carbapenems, metronidazole and quinolones, are recommended[10,80,83].

Abdominal compartment syndrome

Abdominal compartment syndrome (ACS) is very rare in patients with necrotizing pancreatitis and, if the suspicion arises, it most often occurs in the first week after symptom onset[94]. Aggressive fluid resuscitation, retroperitoneal fluid accumulation and ascites may contribute to raised intra-abdominal pressure (transvesical pressure measurements exceeding 12 mmHg). A prevalence of intra-abdominal hypertension up to 61% has been reported in patients with necrotizing pancreatitis[95]. Persisting intra-abdominal hypertension is believed to be a precursor of ACS. The World Society of the

Abdominal Compartment Syndrome[96] defines ACS as 'persisting abdominal pressure above 20 mmHg accompanied by new onset organ failure'.

Several non-invasive strategies may aid in reducing the intra-abdominal pressure: enteral decompression through gastric or rectal tubes, recalibrating the intravenous fluid regimen for a zero-to-negative balance, and increasing abdominal wall compliance through medication. If non-invasive options are not sufficiently effective, the next step of treatment should be aimed at evacuation of excess intra-abdominal or retroperitoneal free fluids, such as ascites, by percutaneous catheter drainage (PCD).

Decompression laparotomy is sometimes applied as a 'last resort' if multiple organ failure escalates However, currently there is no evidence that surgical decompression has a beneficial effect on outcome. If there is no infected necrosis (as in most patients during the first week after admission) the retroperitoneum should not be opened during this procedure to minimize the risk of introducing pathogens[96,97]. Although decompression laparotomy seems effective in individuals without pancreatitis[13,98], ACS in patients with pancreatitis seems mainly associated with massive fluid resuscitation[99]. In these patients, no improvement in overall morbidity and mortality has been documented. A randomized trial is currently investigating the role of percutaneous drainage as a primary means of decompression compared with surgical decompression (DECOMPRESS trial; ClinicalTrials.gov NCT00793715)[100].

Management during the second and third weeks

Infection of pancreatic necrosis

Infected pancreatic necrosis is usually diagnosed during the second or third week after onset[48,81,101]. Other possible sources of infection, such as pneumonia, must be ruled out first, as these tend to occur earlier in the course of the disease[48]. Cross-sectional imaging is indicated to assess the evolution of pancreatic necrosis and peripancreatic fluid collections. Occasionally, CT or MRI may reveal retroperitoneal gas bubbles inside pancreatic fluid collections pathognomonic for infection. These collections rarely show signs of complete encapsulation before the fourth week[102].

Fine-needle aspiration

Fine-needle aspiration (FNA) culture of pancreatic fluid collections is useful if the diagnosis is uncertain and has the added value of optimizing antibacterial therapy. Routine FNA culture was promoted more widely in the past, but has been used more selectively in recent years. The reason for this shift is that, with the more conservative approach currently advocated, FNA results less often lead to a change in management and so aspiration is indicated less frequently. FNA carries a risk of false-negative results in up to 25% depending on timing after onset and indication[103,104]. Therefore, FNA should be used to obtain information about a collection only when the result will direct

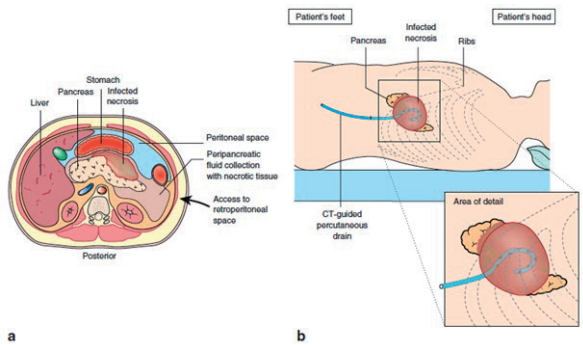
the treatment plan. FNA is warranted, for instance, in patients who fail to recover from organ failure (and thus have persisting high inflammatory parameters so infected pancreatic necrosis cannot be discriminated clinically) and without signs of infection on CECT. A positive FNA would warrant a step up in treatment of the fluid collection.

Percutaneous catheter drainage

Percutaneous catheter drainage (PCD) (*Fig. 3*) is an important adjunct in the care of patients with infection of acute necrotic collections or walled-off necrosis. Once infection occurs, the patient must be treated effectively in a timely manner for a good outcome. Most patients need antibiotics and drainage. The use of PCD is the first step of the step-up approach. Catheters are placed optimally by the left or right retroperitoneal route, depending on the anatomy of the collections. In the absence of solid evidence regarding the optimal timing of PCD, different strategies are applied. A positive FNA during the second or third week leads to PCD in some institutions, whereas in others antibiotics are started first, with PCD in this disease phase only following further clinical deterioration. Early PCD may substantially improve a patient's condition but can also introduce infection in a sterile collection, thereby leading to deterioration, so it is important that infection be documented clearly first.

In the past decade, several specialized centres have reported successful treatment of infected necrotizing pancreatitis with PCD alone in 35–55% of patients[105–107]. The PANTER trial compared PCD as the first step of a step-up approach with primary open necrosectomy for infected necrotizing pancreatitis. Interestingly, more than 30% of those enrolled in the step-up group did not need additional surgical necrosectomy[107]. Available evidence indicates that a subgroup of patients with infected necrotizing pancreatitis can be treated successfully with PCD alone. Unfortunately, it remains unclear which patients will recover successfully after PCD alone and which will need an additional

Figure 3. Preferred route for percutaneous catheter placement for drainage of a typical infected peripancreatic collection. Via the left flank, a catheter can be manoeuvred retroperitoneally between the spleen, colon descendens and kidney using computed tomographic guidance.



endoscopic or surgical necrosectomy. Therefore, the first step in treatment should be percutaneous or endoscopic drainage, followed by surgical or endoscopic necrosectomy only if clinically necessary.

Management during the fourth, fifth and sixth weeks

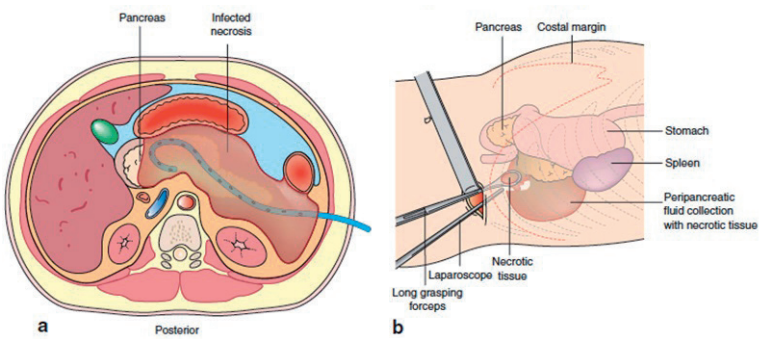
A second peak in mortality is seen in this phase of the disease, mostly associated with infection of the pancreatic or extrapancreatic necrosis[14]. In general, only patients with infected necrosis should undergo invasive interventions[14,20,108]. Interventions such as endoscopic transluminal drainage and necrosectomy, and minimally invasive or open necrosectomy should be delayed if possible to around 4 weeks after the onset of symptoms[102]. This allows the collection to become walled-off, which is believed to facilitate necrosectomy[9] (*Fig. 2*).

Minimally invasive surgical necrosectomy

Two minimally invasive surgical techniques have gained widespread acceptance: sinus tract endoscopy (also referred to as minimal access retroperitoneal pancreatic necrosectomy, MARPN)[109,110] and video-assisted retroperitoneal debridement (VARD)[106] (*Fig. 4)*. In both procedures, access to the necrotic pancreas is achieved by following the tract of a radiologically placed drainage catheter.

In sinus tract endoscopy, pioneered in Glasgow, a nephroscope is inserted into the infected collection after dilatation of the drain tract to 30 Fr under fluoroscopic guidance. Debridement is carried out using long forceps, and the necrotic cavity is flushed using jet irrigation and suction devices. The procedure is repeated if the patient fails to recover and residual infected necrosis is suspected. A median of three to five procedures is needed for adequate necrosectomy[109,110]. A large retrospective cohort

Figure 4. Using the percutaneous catheter as retroperitoneal guide, a 5-cm subcostal incision is made. The first solid debris that is encountered can be removed bluntly using long grasping forceps. Subsequently a 0º laparoscope is introduced into the necrotic cavity and more central necrotic debris can be removed.



series indicated that survival rates are potentially better with MARPN compared with open necrosectomy (19% of 137 patients *versus* 38% of 52 patients)[111]. Additionally, postoperative organ failure and complication rates may be lower in the minimally invasive group.

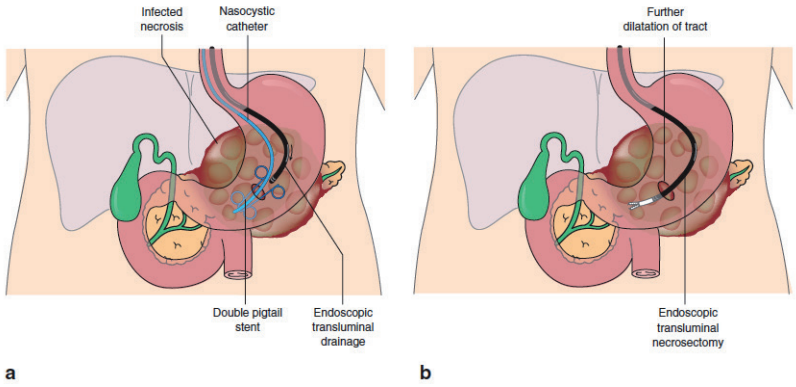
The VARD technique was developed in Seattle, USA. It uses a 5-cm subcostal incision in the left flank near the exit point of the percutaneous drain[112]. The drain is followed closely into the collection. After opening the collection bluntly and clearing the first liquid and solid debris encountered with suction and long grasping forceps, a 0° camera used for laparoscopy is introduced into the necrotic cavity. The camera is placed through a laparoscopic port, which is placed directly through the incision. Carbon dioxide is infused through the percutaneous drain to inflate the cavity. After surgery continuous lavage is started using two large-diameter drains. This technique allows vigorous debridement of the necrotic cavity with a median of one procedure[106]. In the years following the introduction of VARD in Seattle, it became clear that percutaneous drainage alone could also be sufficient in some patients, instead of just serving as a bridge to necrosectomy. This finding generated the hypothesis behind the PANTER trial[113]. In this trial, 88 patients were allocated randomly to either primary necrosectomy via laparotomy or the step-up approach. A significantly lower rate of the composite endpoint of major morbidity or death was found in the step-up group (40 *versus* 69%; $P = 0.006$). New-onset multiple organ failure was also significantly less common in the step-up group (12 *versus* 40%; $P = 0.002$).

A few case series have been published on laparoscopic necrosectomy. This transperitoneal route offers access to the lesser sac and simultaneous management of intra-abdominal organs (for example concurrent cholecystectomy)[113]. However, it also has the disadvantage of introducing a continuum between the peritoneal cavity and the retroperitoneum containing infected pancreatic necrosis[1112114,115].

Endoscopic transluminal drainage or necrosectomy

Parallel to the development of minimally invasive surgical strategies, endoscopic transluminal approaches have been developed[116,117]. Under direct vision or endoscopic ultrasound guidance, the gastric or duodenal wall is punctured to reach the walled-off necrosis (*Fig. 5*). The transluminal tract is dilated sequentially using a balloon. Short pigtail catheter drains or a stent can be used to prevent the access to the retroperitoneum from closing after the first procedure. A nasocystic catheter is placed in the necrotic cavity for continuous irrigation[46]. The use of multiple transluminal gateways has been suggested to improve drainage of the infected material, and successful drainage without the need for additional intervention was achieved in up to 90% in a small cohort of selected patients[118]. Patients in whom endoscopic drainage proves insufficient may benefit from endoscopic necrosectomy. Like sinus tract endoscopy, the transluminal drain tract is dilated further for introduction of an endoscope. Various instruments are used for the

Figure 5. Under direct vision or endosonographic guidance, the gastric or duodenal wall is punctured to evacuate the infected necrotic material. **a.** After serial dilatation of this transluminal tract two double-pigtail catheters are placed to establish a patent drain tract. **b.** Should the need for endoscopic necrosectomy arise, the tract is dilated further through which various endoscopic necrosectomy instruments can be introduced.



actual necrosectomy, such as endoscopic baskets, snares, jet irrigation and forceps[117,119]. A recent systematic review showed that 197 (75.8%) of 260 patients were treated with endoscopic treatment alone, with only two reported deaths. Although these results seem promising, they must be interpreted with caution as they are based predominantly on non-randomized findings in selected patients from experienced institutions. The first randomized trial[52] compared endoscopic necrosectomy with surgical necrosectomy in 22 patients with infected necrotizing pancreatitis. This pilot trial showed that the inflammatory response (interleukin 6 levels) and a composite endpoint of death or major complications were significantly reduced following endoscopy compared with surgery. A large clinical trial following on from this pilot study is currently being conducted. Ninety-eight patients will be randomized to an endoscopic step-up approach or the surgical step-up equivalent (percutaneous drainage followed by VARD or, if not feasible, open necrosectomy) (TENSION trial; ISRCTN 09186711).

Open surgical necrosectomy

Primary open surgical necrosectomy has been the standard treatment of infected necrosis for decades. The classical approach is to enter the retroperitoneum through a laparotomy, after which the necrotic tissue is removed by blunt dissection[120]. Healthy pancreatic tissue is preserved as much as possible, and by doing so the risk of postoperative bleeding or pancreatic fistulas is minimized. Different surgical techniques have been developed over the years, such as open packing, closed packing with planned reoperation or postoperative continuous lavage to remove any residual material[108]. Open necrosectomy remains associated with substantial morbidity[121–123]. These high morbidity rates are generally attributed to the exacerbation of stress induced by the trauma of

surgery in an already critically ill patient, but are also closely associated with the timing of intervention and the presence of persistent organ failure[107,109,124]. The minimally invasive approaches were developed specifically for this reason, although to date no randomized trial has proven the superiority of minimally invasive techniques over open necrosectomy (or laparotomy).

Management after the sixth week

Patients without proof of infection (even after negative FNA) who fail to recover, despite prolonged maximal supportive care, are suspected to have sustained a low-grade infection. In a recent study[104] operative cultures showed proof of infection in 42% of 53 patients who had surgery because they remained persistently unwell despite negative FNA results. Patients in whom a sterile fluid collection causes clinically significant morbidity (gastric or biliary outlet obstruction, pain) should be considered for surgical or endoscopic necrosectomy. A recent randomized trial[125] comprising 40 patients compared endoscopic and open surgical cystogastrostomy. No significant differences were found with respect to recurrence of the fluid collection, reinterventions or complications. Endoscopic cystogastrostomy was associated with a significantly shorter hospital stay (median 2 days *versus* 6 days after open surgery).

Anecdotal evidence exists of spontaneous remission of necrotic collections, even when infection has been proven[116,126]. These highly selected cases demonstrate that even infected pancreatic necrosis can be managed through supportive therapy alone.

Cholecystectomy or, if not deemed feasible, ERCP with sphincterotomy should be considered to minimize the risk of recurrent biliary pancreatitis and other gallstone-related disease. It is generally recommended to postpone intervention until all radiological and biochemical signs of inflammation have subsided[127].

Finally, several other complications may occur during this phase. Vascular complications may be seen on CECT, such as splenic or portal vein thrombosis or, less commonly, splenic artery pseudoaneurysm. These must be dealt with using appropriate application of anticoagulant therapy, endovascular coiling, stenting or embolization, or sometimes even splenectomy. Pancreatic fistulas to various organs may also occur and can be treated quite successfully by endoscopic papillary stenting, thus facilitating drainage of the pancreatic secretion into the duodenum[128].

The impact of the disease and its complications on individual patients often reverberates for years. Psychological as well as physical sequelae, such as exocrine or endocrine insufficiency, may cause lifelong morbidity.

Future directions for research and improvement of outcomes

Frequent clinical evaluation of the patient's condition is of paramount importance at the earliest stages of the disease, as current predictive scoring systems have a mediocre accuracy. New biomarkers may better predict complications in the coming years.

However, early adequate resuscitation in an attempt to prevent organ failure and early detection of any organ failure will remain most important. Based on current literature, liberal goal-directed fluid resuscitation and early enteral nutrition should be provided. Emergency ERCP with sphincterotomy is indicated when cholangitis is suspected, but it is unclear whether it is appropriate for patients with predicted severe biliary pancreatitis. Antibiotic therapy does not prevent infection of necrosis but is indicated if there is proven infection. ACS might occur early in the disease course, and in some critically ill patients decompression laparotomy may improve organ dysfunction temporarily if all non-surgical methods fail, although there is no solid evidence to support this.

In recent years, treatment of infected necrotizing pancreatitis has shifted from early open debridement to postponed minimally invasive step-up strategies, with initial catheter drainage only if needed followed by surgical or endoscopic necrosectomy. As PCD is a relatively simple intervention, this new strategy provides clinicians in general and district hospitals the tools to perform the first step in treatment. Although widespread adaptation of the step-up strategy should be stimulated, it must be stressed that the presence of a multidisciplinary team of physicians is crucial in the treatment of necrotizing pancreatitis. Only a multidisciplinary team including a surgeon, gastroenterologist, radiologist and intensivist will provide adequate care during all disease phases. If such a team is not available around the clock, early transfer of the patient to an expert centre is advised. Several ongoing randomized trials will provide needed recommendations on timing of nutrition, indication for ERCP, optimal route of necrosectomy and indication for decompression in the foreseeable future.

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CHAPTER 9

Overall Summary

SUMMARY

The main objectives of this thesis were to evaluate and, where possible, improve current surgical strategies for mild gallstone pancreatitis. We addressed 1) the clinical and economical consequences of performing cholecystectomy before discharge, 2) the occurrence of gallstone-related complications after surgery and how to prevent them, 3) factors potentially complicating cholecystectomy and 4) strategies to deal with a difficult cholecystectomy. Finally, we discuss management of necrotizing pancreatitis and the role of cholecystectomy in these patients.

In *Chapter 2* we performed a literature search to appraise the *status quo* regarding the scope of gallstone pancreatitis and its treatment. International population based studies have shown that the incidence of acute pancreatitis has been on the rise for at least two decades. This is at least in part attributable to a growing prevalence of gallstones. As gallstones more often occur in women than in men, they are twice as likely to develop gallstone pancreatitis. While its role in patients with predicted severe pancreatitis is still under investigation, early endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy does not improve outcome in patients with mild disease. When signs of biliary tract obstruction persist, ERCP can be performed electively. Only in case of (suspected) ascending cholangitis, urgent ERCP with sphincterotomy is indicated. With regards to prevention of recurrent disease, sphincterotomy fails to provide the same level of long-term protection as cholecystectomy. Only in patients unfit for surgery can sphincterotomy alone be considered as definitive treatment. Overall, thanks to the many scientific efforts that have been made in recent years, management of the biliary tract stones and pancreatitis in general is becoming increasingly clear.

Still, some major and minor issues regarding the role of cholecystectomy remain, mostly in relation to the timing of surgery in patients with mild disease. *Chapter 3* discusses the results of the PONCHO study (Pancreatitis of biliary Origin: optimal timiNg of CHOlecystectomy). In this nationwide, randomized controlled trial, 264 patients with mild gallstone pancreatitis were allocated to cholecystectomy before discharge (N=128) or cholecystectomy after an interval of three to four weeks (N=136). The primary endpoint of readmission for gallstone-related complication or mortality occurred significantly less often in the patients who underwent same-admission cholecystectomy (6 patients in the same-admission group *vs.* 23 patients in the interval group; p=0.002). This included a significant reduction in the number of readmissions for pancreatitis (3 *vs.* 12; p=0.03). Furthermore, over half of all patients in the interval group (51%) reported to have had gallstone colics during the waiting period to cholecystectomy, compared to just 3% of patients in the same-admission group (p<0.001). There were very few surgical complications: in each group, one patient was treated for cystic duct

leakage and one patient underwent a re-intervention for bleeding. These results led us to conclude that same-admission cholecystectomy is safe and reduces the number of gallstone-related readmissions compared with interval cholecystectomy.

Chapter 4 is an analysis of the two previously described strategies from a healthcare-economic point of view. Costs made by the patients after inclusion in the PONCHO trial were evaluated from a health care and societal perspective. These costs included days of admission, surgical costs, radiological and endoscopic examinations and emergency room and outpatient clinic visits. Furthermore, patients recorded pancreatitis-related absence from work. From the healthcare perspective, same-admission cholecystectomy was marginally more costly than interval cholecystectomy (€144). This was mainly due to six patients in the former group with protracted admission periods following complications, resulting in a slightly higher mean. However, patients in the same-admission groups reported less sick days, leading to an overall economic benefit of €234 per patient. Overall, in this randomized trial, same-admission cholecystectomy was not only more effective in patients with mild gallstone pancreatitis but also less costly.

From the previous chapters we have learned that gallbladder removal does not completely obviate the risk of new gallstone-related complications. In *Chapter 5* we studied the frequency, type and severity of postoperative gallstone-related events. Healthcare resource usage was prospectively collected for the participants the PONCHO trial. Furthermore, patients were instructed to record postoperative gallstone colics. During the six-month follow-up period, 25 (10%) of the included 262 patients underwent postoperative hospital care. Readmission for recurrent gallstone disease was needed in 7 of these patients (3%); 4 with recurrent pancreatitis, 2 with gallstone colics and 1 with clinical manifestation of choledocholithiasis. Furthermore, 28 of the 191 patients (15%) returning the gallstone questionnaires reported to have experienced postoperative gallstone colics. In half of these cases this was an isolated event. Furthermore, these events occurred in the first two months after cholecystectomy in 22 of the 28 patients (79%). Only 4 of the 191 patients (2%) reported gallstone colics during the last month of follow-up. No risk factors for the development of postoperative complications could be identified. The rate and severity of these postoperative complications compare favorably to those of not performing cholecystectomy. However, these risks should be discussed properly with the patient prior to surgery.

The technical aspects of cholecystectomy following mild pancreatitis were explored in *Chapter 6*. Data regarding surgical difficulty, the presence or absence of adhesions and surgeon's experience were prospectively collected on PONCHO case record forms. Surgical difficulty was scored on a 0 to 10 visual analogue scale (VAS) by the most experienced attending surgeon. We investigated whether it was possible to predict if a

cholecystectomy would be technically challenging, according to risk factors identified in previous studies. A 'difficult cholecystectomy' was defined by presence of at least one of the following features: a VAS-difficulty beyond the 75th percentile (i.e. 8 or higher), conversion, subtotal cholecystectomy or duration of the procedure beyond the 75th percentile (*i.e.* 75 minutes or longer). According to these criteria, cholecystectomy was difficult in 82 out of the 249 participants (33%). After multivariable analysis male sex (OR 1.80, 95% CI 1.04-3.13; p=0.037), prior sphincterotomy (OR 1.79, 95% CI 1.01-3.16; p=0.046), and delaying cholecystectomy until after 2 weeks after admission (OR 1.81, 95% CI 1.04-3.16; p=0.036) were independent predictors of the combined endpoint. These risk factors coincide with those predictive of a conversion in studies on unselected cohorts of patients. However, when including only the surgeons who had performed at least 100 prior laparoscopic cholecystectomies (*i.e.* experienced surgeons), no predictive factors could be identified.

In cases where inflammation has rendered surgically important landmarks not safely identifiable, conversion from laparoscopy to laparotomy is traditionally advised. An increasingly used alternative to conversion is partial or subtotal cholecystectomy. *Chapter 7* presents an overview of the literature on the results and consequences of laparoscopic subtotal cholecystectomy. Using the search terms 'partial', 'subtotal' and 'incomplete', a systematic search was conducted in the Pubmed and Cochrane databases. Outcomes included bile duct injury or bile leak, symptomatic gallstones in the remnant gallbladder, need for postoperative ERCP or other additional interventions and mortality. Fifteen studies were included in the review, reporting on 625 patients. Multiple methods for performing subtotal cholecystectomy were described. In 10% of cases, conversion was needed nonetheless. Only one case of bile duct injury was reported, while postoperative bile leak occurred in 10% of patients. Recurrent symptoms from gallstones were reported in 2% of patients. Furthermore, postoperative ERCP was needed in 8% and other interventions in 4% of patients. Based on these results, subtotal cholecystectomy seems a feasible and safe alternative to conversion.

In Chapters 2 through 7, the focus has been on what to do when gallstones induce mild pancreatitis. In the Western world gallstones are also the most prominent cause of acute necrotizing pancreatitis. While in mild pancreatitis cholecystectomy has a dominant place in the prevention of further attacks, in severe necrotizing pancreatitis the role and timing of cholecystectomy is of lesser importance. In *Chapter 8*, we summarized current insights in the medical and surgical management of necrotizing pancreatitis. As these patients may develop various complications during the different stages of the disease, we proposed management strategies for each of these stages. The most recent recommendations of the American Gastroenterological Association, the International Association of the Pancreas and the American Pancreatic Association are incorporated

in this review. For issues where no clear consensus exists, the views of the international expert co-authors and those of the Dutch Pancreatitis Study Group were expressed. As the reliability of the various severity prediction models falls short, frequent clinical and biochemical evaluation of the patient's condition remains critical, at least in the first 24 to 72 hours. During this period, liberal intravenous fluid administration is advised. Antibiotic prophylaxis does not prevent the infection of the necrotic pancreatic tissue. Therefore, antibiotics should be reserved for bacteriologically confirmed infection. Should secondary infection occur and the patient continues to deteriorate despite maximal antibiotic and supportive therapy, invasive therapy is indicated. Ideally, this decision should be made by a multidisciplinary team consisting of at least a surgeon, gastroenterologist and radiologists. A step-up approach is advised, in which the first step is percutaneous or endoscopic drainage of the infected matter. If the patient does not improve despite adequate drainage and supportive therapy, endoscopic or surgical debridement of the remnant infected necrotic tissue can be performed. This step is usually delayed until the acute necrotic collection shows signs of encapsulation. Overall, outcome has steadily improved in these patients over the last few decades, at least in part due to this staged, multidisciplinary and step-up approach. Cholecystectomy comes into consideration once the acute necrotizing phase has been successfully dealt with and the patient has fully recovered. This may take 6 to 12 months. There are no reliable data available to guide patient and doctor through the discussion on whether or not to remove the gallbladder.

In the next chapter it will be discussed to what extent the questions posed in the introduction of this thesis have been answered, and which areas require further investigation.

CHAPTER 10

General Discussion and Future Perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Acute gallstone pancreatitis remains a major cause of morbidity in Western societies. Its incidence has consistently increased over the last few decades, and is expected to continue to increase based on prevalence of gallstones presented in population studies.[1] Even though approximately half of all cases of pancreatitis are preceded by gallstone colics in most Western countries, these are often either treated conservatively or diagnosed in hindsight.[2] In the majority of patients, fortunately, the disease is mild and self-limiting. In the absence of cholangitis, biliary tract management (i.e. removal of gallstones from the common bile duct) in the acute phase does not seem to affect outcome in terms of major morbidity or mortality in patients with mild pancreatitis.[3] Initial treatment of pancreatitis consists primarily of pain control and fluid therapy to restore pancreatic microcirculation and counteract hypovolemia due to third spacing. The next step in management is prevention of recurrence in the long-term. While endoscopic sphincterotomy can be helpful for both bile duct clearance and preventing future attacks of cholangitis and pancreatitis, it does not provide the same level of protection as the traditional treatment of cholecystectomy.

The major issue in the treatment of patients with mild gallstone pancreatitis, which is the timing of cholecystectomy, was extensively discussed in *Chapters 3 and 4*. Following contradictory reports on the safety of cholecystectomy in the late 1980s, timing of surgery has been a controversial subject for years.[4-6] Where some advocate a proactive approach in early removal of the gallbladder to reduce the risk of recurrence or potentially worse attacks of pancreatitis, others advise to be more patient on behalf of the perceived increased risk of bile duct lesion. Despite the fact that these fears of bile duct injury were never substantiated in patients with mild disease, doubts regarding the risk of surgical complications are still commonplace in clinical practice today. Both due to these concerns and logistical considerations (i.e. planning turns out to be easier than (sub)acute surgery), cholecystectomy is generally delayed until several weeks after discharge.[7,8] However, during this interval patients remain at risk of developing new gallstone-related complications, such as recurrent pancreatitis. In the PONCHO trial (Pancreatitis of biliary Origin, optimal timiNg of CHOlecystectomy), we compared interval cholecystectomy with same-admission cholecystectomy.[9] The latter strategy reduced the risk of the primary endpoint, acute readmissions for recurrent disease or mortality with 12 percentage points, demonstrating its superiority over interval cholecystectomy in terms of prevention of morbidity. Additionally, this strategy also proved preferable from a socioeconomic perspective, as patients in this group reported less pancreatitis-related sick leave. While the PONCHO trial, the cornerstone of this thesis, provides high-level evidence for same-admission cholecystectomy for future guidelines, several important questions remain for future discussion and study.

Optimal timing of cholecystectomy

The PONCHO trial was not specifically designed to explore the optimal moment of surgery, but rather to compare same-admission with fixed interval cholecystectomy. According to the PONCHO study protocol, patients were randomized after they had made complete clinical (i.e. resumed oral diet, no more need for opioid analgesics) and biochemical recovery (i.e. normalization of pancreatic enzymes, declining CRP levels). These criteria were established partly to reduce the risk of including patients with non-mild disease, and partly to provide objective parameters to determine whether a patient was fit for surgery. Additionally, in the same-admission group, a 72-hour time window for cholecystectomy was allowed as a concession to logistical considerations of planning in usually very busy operating rooms in the participating centers. This effectively meant that patients, fully recovered and ready for discharge, could spend up to 72 hours awaiting cholecystectomy in the hospital for no other reason than to facilitate surgical planning.

In comparison, in an earlier trial on the timing of cholecystectomy in mild biliary pancreatitis, a more aggressive approach was used.[10] In this study published in 2010, 50 patients with predicted mild gallstone pancreatitis were randomized to cholecystectomy within or after 48 hours of admission, irrespective of normalization of clinical or laboratory values (*i.e.* during pancreatitis). As pancreatitis may progress from mild to severe during the first 48 hours after onset, we believe patients should be observed at this stage of the disease and not be exposed to the additional risks of surgery.[11,12] This is in line with the strategy as proposed by the international guidelines.[13,14]

However, since none of the patients in this previous trial developed complications following this strategy of immediate cholecystectomy, the question is raised whether normalization of clinical and biochemical parameters are necessary before cholecystectomy can safely be performed. In other words, the 2010 trial and the PONCHO trial represent the two extremes of the concept of 'early' cholecystectomy, and the true optimal moment of surgery is likely to be somewhere in between. From a medical point of view, further determination of this cholecystectomy 'sweet spot', is not very interesting. Nevertheless, given the high incidence of mild gallstone pancreatitis, we believe that this step should be undertaken to optimize care in these patients. To illustrate, the following case is presented. Patient A, without a relevant medical history, is admitted to the medical ward with predicted mild gallstone pancreatitis. After several days of observation and supportive care, a surgeon is consulted. The surgeon, having concluded that the patient is fit for surgery, then has to start making arrangements for cholecystectomy. If the surgery lists permit it, he or she will undergo cholecystectomy before discharge. If not, the patient is discharged and planned for elective cholecystectomy. Ideally, in the near future, the same case will play out as follows: Patient A, with no relevant medical history, is admitted to the *surgical* ward with predicted mild gallstone pancreatitis.[15] Having observed the patient for 48 hours, it is concluded that pancreatitis is unlikely to progress

in severity.[11] The surgeon can start making preparations for cholecystectomy and place the patient on the sub-acute surgery list, for which the operating theatre reserves a half day operating list every fortnight.[9,16]

On a national level, the second scenario is potentially far more cost-effective. Realization of this scenario, however, would require several large changes to the status quo. Aside from the infrastructural modifications that may be needed to comply with (sub-)acute cholecystectomy, a change in the mindset towards the urgency of surgery in this setting is paramount. To this end studies like the PONCHO are needed that clearly demonstrate the superiority of one strategy over another. In the case of optimal timing of cholecystectomy, it will be challenging to explore which strategy is best in the setting of a randomized trial. The low number of expected serious surgical complications would require very large numbers of patients, even with concessions impairing the study quality, such as combined end points. Furthermore, the clinical premise does not lend itself easily to form a relevant equipoise that can be studied in the form of a randomized trial ('safe' or 'safer'?). Rather, a well-designed prospective study performed in one or preferably more high-volume cholecystectomy centers may be more feasible. Patient safety in the form of surgical and peri-operative complications should be the focus of such a study, but it would also present an opportunity to investigate the (contingent) anatomic repercussions of mild pancreatitis, which will be discussed in the following paragraph.

Safety of surgery

Given the low incidence in significant cholecystectomy-related complications (i.e. bile duct injury), a primary endpoint focusing on safety of surgery was deemed impractical in the PONCHO trial, as this would require thousands of patients. Instead, a combined endpoint of readmissions for recurrent gallstone-related disease and mortality was chosen. In hindsight, the addition of death to the primary endpoint may have been unwarranted, as mortality is a very rare complication in this patient group. This is a complexity in general, when a combined endpoint is necessary to design a study of 3 to maximal 5 years duration, proper powering and clinical relevant outcome.

Regarding readmissions for recurrent gallstone-related disease, it is fairly obvious that these are more likely to occur when the gallbladder is left *in situ* for an extended period of time. Although the trial has provided much needed evidence for same-admission cholecystectomy, ideally the study would have dealt with the safety theme as well. The belief that a recent attack of acute pancreatitis increases the difficulty of surgery remains one of the two principal arguments to postpone cholecystectomy, the other being the logistical advantage of interval cholecystectomy. In our studies, none of our findings supported this theory of increased difficulty. In *Chapter 3*, only four cholecystectomy-related complications requiring re-intervention occurred in 263 patients who underwent the procedure (1.5%). This subject was explored in more depth

in *Chapter 6*. The median overall difficulty grade as reported by the surgeons was a score of 6 out of 10, only slightly more difficult than a regular cholecystectomy (defined as a score of 5 out of 10). Risk factors for a particularly arduous procedure in our patient group did not differ from those described in cholecystectomies for other indications. In fact, contrary to the skepticism of same-admission cholecystectomy, our data showed that surgery tended to be more difficult when the procedure was postponed.

However, as remarked at the beginning of this paragraph, the PONCHO trial was not powered to detect any differences (or even reliable incidence figures for that matter) in the occurrence of bile duct injuries. While older studies in patients with mild pancreatitis have reported similar findings, it is nevertheless conceivable that the biliary tract in patients with proven choledocholithiasis may present a surgically more hostile territory than in patients with simple cholecystolithiasis.[10,17,18] Still, there are currently no indications that mild pancreatitis directly leads to increased surgical risk, much less that this risk can be averted by postponing cholecystectomy for a few weeks (i.e. interval cholecystectomy). As such, we believe the technical difficulty of surgery to be only marginally increased at most, and should not be an argument for postponing cholecystectomy for the trained gastrointestinal surgeon.

To increase our comprehension on the circumstances which significantly affect biliary anatomy, or more specifically lead to bile duct injury, studies are needed that take into account indication of cholecystectomy (i.e. pancreatitis, cholecystitis, cholecystolithiasis), time between onset of complaints and surgery and the severity of symptoms before surgery (e.g. pancreatic necrosis or fluid collections, gangrenous gallbladder or perforation). These data can be acquired retrospectively, but to assemble a representative cohort it would be necessary to perform such a study on a multicenter or even national scale. Furthermore, as proposed at the end of the previous paragraph, prospective studies including patients with all types of pancreatitis (mild, moderate and severe) are needed to investigate how pancreatitis itself influences biliary anatomy.

Difficult cholecystectomy

In *Chapter 7*, we explored surgical management of patients in which cholecystectomy is complicated by severe inflammation or dense adhesions of and around the gallbladder. Traditionally, conversion is advised in these situations to reduce the risk of iatrogenic bile duct injury. However, with increasing experience and confidence in their laparoscopic skills, surgeons from around the world are developing laparoscopic alternatives. Although a variety of methods have been described (routine drain use or not, coagulation of the remnant gallbladder wall, open or closed gallbladder and cystic stumps), the published results on surgical and postoperative complications are promising. It should be noted that these results are mostly from case series and the surgical prowess required to safely complete a laparoscopic subtotal cholecystectomy may be beyond the skillset of the

average surgeon. Nevertheless, these are interesting developments in the surgical world, in which the boundaries of laparoscopy are pushed forward.

Postoperative gallstone related complications

Another issue that remains incompletely settled is the occurrence, and more importantly, prevention of postoperative gallstone-related complications. As the short- and long-term management of mild biliary pancreatitis is becoming increasingly well defined, preventing postoperative events will present a challenging but interesting area for future research. While cholecystectomy, especially in combination with endoscopic sphincterotomy, substantially reduces the risk of new gallstone-induced morbidity, some patients will nevertheless develop postoperative symptoms.[8,9,19] In the PONCHO cohort, 10% of patients required additional postoperative hospital care while 15% reported to have experienced gallstone colics after surgery (*Chapter 5*). No risk factors for the occurrence of postoperative symptoms could be identified. Whether these are the result of pre-existent choledocholithiasis, or gallstones iatrogenically forced into the common bile duct during surgery, is unclear. As the latter may be the case, the most logical moment for the examination of persisting choledocholithiasis would be directly postoperatively, using modalities highly sensitive for intraductal gallstones (*i.e.* endoscopic ultrasound or magnetic resonance cholangiopancreatography). Intraoperative cholangiography should theoretically also be an effective method, but studies comparing routine IOC with no IOC have found no benefit in preventing postoperative events.[20,21] Prospective, large-scale studies in which perioperative choledocholithiasis is routinely investigated using both imaging and biochemical data may help improve identifying patients at risk of developing postoperative gallstone-related complications. While the natural discourse of retained common bile duct stones is interesting (How often does this occur? How many of these stones pass spontaneously? Which ones cause symptoms?), the expected yield is unfortunately quite low. In the PONCHO trial, only round 3% of patients developed symptoms serious enough to warrant readmission. All other symptoms were either self-limiting or managed conservatively through the outpatient clinic. Therefore, while single-center prospective studies on the subject should be encouraged, the clinical significance of postoperative gallstone complications may be too low to invest our scarce time and financial resources in the form of a national study. Alternatively, we can accept this as a fact and use this knowledge to inform our patients of the possible outcomes after cholecystectomy.

Timing of cholecystectomy in severe pancreatitis

Lastly, as briefly discussed in *Chapter 8*, the role of cholecystectomy in patients with severe pancreatitis remains a subject of so far completely unresolved debate. Based on the findings of a small number of studies, surgery during the acute phase of necrotizing pancreatitis is widely discouraged.[4,22,23] Current guidelines recommend delaying

cholecystectomy in patients with severe disease until all symptoms have subsided, which is usually around 6 weeks after pancreatitis onset.[13,14]

In last two decades, however, very little research has been done on how to provide intermediate and long-term prevention from new gallstone-related complications, or whether this should be done at all. What are the risks and characteristics of new biliary events? Does necrotizing pancreatitis affect biliary anatomy? Is the combination of necrosectomy and cholecystectomy in the same operation warranted? In times of open necrosectomy this was feasible, but the surgeon tended to be preoccupied with necrosectomy and should admit that cholecystectomy might have been feasible and safe, but, to his own regret, forgotten to perform *en passant*. Should a patient recovering from a life-threatening episode of necrotizing pancreatitis be exposed to the risks and psychological stress of cholecystectomy, or does endoscopic sphincterotomy suffice? If cholecystectomy is to be delayed until after all symptoms have subsided, should sphincterotomy be performed as a bridge to surgery? These are important clinical dilemmas that can be addressed retrospectively (the first issue), prospectively (the second issue) or through randomization (the last two issues). Answers to these issues are needed to improve care in these vulnerable patients. Like the other points of future research discussed in this chapter, these issues require relatively large cohorts.

Due to its low incidence, such studies require pooling of resources and collaboration between centers on a national or perhaps even international level. A fine example is the APEC trial, which is currently being performed in the Netherlands. In this national multicenter trial, the effect of early sphincter of Oddi decompression on progression of disease severity is investigated. For this study, 232 patients with predicted severe disease will be randomized to either early endoscopic sphincterotomy or conservative treatment. According to the hypothesis, decompression of the pancreatic and biliary ducts during the first few hours after disease onset will reduce the risk of pancreatic necrosis and its subsequent complications (i.e. infection of said necrosis or peripancreatic fluid collections).

The Dutch Pancreatitis Study Group has successfully performed several of these multicenter studies, proving that through cooperation, coordination and endeavor these problems can be addressed. There is, however, also a limit to the Study Group's span of control, indicating that for larger studies international collaboration is necessary. This certainly puts an extra strain on logistics, finances, data control and collection of follow-up sheets and daily unexpected events. Lastly, the plethora of regulation around clinical studies is making it increasingly difficult to perform studies in a national, let alone international setting, although this concern is beyond the scope of this thesis.

Conclusion

In patients with mild biliary pancreatitis, cholecystectomy before discharge reduces the risk of readmission due to recurrent gallstone-related disease. This strategy also reduces

pancreatitis related sick leave, making this approach preferable from a socioeconomic point of view. The true pathophysiological effect of acute pancreatitis on biliary anatomy, and thereby difficulty of surgery, remains at least partly unresolved. However, there are currently no indications that patients with mild disease have an increased risk of bile duct injury when cholecystectomy is performed shortly after resolution of symptoms. Furthermore, patients should be informed that cholecystectomy does not completely preclude the risk of future gallstone-related disease. In patients with severe pancreatitis, cholecystectomy should be postponed until symptoms have subsided, although it should be mentioned that the details regarding timing and indication of cholecystectomy (with or without previous endoscopic sphincterotomy) remain largely unclear.

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APPENDICES

Nederlandse Samenvatting

NEDERLANDSE SAMENVATTING

In de artikelen in dit proefschrift worden de huidige behandelstrategieën van milde biliaire pancreatitis vanuit een chirurgisch perspectief geëvalueerd, met als doel potentiele verbeterpunten te identificeren. Hiervoor brachten wij in kaart 1) de klinische en economische gevolgen van het verrichten van cholecystectomie vóór ontslag, 2) de prevalentie van galsteen gerelateerde complicaties na chirurgie en of dezen voorkomen kunnen worden, 3) factoren die het technisch uitvoeren van cholecystectomie kunnen compliceren en 4) chirurgische opties voor het uitvoeren van een dergelijke moeizame cholecystectomie om te gaan. Ten slotte bespraken wij de huidige inzichten met betrekking tot de behandeling van patiënten met ernstige, necrotiserende pancreatitis en wat de rol van cholecystectomie bij deze patiënten is.

Hoofdstuk 2 is een uiteenzetting van de beschikbare literatuur over biliaire pancreatitis en de behandeling hiervan. Grofweg 80% van de patiënten heeft te kampen met een relatief milde vorm van de ziekte, en kan na ongeveer een week ziekenhuisopname in goede conditie met ontslag. Bij de overige 20% kunnen pancreasnecrose (het afsterven van alvleesklierweefsel) en orgaanfalen (verminderde functie van hart, longen of nieren of een combinatie hiervan) leiden tot levensbedreigende situaties. Deze patiënten liggen vaak maanden opgenomen met een zeer hoge zorgbehoefte. Ondanks de verbeteringen in ondersteunende zorg technieken blijft de kans op sterfte in deze patiëntengroep hoog, zeker wanneer het ziektebeeld verder gecompliceerd wordt door bacteriële infecties van het pancreas of omliggend weefsel.

Uit internationale studies blijkt de algehele incidentie van acute pancreatitis in de afgelopen twintig jaar langzaam maar zeker blijft toenemen. Deze stijging wordt deels toegekend aan een verhoogd percentage van mensen met galstenen. Galstenen ontstaan doorgaans in de galblaas door het samenklonteren van de galkristallen. De meest voorkomende oorzaak van pancreatitis is wanneer een galsteen door de galwegen is gemigreerd en het gezamenlijke afvoerkanaal van de galwegen en het pancreas verstopt ('biliaire pancreatitis'). Galstenen komen vaker voor bij vrouwen, waardoor zij een tweevoudig verhoogd risico op het ontwikkelen van acute pancreatitis hebben. Het vroeg uitvoeren endoscopische retrograde cholangiopancreatografie (ERCP; een onderzoek van de galwegen om het afvoerkanaal van de gal- en pancreaswegen te ontstoppen) heeft geen invloed op de uitkomst bij patiënten met de milde vorm van de ziekte. Of deze behandeling in het vroege stadium zin heeft bij patiënten met (voorspeld) ernstige ziekte wordt momenteel onderzocht. Wanneer uit bloed- of radiologisch onderzoek blijkt dat de galwegen verstopt zijn, kan ERCP electief uitgevoerd worden. Alleen wanneer bij een vermoeden op een bijkomende bacteriële infectie van de galwegen, wordt aangeraden om de ERCP per direct uit te voeren.

Door via ERCP de uitgang van de galwegen te verruimen ('sfincterotomie' of 'papillotomie' van de papil van Vater) kunnen toekomstige stenen makkelijker de galwegen passeren, wat het risico op een volgende episode van acute pancreatitis verkleint. Sfincterotomie is echter minder effectief als bescherming op de lange termijn dan het verwijderen van de galblaas (cholecystectomie). Bij patiënten die vanwege co-morbiditeit geen operatie kunnen ondergaan kan sfincterotomie als definitieve behandeling overwogen worden.

Hoewel de behandeling van biliaire pancreatitis de afgelopen decennia duidelijk is verbeterd, zijn sommige aspecten met betrekking tot het uitvoeren van cholecystectomie nog niet geheel helder. Met name het moment van operatie is een betwist onderwerp. In *Hoofdstuk 3* staan de resultaten van de PONCHO trial (Pancreatitis van biliaire Origine: optimale timiNg van CHOlecystectomie), waarin dit aspect verder is uitgediept. In deze nationale, multicenter studie werden patiënten met milde biliaire pancreatitis gerandomiseerd tussen cholecystectomie vóór ontslag ('vroege cholecystectomie', N=128) of cholecystectomie na een interval van 25 tot 30 dagen ('interval cholecystectomie', N=136). Het primaire eindpunt van acute heropname vanwege galsteen gerelateerde problematiek of mortaliteit kwam significant minder vaak voor in de 'vroege cholecystectomie' groep (6 patiënten in de vroege groep versus 17 patiënten in de interval groep; p=0.002). Dit kwam met name door een reductie in het aantal recidief pancreatitiden (3 versus 12 patiënten; p=0.03). Daarnaast bleek meer dan de helft van de patiënten in de interval groep (51%) galsteenklachten te rapporteren in de wachttijd tot operatie, waar dit maar 3% van de patiënten betrof in de vroege groep (p<0.001). Chirurgische complicaties kwamen weinig voor: in beide groepen werd één patiënt behandeld voor postoperatieve gallekkage en ontwikkelde één patiënt een bloeding. Aan de hand van deze resultaten concludeerden wij dat cholecystectomie vóór ontslag op een veilige manier het risico op een nieuw optreden van galsteenproblematiek verlaagt ten opzichte van de huidige praktijk van interval cholecystectomie.

Hoofdstuk 4 gaat verder in op de timing van cholecystectomie vanuit een economisch oogpunt. In deze studie werden de gemaakte kosten van alle patiënten in de PONCHO trial geanalyseerd vanuit een medisch en sociaal perspectief. Tot deze kosten hoorden ligdagen in het ziekenhuis, operatiekosten, kosten van beeldvorming en andere ingrepen zoals endoscopie en bezoeken aan de Spoedeisende Hulp en de polikliniek. Daarnaast werd rekening gehouden met pancreatitis-gerelateerd ziekteverzuim. Vanuit het medisch perspectief bleek vroege cholecystectomie marginaal duurder dan interval cholecystectomie (€144). Dit verschil kwam met name door het gecompliceerd beloop met hierdoor lange opnameperiodes van zes patiënten in de vroege groep. Daarentegen meldden de patiënten in de vroege groep minder ziekteverzuim, waardoor deze strategie een economisch voordeel van €234 per patiënt met zich meedroeg. Samenvattend bleek

vroege cholecystectomie in het kader van de PONCHO trial de meer effectieve strategie, maar ook aantrekkelijker vanuit economisch oogpunt.

Hoewel cholecystectomie het risico op nieuwe galsteen-gerelateerde complicaties sterk verlaagt, leiden achtergebleven stenen in de galwegen bij een klein percentage patiënten alsnog tot problemen. In *Hoofdstuk 5* onderzochten we binnen de PONCHO trial het aantal, type en hevigheid van deze postoperatieve problemen. Van alle participanten werd het postoperatief zorggebruik uitgezocht. Daarnaast ontvingen alle patiënten voorafgaand aan de operatie een speciaal dagboek met instructies gedurende zes maanden galsteenkolieken bij te houden. Tijdens deze follow-up periode bleek bij 25 van de 262 patiënten (10%) aanvullende zorg nodig. Van deze patiënten werden 7 (3%) heropgenomen vanwege galsteenproblematiek: 4 met recidief pancreatitis, 2 met galsteenkolieken en 1 met een obstruerende steen in de ductus choledochus. In de overige gevallen werd de zorg via de polikliniek geleverd.

Met betrekking tot de galsteendagboeken rapporteerden 28 van de 191 respondenten (15%) postoperatieve koliekaanvallen in de thuissituatie. Dit was in de helft van alle gevallen een enkele aanval. Het merendeel van de aanvallen, bij 22 van de 28 patiënten (79%) trad binnen twee maanden na cholecystectomie op. In slechts 4 van de 191 gevallen (2%) werden klachten in de laatste maand van follow-up gerapporteerd.

Risicofactoren voor het ontwikkelen van postoperatieve complicaties konden niet worden geïdentificeerd. Hoewel het risico op deze complicaties veel lager is in vergelijking met de risico's van het niet uitvoeren van cholecystectomie, moet de patiënt voorafgaand aan de operatie van deze mogelijke complicaties op de hoogte zijn gesteld.

Op de technische aspecten van cholecystectomie na milde pancreatitis werd verder ingegaan in *Hoofdstuk 6*. Bij alle patiënten in de PONCHO trial werden prospectief data verzameld met onder andere betrekking tot de moeilijkheidsgraad, aan- of afwezigheid van adhesies en ervaring van de operateur. Moeilijkheidsgraad werd op een schaal van 0-10 (makkelijk-moeilijk) door de meest ervaren operateur gerapporteerd. In deze studie onderzochten we of het mogelijk was een 'moeilijke cholecystectomie' te voorspellen aan de hand van bekende risicofactoren. Onder 'moeilijke cholecystectomie' werd verstaan: een moeilijkheidsgraad in het 75ste percentiel (een 8 of hoger), de noodzaak tot conversie van scopisch naar open, een subtotale cholecystectomie of een operatieduur in het 75ste percentiel (75 minuten of langer). Aan de hand van deze criteria was er sprake van een 'moeilijke cholecystectomie' bij 82 van de 249 patiënten (33%). Onafhankelijke voorspellers van dit gecombineerde eindpunt bleken na multivariate analyse 1) een mannelijk geslacht (Odd's Ratio [OR] 1.80, 95% CI 1.04-3.13; p=0.037), 2) status na sfincterotomie (OR 1.79, 95% CI 1.01-3.16; p=0.046) en 3) uitstel van cholecystectomie tot twee weken na opname (OR 1.81, 95% CI 1.04-3.16; p=0.036). Na correctie voor

ervaring van de operateur (minstens 100 laparoscopische cholecystectomieën) verviel het effect van deze risicofactoren.

In extreme gevallen leidt een heftige ontstekingsreactie tot verminderde herkenbaarheid van de structuren die voor cholecystectomie van belang zijn. In combinatie met straffe verklevingen kan men niet anders dan de galblaas slechts gedeeltelijk te verwijderen. In dergelijke gevallen werd tot voor kort geadviseerd de laparoscopische procedure te staken en de subtotale cholecystectomie via laparotomie af te maken. In de literatuur wordt echter in toenemende mate gerapporteerd over het laparoscopisch afmaken van de procedure als alternatief voor conversie. *Hoofdstuk 7* is een overzicht van deze literatuur tot januari 2012 over de laparoscopische subtotale cholecystectomie. Met de zoektermen 'partial', 'subtotal' en 'incomplete' en 'cholecystectomy' werd een systematische zoektocht in Pubmed en de Cochrane bibliotheek verricht. Gekozen uitkomsten waren galwegletsel, gallekkage, symptomatische galstenen in de overgebleven galblaas, postoperatieve ERCP en andere interventies en mortaliteit. Alleen studies met patiënt series werden geïncludeerd. Na selectie bleven 15 artikelen met in totaal 625 patiënten over voor het review. Meerdere technieken voor laparoscopische subtotale cholecystectomie werden beschreven. In 10% van de gevallen is alsnog geconverteerd tot een open procedure. Bij eveneens 10% van de patiënten werd postoperatief gallekkage beschreven, wat bij slechts 1 patiënt berustte op galwegletsel. Recidief symptomen kwamen voor bij 2% van de patiënten. Postoperatieve ERCP werd verricht bij 8% van de patiënten, overige ingrepen bij 4%. Van de 625 patiënten overleden 3 (0.005%), waarvan 2 aan een hartinfarct en 1 ten gevolge van pneumosepsis.

Op basis van deze bevindingen lijkt laparoscopische subtotale cholecystectomie een goed en veilig alternatief voor conversie.

In de voorgaande hoofdstukken lag de focus op de behandeling van patiënten met milde pancreatitis. Galstenen zijn echter ook in veel gevallen de oorzaak van ernstige pancreatitis. Waar cholecystectomie bij patiënten met milde ziekte van belang is voor het voorkomen van recidief of andere galsteen-gerelateerde complicaties, speelt de procedure en timing hiervan een minder grote rol bij patiënten met ernstige pancreatitis. *Hoofdstuk 8* is een samenvatting van de huidige inzichten in de algemene en chirurgische behandeling van necrotiserende pancreatitis. Aangezien verschillende soorten complicaties in de verschillende stadia van de ziekte voor kunnen komen, droegen wij een model aan met behandelstrategieën per stadium. De aanbevelingen van de American Gastroenterological Association en de International Association of the Pancreas / American Pancreatic Association werden in dit model verwerkt. Met betrekking tot zaken waar geen duidelijke consensus over bestaat werden de meningen van de internationale co-auteurs en de Pancreatitis Werkgroep Nederland aangedragen als 'expert opinie'.

Bij opname wordt, naast ruime intraveneuze vochttoediening, geadviseerd de patiënten de eerste 72 uur nauwgezet klinisch en biochemisch te vervolgen. Hoewel in de afgelopen jaren verscheidene methoden zijn aangedragen om bij opname de ernst van de ziekte te voorspellen, zijn slechts van beperkte waarde gezien hun matige accuratesse. Behandeling met profylactische antibiotica leidt niet tot een reductie in incidentie van infectie van peripancreatische necrose en wordt derhalve niet geadviseerd. Antibiotica worden pas ingezet bij microbiologisch bewezen bacteriële infecties. De behandeling blijft zo lang mogelijk medicamenteus, maar indien de patiënt onder maximale antibiotische en ondersteunende therapie klinisch verslechtert, dient een invasieve interventie te worden overwogen. Idealiter gebeurt een dergelijke interventie in de setting waar een multidisciplinair team te allen tijde beschikbaar is, bestaande uit minstens een chirurg, een MDL arts, een radioloog en een intensivist. Benadering via de opstap methode wordt geadviseerd, waarbij de eerste interventie bestaat uit endoscopische of percutane drainage van het geïnfecteerde vocht. Mocht drainage onvoldoende soelaas bieden, kan endoscopische of video-geassisteerde percutane debridement van het geïnfecteerde necrotisch weefsel worden overwogen. De klinische uitkomst van patiënten met necrotiserende pancreatitis is de afgelopen twintig jaar langzaam maar zeker verbeterd, onder andere door deze multidisciplinaire opstap benadering.

Cholecystectomie wordt pas aangeraden nadat alle tekenen van ontsteking goed en wel onder controle zijn. Dit kan tot wel 6 tot 12 maanden na aanvang van de ziekte zijn. Data met betrekking tot de indicatie en timing van cholecystectomie in deze groep zeer kwetsbare patiënten zijn schaars. Een eenduidig beleid kan derhalve niet uit de beschikbare literatuur worden gefiltreerd. De arts zal per geval moeten beoordelen in hoeverre cholecystectomie raadzaam en haalbaar is.

Conclusies

Biliaire pancreatitis blijft een significant probleem in de Westerse gezondheidszorg. Naar aanleiding van een grote hoeveelheid studies binnen het ziektebeeld is de indicatiestelling rondom cholecystectomie en sfincterotomie sterk verduidelijkt en hiermee de uitkomsten van de patiënten. De resultaten van de PONCHO trial hebben laten zien dat cholecystectomie vóór ontslag gezondheidswinst kan opleveren doordat via deze strategie aanzienlijk minder recidieven zullen optreden in vergelijking met interval cholecystectomie. Ook het aantal galsteenkolieken in de wachttijd tot operatie wordt via deze strategie geminimaliseerd. Bovendien bleek de behandelmethode ook economisch aantrekkelijker doordat patiënten sneller terug aan het werk konden. Hoewel cholecystectomie de best mogelijke risicoreductie geeft wat betreft recidief galsteenproblematiek, is de behandeling geen sinecure. Een klein aantal patiënten zal toch na de procedure klachten ervaren. Deze klachten laten zich moeilijk voorspellen en kunnen sterk in ernst varieren. Patiënten dienen van dit risico op de hoogte te worden gesteld voordat overgegaan wordt tot operatie.

In tegenstelling tot wat door sommigen gedacht werd, hebben we geen aanwijzingen kunnen vinden dat relatief vroeg opereren verhoogde kans op operatieve complicaties geeft. Sterker nog, uit een van de nevenstudies bleek het uitstellen van de operatie tot na twee weken na opname een onafhankelijke voorspeller van een moeizame operatie. Bij dergelijke moeizame operaties kan, mits bekwaam, de chirurg kiezen om de procedure laparoscopisch voort te zetten, met vergelijkbare complicatierisico's als conversie.

De rol van cholecystectomie bij patiënten met ernstige (necrotiserende) pancreatitis is onvoldoende onderzocht. Geadviseerd wordt de procedure pas in gang te zetten wanneer alle tekenen van inflammatie zijn uitgedoofd, maar de indicatie en timing zullen per geval in goed overleg tussen arts en patiënt moeten worden beoordeeld.

APPENDICES

Dankwoord

DANKWOORD

Aan het begin van vrijwel ieder proefschrift is een lijst met stellingen te vinden met de belangrijkste bevindingen van het betreffend onderzoek. Vaak worden die bevindingen aangevuld met een paar citaten die de auteur nauw aan het hart liggen, variërend van Johan Cruyff wijsheden tot *Star Wars* filosofie. Nou staat de Radboud Universiteit Nijmegen slechts twee citaten van niet-wetenschappelijke aard toe, maar tijdens het schrijven van dit proefschrift ben ik enkele gezegden tegengekomen waarvan ik twee te toepasselijk vond om ze ongenoemd te laten.

Ten eerste wordt in het Engels weleens gezegd *'no piece of writing is ever finished, only abandoned'*. De variatie op dit gezegde van de Amerikaanse schrijver Chuck Palahniuk komt waarschijnlijk nog dichter bij de werkelijkheid, maar elke promovendus zal de essentie van deze uitspraak maar al te goed bevatten. Een manuscript voelt, na weken of maanden werk, nooit echt *af*. 'Zijn dit de goede vragen?' en 'zijn dit de goede antwoorden?' en talloze andere vragen blijven door je heen schieten, waardoor het lastig kan zijn het overzicht te behouden. Gelukkig sta je er als promovendus, als het goed is tenminste, niet alleen voor en krijg je soms uit de meest onverwachte hoeken de nodige ondersteuning of sturing.

Dat brengt mij tot het tweede gezegde: *'nanos gigantum humeris insedent'*. Deze is extra leuk omdat hij ook letterlijk vrij waarheidsgetrouw is. De figuurlijke betekenis zal ik kort toelichten. De coördinatie van de PONCHO trial heb ik in 2013 van (destijds arts-onderzoekers) Nicolien Schepers en Stefan Bouwense overgenomen. Zij hebben het gedachtegoed uitgewerkt van door de wol geverfde post-docs als Djamila Boerma, Marc Besselink en Hjalmar van Santvoort, op hun beurt weer ingewijd door internationale zwaargewichten zoals professoren Hein Gooszen en Marco Bruno. Het succes van de Pancreatitis Werkgroep Nederland valt, mijns inziens, voornamelijk toe te schrijven aan de bundeling van krachten en het uitwisselen van de inmiddels enorme kennis op het gebied van het opzetten, uitvoeren en uitwerken van klinisch onderzoek. In één woord: samenwerking. Ik ben me dan ook zeer bewust van het feit dat de studies in dit proefschrift zeker niet alleen mijn persoonlijke verdienste zijn en dat ik een groot aantal mensen hiervoor dank verschuldigd ben. Dus hier gaan we.

Allereerst mijn dank aan en respect voor de patiënten en hun families die in een tijd van ziek zijn en onzekerheid hebben willen meewerken aan dit onderzoek.

Mijn dank gaat uiteraard uit naar alle co-auteurs van de trial en de nevenstudies voor de samenwerking.

Geachte promotor prof. dr. H.G. Gooszen, beste Hein. Beter dan wie dan ook zal jij begrijpen dat de afronding van mijn proefschrift een belangrijke mijlpaal voor mij is. Het is ook de afronding van een zeer onzekere periode, waarbij het nu eindelijk voelt alsof ik weer de regie over mijn carrière heb. In de hele periode stond je voor me klaar met advies en ondersteuning. Niet alleen rondom het onderzoek, maar vooral ook met het solliciteren. Nooit zwaarmoedig, altijd met een lach. Als onderzoeker heb ik van je geleerd om altijd (***altijd***) kritisch te blijven ten aanzien van je eigen werk, want alleen dan kom je echt verder. Als persoon heb je me het vertrouwen gegeven waarmee ik, ook in het licht van tegenslagen, mijn eigen weg heb kunnen kiezen. Voor beide, maar met name het laatste, ben ik je voor altijd dankbaar.

Hoe onze wegen hebben gekruist zou men in het Engels '*serendipity*' noemen: een samenloop der omstandigheden met een onverwachte, positieve uitkomst. In mijn geval heb ik er niet alleen een promotie maar ook een goede vriend aan over gehouden.

Copromotoren Dr. M.G.H. Besselink en dr. H.C. van Santvoort. Marc en Hjalmar, *the unstoppable force* en *the immovable object.* Een tegenstrijdiger duo kan haast niet, maar samen hebben jullie het pancreatitis onderzoek naar een hoger niveau getild en de PWN wereldberoemd gemaakt. Het is een eer om jullie als copromotoren te hebben!

Beste Marc, aan jou heb ik mijn periode als onderzoeker te danken. Je hield het tempo van mijn studies hoog: als ik op vrijdagochtend een manuscript ter beoordeling stuurde, kreeg ik het vrijdagmiddag voorzien van commentaar terug. Hoe je dat blijft doen met alle onderzoekers die je begeleidt is me een raadsel, maar ik ben je er zeer erkentelijk voor. Dank voor het vertrouwen in mij en alle hulp tijdens het onderzoek!

Beste Hjalmar, wat heb ik veel van je geleerd tijdens de PWN vergaderingen en het opschrijven van PONCHO. Altijd kritisch, perfectionistisch en met je begrip voor de krachten en beperkingen van klinisch wetenschappelijk onderzoek kan ik met recht zeggen dat ik onder jouw begeleiding een betere onderzoeker ben geworden. Dankzij jou ben ik het onderzoek veel meer gaan waarderen en ben ik enthousiast geworden om ook in de toekomst wetenschappelijk actief te blijven. Heel veel dank daarvoor.

Dr. D. Boerma, beste Djamila, PONCHO is natuurlijk jouw idee en zonder PONCHO geen promotie. Het was geweldig om deze trial af te mogen maken. Ik ken geen enkele andere studie die zo rechttoe-rechtaan en direct klinisch toepasbaar is, en heb altijd met heel veel plezier aan de studie gewerkt en de resultaten gepresenteerd. Ik hoop in de toekomst nog meer biliaire studies met je te kunnen doen in het St. Antonius.

Mijn hartelijke dank aan de leden van de manuscript commissie voor het beoordelen van mijn manuscript: prof. dr. P.D. Siersema, prof. dr. O.R.C. Busch en prof. dr. W.M. Prokop, en de opponenten.

Bijna-dr. Th.L. Bollen, beste Thomas, ten eerste veel dank voor het reviseren van de scans van de PONCHO patiënten. Veel belangrijker, aan jou (en aan Elvin) heb ik mijn opleidingsplek in het St. Antonius te danken. Door jou had ik nog net op tijd mijn brief bij dr. van Heesewijk; twee maanden later zat ik oude scans voor The Magician te openen in IMPAX. Ik kijk er naar uit om de komende jaren door je teruggefloten te worden op exotische diagnoses!

Dr. M.G. Dijkgraaf, beste Marcel, enorm veel dank voor je hulp met de statistiek bij PONCHO, maar vooral ook met de kosteneffectiviteitsanalyse! Een 'drukke agenda' is in jouw geval een understatement, en toch heb je tijd voor me gemaakt voor beide studies. Met je 'erop-en-erover' aanpak bij de revisies hebben we twee prachtige publicaties in toptijdschriften weten te bewerkstelligen. Mijn hartelijke dank en ik hoop in de toekomst weer met je samen te kunnen werken.

Dr. O.J. Bakker, beste Olaf, ik heb enorm veel van je geleerd tijdens het schrijven van ons review in de BJS. Korte zinnen en to-the-point, advies waar ik nog heel regelmatig baat bij heb. Veel werk, maar een prachtige kans om in de pancreatitis literatuur te duiken en met enkele internationale coryfeeën samen te werken. De extra beloning was bovendien een eerste plaats als *'most read article'* van de BJS in 2015, waar ik erg trots op ben!

De (oud) onderzoekers van de PWN:
Doctor Stefan Bouwense! Het was me een genoegen om samen met jou het eerste auteurschap te delen. Ondanks alle drukte altijd enthousiast om over PONCHO te sparren en altijd geïnteresseerd in hoe het met de sollicitatieperikelen stond. Onze telefoongesprekken voor beide gelegenheden heb ik erg gewaardeerd!

Nicolien Schepers, onvermoeibaar heb je je ingezet voor de PWN! De hoge inclusiesnelheid en response rates van de vragenlijsten zijn absoluut aan jou te danken. Een jaar lang PONCHO draaiende houden en een nieuwe trial opzetten, het is indrukwekkend hoeveel jij met al je harde werken gedaan hebt gekregen. Af en toe ten koste van jezelf, maar ik heb er, zeker met de komst van Pieter, veel vertrouwen in dat jij en Rein daar in de toekomst beter op gaan letten.

Sandra van Brunschot. Het hele reilen en zeilen van de PWN heb jij persoonlijk mogelijk gemaakt. Jij durfde altijd ook de minder makkelijke beslissingen te nemen, maar altijd voor het goed van de PWN. En ondertussen dag en nacht bereikbaar blijven voor inclusies in zeer ingewikkelde patiëntpopulaties. Ik wens je heel veel succes met het afronden van TENSION!

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Xavier Smeets, Noortje Hallensleben, Sven van Dijk, Rens Kempeneers. Nu de meer voor de hand liggende studies wel zo'n beetje zijn uitgewerkt zal het pancreatitis onderzoek in de toekomst waarschijnlijk wel wat ingewikkelder worden. Ik ga mijn best doen om jullie daar in bij te staan en weer wat meer betrokken te raken met de lopende studies.

Prof. dr. M.J. Bruno en prof. dr. H. Van Goor. Beste Marco en Harry, veel dank voor al jullie werk en onvermoeibare inzet als voorzitters van de PWN. De vergaderingen en AA overleggen zijn erg waardevolle momenten voor ons arts onderzoekers en ik had altijd het gevoel met meer kennis en beter inzicht van deze bijeenkomsten weg te lopen.

De (oud) onderzoeksverpleegkundigen van de PWN Vera Zeguers, Anneke Roeterdink, Stefan Jans en Hetty van der Eng voor al jullie harde werk in het verzamelen van patiëntgegevens.

Dr. B.C. Vrouenraets en alle chirurgen in het OLVG West. Beste Bart, in een parallel universum gaat dit proefschrift niet over pancreatitis maar lymfekliermetastasering bij coloncarcinoom. Niet alleen mijn eerste stappen als zelfstandig arts maar ook mijn eerste ervaring met wetenschappelijk onderzoek heb ik bij jullie op kunnen doen (2500 lymfeklieren handmatig meten op de zaterdag, ook dat is wetenschap!). Mijn hartelijke dank voor jullie betrokkenheid en geweldige steun tijdens maar vooral ook na mijn jaar bij jullie.

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die je nodig hebt en de sfeer is altijd goed. Een veiliger opleidingsklimaat is haast niet denkbaar. Ik heb enorm veel zin in de komende paar jaren!

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De KGB en KGBabes (en KGBabies). We kennen elkaar inmiddels zo'n 20 jaar en onze vriendschap wordt alleen maar hechter. Een voor allen en allen voor een, zo hebben we dat altijd gevoeld en zo zal het altijd blijven. Onze band is werkelijk uniek en het is geweldig om te zien hoe de KGB een begrip aan het worden is in al onze kringen. Heel veel dank voor hoe jullie de afgelopen tijd voor Breg en mij hebben klaar gestaan, het betekent enorm veel voor mij.

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Dorine, heel erg bedankt voor de bijdrage aan dit proefschrift.

Rein-Jan de Nes, heel veel dank voor het drukken van mijn manuscript!

Familie da Costa en van Bokhorst, ik ben altijd zo vreselijk blij met en trots op jullie geweest. Zomers in Italië, winters in Vermont, veel van mijn beste herinneringen zijn met jullie. Ik hoop heel erg in de toekomst nog veel met elkaar te kunnen blijven doen!

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APPENDICES

List of publications

LIST OF PUBLICATIONS

1. da Costa DW, Schepers NJ, Bouwense SA, Hollemans RA, Doorakkers E, Boerma D, Rosman C, Dejong CH, Spanier BW, van Santvoort HC, Gooszen HG. *"Recurrent gallstone colics and related complications after cholecystectomy for mild gallstone pancreatitis"*. **Submitted**.

2. da Costa DW, Schepers NJ, Bouwense SA, Hollemans RA, van Santvoort HC, Bollen TL, Boerma D, Consten EC, van Goor H, Gooszen HG, Besselink MG. *"Predicting a difficult cholecystectomy after mild biliary pancreatitis"*. **Submitted**.

3. da Costa DW, Dijksman LM, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, Boerma D, Dijkgraaf MG. *"Cost effectiveness of same-admission cholecystectomy for mild biliary pancreatitis"*. **British Journal of Surgery**; 2016 Nov;103(12):1695-1703.

4. Smeets X, da Costa DW, Besselink MG, Bruno MJ, Fockens P, Mulder CJ, van der Hulst RW, Vleggaar FP, Timmer R, Drenth JP, van Geenen EJ. *"Systematic review: Periprocedural hydration in the prevention of post-ERCP pancreatitis"*. **Alimentary Pharmacology & Therapy:** 2016 Sep;44(6):541-53.

5. da Costa DW*, Schepers NJ*, Römkens TE, Boerma D, Bruno MJ, Bakker OJ. *"Endoscopic sphincterotomy and cholecystectomy in biliary pancreatitis"*. **The Surgeon**; 2016 Apr;14(2):99-108. *Authors contributed equally

6. da Costa DW*, Bouwense SA*, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S, Bakker OJ, Bollen TL, Dejong CH, van Goor H, Boermeester MA, Bruno MJ, van Eijck CH, Timmer R, Weusten BL, Consten EC, Brink MA, Spanier BW, Spillenaar Bilgen EJ, Nieuwenhuijs VB, Hofker HS, Rosman C, Voorburg AM, Bosscha K, van Duijvendijk P, Gerritsen JJ, Heisterkamp J, de Hingh IH, Witteman BW, Kruyt PM, Scheepers JJ, Molenaar IQ, Schaapherder AF, Manusama ER, van der Waaij LA, van Unen J, Dijkgraaf MG, van Ramshorst B, Gooszen HG, Boerma D. *"Same-admission versus interval cholecystectomy after mild biliary pancreatitis"*. **The Lancet;** 2015 Sep 26;386(10000):1261-8. *Authors contributed equally

7. da Costa DW, Vrouenraets BC, Witte BI, van Dekken H. *"Pathological lymph node evaluation in colon cancer: assessment of the N-stage by analysis of the 5 largest nodes"*. **International Journal of Surgical Pathology**; 2015 Dec; 23(8): 623-8.

8. da Costa DW, van Dekken H, Witte BI, van Wagensveld BA, van Tets WF, Vrouenraets BC. *"Lymph node yield in colon cancer: individuals can make the difference"*. **Digestive Surgery**; 2015; 32(4): 269-74.

9. De Vries FE, da Costa DW, van der Mooren K, van Dorp TA, Vrouenraets BC. *"The value of pre-operative CT scan for evaluation of the N-stage in colon cancer"*. **European Journal of Surgical Oncology**; 2014 Dec; 40(12): 1777-81.

10. da Costa DW, Boerma D, van Santvoort HC, Horvath KD, Werner J, Carter CR, Bollen TL, Gooszen HG, Besselink MG, Bakker OJ. *"Staged, multidisciplinary step-up management for necrotizing pancreatitis"*. **British Journal of Surgery**; 2014 Jan;101(1):e65-79.

11. da Costa DW[*], Henneman D[*], Vrouenraets BC, van Wagensveld BA, Lagarde SM. *"Laparoscopic partial cholecystectomy for the difficult gallbladder: a systematic review"*. **Surgical Endoscopy**; 2013 Feb;27(2):351-8. [*]Authors contributed equally.

APPENDICES

Curriculum vitae

CURRICULUM VITAE

De auteur van dit proefschrift werd op 31 januari 1983 in Leiden geboren. Van 1986 tot 1993 woonde hij op Curaçao, waarna het gezin terug verhuisde naar Nederland. Na zijn Gymnasium te hebben gehaald in 2002 te hebben gehaald aan het Stedelijk Gymnasium Leiden, werd David met een klein beetje geluk ingeloot voor de studie Geneeskunde aan het Leids Universitair Medisch Centrum. Tussen oktober 2007 en juli 2008 deed hij zijn wetenschappelijke stage bij de afdeling Neurochirurgie in het Alfred Hospital te Melbourne, Australië. Na twee jaar co-schappen te hebben gelopen in Den Haag verhuisde hij naar Amsterdam waar hij twee jaar ANIOS Chirurgie was (eerst één jaar in het Sint Lucas Andreas Ziekenhuis, opleiders dr. E.P. Steller en dr. B.C. Vrouenraets, daarna een jaar in het Academisch Medisch Centrum, opleider prof. dr. O.R.C. Busch). Via zijn co-promotor dr. M.G. Besselink werd hij in de gelegenheid gesteld om te beginnen bij de Pancreatitis Werkgroep Nederland als coördinator van de PONCHO trial (Pancreatitis of biliary origin: Optimal timiNG of CHOlecystectomy). De studies die uit deze trial voortkwamen vormen de basis van dit proefschrift, dat hij met veel plezier onder begeleiding van zijn promotor prof. dr. H.G. Gooszen heeft geschreven.

Sinds januari 2016 is hij in opleiding tot radioloog in het St. Antonius Ziekenhuis, Nieuwegein, met als opleiders dr. H.W. van Es, dr. J.P.M. van Heesewijk en dr. R.G.M. Keijsers.

David woont in Amsterdam met zijn vrouw Bregje.