ASPECTS ON ADVANCED PROCEDURES DURING ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY FOR COMPLEX HEPATOBILIARY DISORDERS

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Aspects on Advanced Procedures during Endoscopic Retrograde Cholangiopancreatography (ERCP) for Complex Hepatobiliary Disorders

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To Isabelle and Willem, Dané and Ivan

"In a world deluged by irrelevant information, clarity is power."

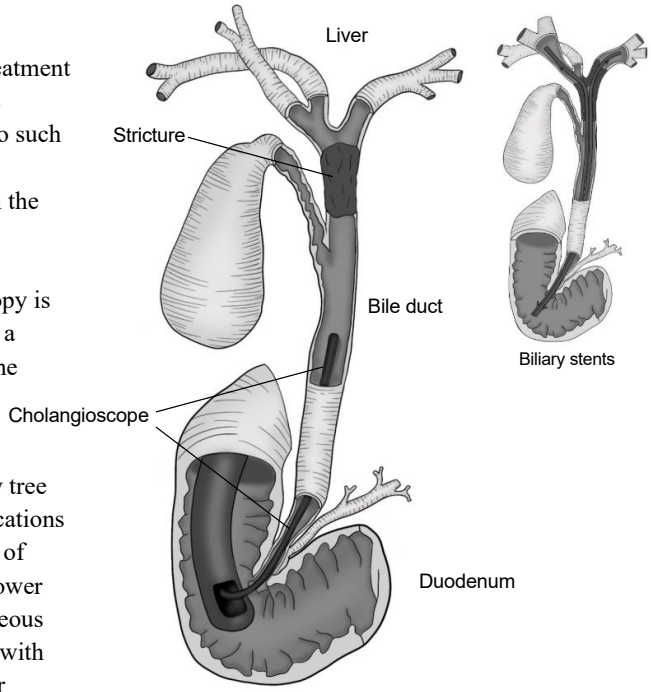
Yuval Noah Harari

POPULAR SCIENCE SUMMARY OF THE THESIS

Every 24-hours between 400 and 800 ml of bile passes through the bile duct from the liver to the duodenum where it assists in digesting and absorbing the food we consume. Obstruction of this 3-6 mm wide duct not only decreases absorption of nutrients but also increases the risk for life threatening infection throughout the biliary ductal system. The two most common causes for bile duct obstruction are gallstones and strictures (which can be cancerous or non-cancerous). Through time medical science has advanced to allow for better access to the relatively inaccessible biliary tree to diagnose and treat obstruction. The bile duct can be reached with a camera introduced through the mouth (endoscopy) or via a puncture through the skin and liver (percutaneous). An even smaller camera placed through the endoscope (cholangioscopy) has the advantage of fitting into the bile duct, allowing for first-hand visualisation of disease located there. Biliary stents are tubes made of plastic or metal which are placed through strictures in the bile duct to restore bile flow to the bowel.

Cholangioscopy is a relatively new technology and as biliary stenting is becoming more widespread, the dissertation aims to determine several aspects. Firstly, it explores how cholangioscopy in Sweden assists the clinician to diagnose and treat stones and strictures. Secondly, it considers whether harm can be done if patients undergo a cholangioscopy procedure. Thirdly, it investigates how bile duct stents perform when they are placed in different locations in the bile duct (high vs. low) and lastly, which of an endoscopic or percutaneous route for stent placement would be more advantageous for the patient. The Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks) was consulted to answer some of the questions, while patients in South Africa also participated in the research.

Results showed that cholangioscopy is mostly performed in specialised units adapted to the treatment of challenging diseases of the biliary tree. It has significant value in 63% of patients that undergo such a procedure. Most value lies in the treatment of gallstones, but a second important function is in the diagnosis whether strictures are cancerous. Importantly, the research found that there is an increased risk for complications if cholangioscopy is added to an endoscopic procedure, and that it is a specialised procedure in which clinicians become more skilled over time.



Regarding biliary stents, results revealed that cancerous strictures located higher in the biliary tree are more challenging to treat with more complications at the time of stent placement, and a higher risk of blockage over time compared to stents placed lower down in the bile duct. Endoscopic and percutaneous routes for stent placement performed similarly, with endoscopically placed stents remaining open for longer, probably because more stents could be placed at the time of the procedure. Results suggested, however, that the two routes each have advantages as well as disadvantages, and in future can be used complimentary rather than competitively.

In conclusion, it is challenging to manage diseases of the small and inaccessible bile duct. Technological advancement together with associated increased clinician skills have resulted in improved diagnosis and treatment by means of cholangioscopy and biliary stenting. This, however, comes at the risk of increased complications and therefore cholangioscopy should be used for specific indications at specialised units. Both endoscopic and percutaneous routes for stent placement perform well but there is a clear increased risk for complications when stents are placed higher in the biliary tree.

ABSTRACT

Background: The rapid development in endoscopic technology and associated skills has led to an increase in more advanced procedures being performed during endoscopic retrograde cholangiopancreatography (ERCP). Knowledge is limited regarding clinical value, integration, and outcomes for single operator cholangiopancreatoscopy (SOCP) and endoscopic intervention in the different Bismuth-Corlette (B-C) locations in the hepatic hilum.

Objectives: To determine the clinical value of SOCP in the diagnosis and treatment of complex hepatobiliary and pancreatic disease. To describe the nationwide integration of SOCP and the extent to which adverse events are influenced when SOCP is added to ERCP. To compare adverse events and reintervention rates after endoscopic stenting for malignant obstruction in the distal and hilar locations of the biliary tree. To compare outcomes after endoscopic transpapillary (ETP) and percutaneous transhepatic (PTH) stenting in the palliation of malignant hilar obstruction (MHO).

Methods: In study I all SOCP procedures performed between March 2007-December 2014 at a tertiary high-volume endoscopy unit were separately graded according to a predefined 4-graded scale estimating therapeutic value and diagnostic yield. Study II was a nationwide case-control study nested within the cohort of ERCP procedures, with- or without SOCP, and registered in the Swedish Registry for Gallstone Surgery and ERCP (GallRiks) between 2007-2012. To assess risk factors for adverse events, multivariate logistic regression was performed, and odds ratios (OR) calculated. The GallRiks registry was also utilised in study III where all patients undergoing endoscopic stenting for malignant biliary obstruction between 2010-2017 (based on International Classification of Diseases (ICD) coding), were included. Kaplan-Meier analysis was employed to calculate stent patency and Cox proportional hazard models to calculate the risk for recurrent biliary obstruction after single metal stent placement. To compare ETP and PTH drainage approaches, a retrospective deconstructed analysis of palliative stenting procedures for MHO at two specialised referral centres over a 5-year period was performed. Within-group analyses were performed to explore outcomes for different B-C types and Kaplan-Meier and restricted mean survival time analyses were performed to calculate and compare duration of therapeutic success.

Results: In 365 SOCP procedures, SOCP was found be of pivotal importance in 19% of patients, of great clinical significance in 44%, and did not affect clinical decision-making or alter clinical course in 37% of patients. In study II a learning curve was observed after first introduction of 408 SOCP procedures, and postprocedural adverse events (19.1% vs. 14.0%), pancreatitis (7.4% vs. 3.9%) and cholangitis (4.4% vs. 2.7%) were more prevalent when SOCP was added to ERCP. After multivariate analysis, the risk for postprocedural adverse events remained (OR 1.35, 95% CI [1.04 - 1.74]). In 4623 ERCP procedures performed for stenting of malignant strictures (1364 hilar), adverse events and 6-month reintervention rates were increased after hilar stenting compared to distal stenting (17.2% vs. 12.0%, 73.4% vs. 55.9%). On multivariate analysis the risk for reintervention was three times higher after single metal stent placement in the hilum compared to the distal biliary tree (HR 3.47, 95% CI [2.01-6.00], $p<0.001$). In 293 patients undergoing palliative stenting for MHO (52.2% ETP, 47.8% PTH), access and bridging success in the ETP and PTH groups were 83.5% vs. 97.2% and 90.2% vs. 84.5%, respectively. Technical and therapeutic success were equivalent between the two groups, but duration of therapeutic success was longer after ETP drainage, with a 3-month gain in duration of therapeutic success after adjustment for B-C type (95% CI [26-160], $p=0.006$). Cholangitis rates were equivalent (21.4% vs. 24.7%), while pancreatitis was more common in the ETP group and deaths more common in the PTH group.

Conclusions: When added to ERCP, SOCP contributes significant clinical value in 64% of cases. However, there is an increased risk of intra- and postprocedural adverse events which, together with a learning curve, suggests that it should likely be performed in specialised high-volume centres. Regarding endoscopic intervention for MHO, stenting in the hepatic hilum compared to the distal biliary tree is associated with more adverse events and decreased stent patency. When comparing palliative ETP with PTH stenting for MHO, both approaches have similar technical and therapeutic success, with ETP drainage being more durable. Future studies should explore the complimentary role of both approaches in specific B-C types.

LIST OF SCIENTIFIC PAPERS

I. Marcus Reuterwall, Jeanne Lubbe, Lars Enochsson, Lars Lundell, Magnus Konradsson, Frederik Swahn, Marco Del Chiaro, Matthias Löhr and Urban Arnelo
The clinical value of ERCP-guided cholangiopancreatoscopy using a single-operator system
BMC Gastroenterology, 2019, 26;19(1):35

II. Jeanne Lubbe, Urban Arnelo, Lars Lundell, Fredrik Swahn, Björn Törnqvist, Eduard Jonas, Matthias Löhr, and Lars Enochsson
ERCP-guided cholangioscopy using a single-use system: nationwide register-based study of its use in clinical practice
Endoscopy, 2015, 47(9):802–7

III. Jeanne Lubbe, Gabriel Sandblom, Urban Arnelo, Eduard Jonas, and Lars Enochsson
Endoscopic stenting for malignant biliary obstruction – results of a nationwide experience
Submitted manuscript

IV. Jeanne Lubbe, Jessica Lindemann, Washington Ghondo, Nina Kolev, Peter Aclavio, Stefan Hofmeyr, and Eduard Jonas
Endoscopic versus percutaneous drainage of malignant hilar bile duct obstruction – a comparative cohort study
Submitted manuscript

RELATED PUBLICATIONS

(Not included in the thesis)

Greger Olsson, Jeanne Lubbe, Urban Arnelo, Eduard Jonas, Björn Törnqvist, Lars Lundell and Lars Enochsson
The impact of prophylactic pancreatic stenting on post-ERCP pancreatitis: A nationwide, register-based study
United European Gastroenterology Journal, 2017, 5(1):111–8

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Bimodal ERCP, a new way of seeing things.
Endoscopy International Open, 2020, 8(3):E368–76

CONTENT

LIST OF ABBREVIATIONS

PSC	Primary sclerosing cholangitis
CC	Cholangiocarcinoma
MHO	Malignant hilar obstruction
ETP	Endoscopic transpapillary
PTH	Percutaneous transhepatic
ERCP	Endoscopic retrograde cholangiopancreatography
SOCP	Single operator cholangiopancreatoscopy
PS	Plastic stent
SEMS	Self-expanding metal stent
uSEMS	Uncovered self-expanding metal stent
cSEMS	Covered self-expanding metal stent
B-C	Bismuth-Corlette
EPLBD	Endoscopic papillary large balloon dilation
IPMN	Intraductal papillary mucinous neoplasm
EUS-GD	Endoscopic ultrasound-guided drainage
RCT	Randomised controlled trial
NSAID	Non-steroidal anti-inflammatory
ESGE	European Society of Gastrointestinal Endoscopy
ASGE	American Society for Gastrointestinal Endoscopy
CI	Confidence interval
OR	Odds ratio
HR	Hazard ratio
PIEC	Percutaneous internal-external catheter
SIS	Stent-in-stent
SBS	Side-by-side
MDT	Multidisciplinary team
ASA	American Society of Anesthesiologist
ICD	International Classification of Diseases
TB	Total bilirubin
ECOG	Eastern Cooperative Oncology Group

1 INTRODUCTION

In healthy individuals between 400-800 ml of bile pass via the bile duct into the duodenum every 24 hours. The two most common ailments affecting this 3-6 mm inaccessible ductal system are gallstones and biliary strictures. Obstruction to the flow of bile leads to upstream dilation, secondary bacterial infection (cholangitis), and in time, secondary biliary cirrhosis. Diagnosis as to the cause and ways in which to relieve biliary obstruction have posed a challenge to physicians for many years.

The most common benign cause of biliary obstruction is gallstone disease. Gallstones can be cholesterol or bilirubinate stones that form primarily in the gallbladder and then migrate into the bile duct, or primary intraductal stones that are formed due to stasis and chronic low-grade infection. Benign stricture formation (30% of all strictures) can be due to primary sclerosing cholangitis (PSC), iatrogenic injury, Mirizzi syndrome, anastomotic fibrosis or associated with chronic pancreatitis.[1] Choledochal cysts, haemobilia (blood in the biliary system) and radiotherapy are rarer causes of benign biliary obstruction. Infections and parasitic infestations are predominantly seen in developing countries. Malignant biliary strictures are mostly due to pancreatic / periampullary carcinoma or intra- or extrahepatic cholangiocarcinoma (CC). Malignant hilar obstruction (MHO) is less frequently caused by gallbladder cancer or centrally located hepatocellular cancer.[2] Lymphoma and malignancy arising anatomically distant from the biliary system can lead to MHO by means of metastasis to periportal lymph nodes or the liver parenchyma surrounding the perihilar area. The incidence of both pancreatic adenocarcinoma and CC has increased in recent years and, as most patients present at an advanced stage of disease, treatment is mostly aimed at palliation of symptoms.[3,4]

Imaging of the biliary tree in the 1920s consisted of the oral cholecystogram whereby orally ingested iodinated phenolphthalein (selectively secreted into bile) provided radiographic images of the gallbladder and bile ducts.[5] As the bile duct was not accessed directly, therapeutic intervention was not an option. It was not until 1955 when Doubilet and Mulholland injected contrast into the ampulla of Vater (transpapillary) during open surgery, that direct access to the biliary tract became feasible.[6] Their initial images were static and two-dimensional but were soon followed by dynamic fluoroscopic imaging and eventual percutaneous biliary access that followed 30 years later.[7]

Direct fiberoptic visualization of the bowel lumen was first described in 1957 by Basil Hirschowitz, and in 1968 McCune was the first to publish a report on endoscopic wire cannulation of the bile duct in a living patient.[8,9] Rapid advancement in endoscopic technology led to the development of the side-viewing duodenoscope.[10]

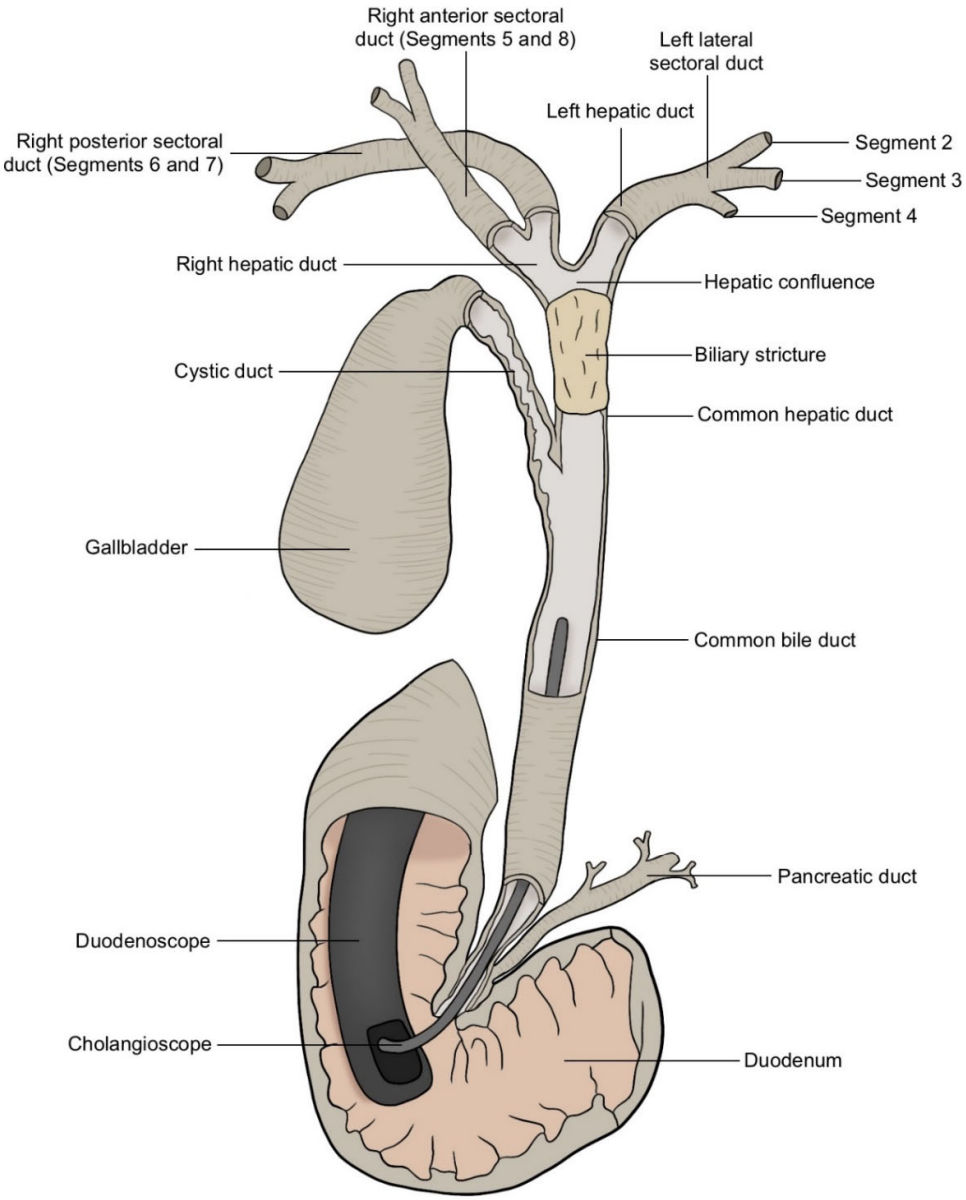


Figure 1. *Endoscopic retrograde cholangiopancreatography (ERCP) combined with single operator cholangiopancreatoscopy (SOCP). Adapted and printed with permission from Frederik Swahn.*

Endoscopic retrograde cholangiopancreatography (ERCP) is the process by which a side-viewing duodenoscope is used to access the bile duct via the ampulla of Vater in order to obtain fluoroscopic images (**Figure 1**).

Currently, the most common means of access to the biliary tree is either via an endoscopic transpapillary (ETP) approach or a percutaneous transhepatic (PTH) approach. The drive to be able to perform therapeutic maneuvers during ERCP led to reports of the division of the sphincter of Oddi (sphincterotomy) both in Germany and Japan in the 1970s, allowing wider access for insertion of devices into the biliary tree.[11,12] In the following years, basic therapeutic mechanisms were developed. These were aimed at the removal of stones with balloons or baskets and stenting of strictures with plastic or metal stents.

In 1961, a cholangioscope was introduced directly into the bile duct during open surgery.[13] The advancement from fiberoptic to video-endoscopes allowed for the development of progressively smaller caliber scopes with sustained good image quality. Currently, less invasive peroral cholangioscopy can be performed in one of three ways: by directly introducing a cholangioscope via the mouth into the ampulla of Vater (direct peroral cholangioscopy), by utilizing a specially designed duodenoscope and custom made cholangioscope (mother-baby system), or by means of the single operator cholangiopancreatoscopy (SOCP) system. The most common SOCP system is the SpyGlass^{TM} Direct Visualisation System (Boston Scientific, USA) that passes through a standard duodenoscope and houses three ports: an optical port that allows passage of optical fibers for visualisation, an irrigation port that ensures continued optimisation of the visual field, and a working port through which instruments can be introduced (biopsy forceps or lithotripsy apparatus). Its single operator status has ensured that it is the most widely adopted means of performing cholangioscopy in current endoscopic practice. The second-generation digital SOCP system was introduced in 2015 and allows for improved resolution and a 110° field of vision. Application in the pancreatic duct is increasingly being reported.

Both the improved visualization of the biliary tree and increased ease of access to the biliary tree led to ERCP changing from a previously diagnostic modality to mostly a therapeutic intervention in current practice. Nasobiliary drainage was first reported in 1980, with the placement of a plastic biliary stent described soon thereafter.[14,15] Currently, plastic and metal stents are used.

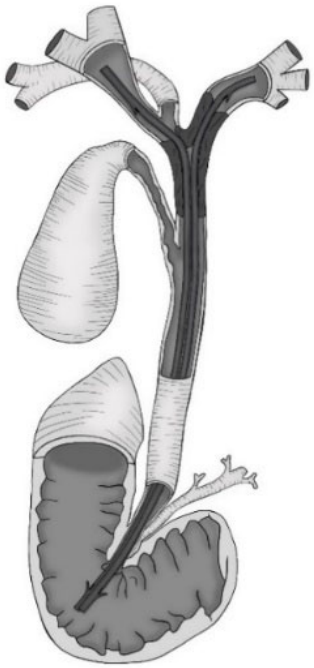


Figure 2. *Bilateral plastic stents.*

Plastic stents (PS) have a low cost and small diameter (maximum of 12F). A tendency to migration and biofilm formation results in a limited patency of 3-6 months (**Figure 2**). Plastic stents are mostly used for temporary or short-term stenting of the bile duct as they can easily be removed and/or replaced, although repeated exchanges decrease quality of life and escalate costs.

Self-expanding metal stents (SEMS) are 10-30 times more expensive than PS but have a larger diameter (10mm/30F on an 8.5F delivery system) and thus a patency of 6-12 months (**Figure 3**). SEMS occlusion is mostly due to ingrowth in uncovered SEMS (uSEMS) and overgrowth or migration in covered SEMS (cSEMS). The ingrowth occurring in uSEMS makes removal difficult and precludes its use in scenarios where temporary stent placement is planned. Similar to PS, cSEMS can be removed and are thus considered for short-term stenting in benign disease. Partially covered SEMS (pcSEMS), where the flanges are left uncovered, hope to combine the benefits afforded by both uSEMS and cSEMS. Regarding ease of placement, the pointed tip and thin delivery system on which SEMS are preloaded facilitate passage through tight strictures, whilst PS passage might have to be preceded by balloon dilation of very tight strictures.

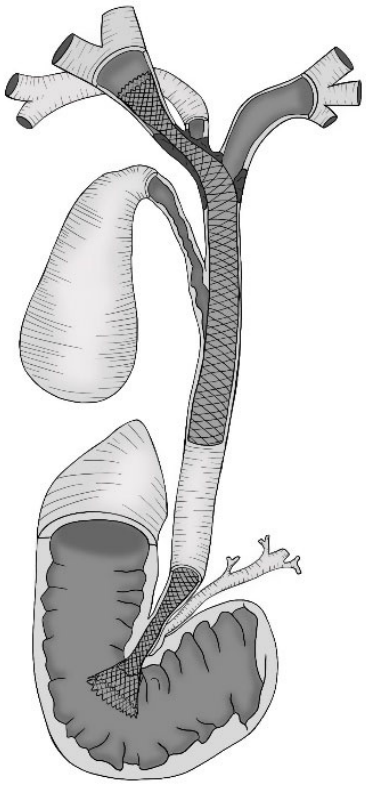


Figure 3. *Unisectoral self-expanding metal stent.*

Due to the location of the papilla in the duodenal lumen, distal (periampullary) pathology can be accessed under direct duodenoscopic vision, making therapeutic techniques at this site relatively straightforward. In contrast, the hepatic hilum can only be indirectly represented on two-dimensional fluoroscopic imaging or via cholangioscopy. Due to its relative 'further' placement from the duodenal lumen and endoscopist, therapeutic procedures in the hilar biliary system are technically much more challenging.

Adverse events associated with ERCP are well defined and graded as per consensus agreement.[16] Adverse events include pancreatitis, cholangitis, bleeding, perforation, cholecystitis and cardiopulmonary events. Of these, pancreatitis is the most common. Based on large prospective series, accepted adverse event rate after ERCP varies between 3%-10% depending on diagnostic or therapeutic intent.[17] When more advanced procedures such as cholangioscopy and/or stenting are added to ERCP, or when intervention is located in the hepatic hilum as opposed to the periampullary area, intervention and location-specific complications can arise.

2 BACKGROUND

2.1 THE HEPATOBILIARY SYSTEM

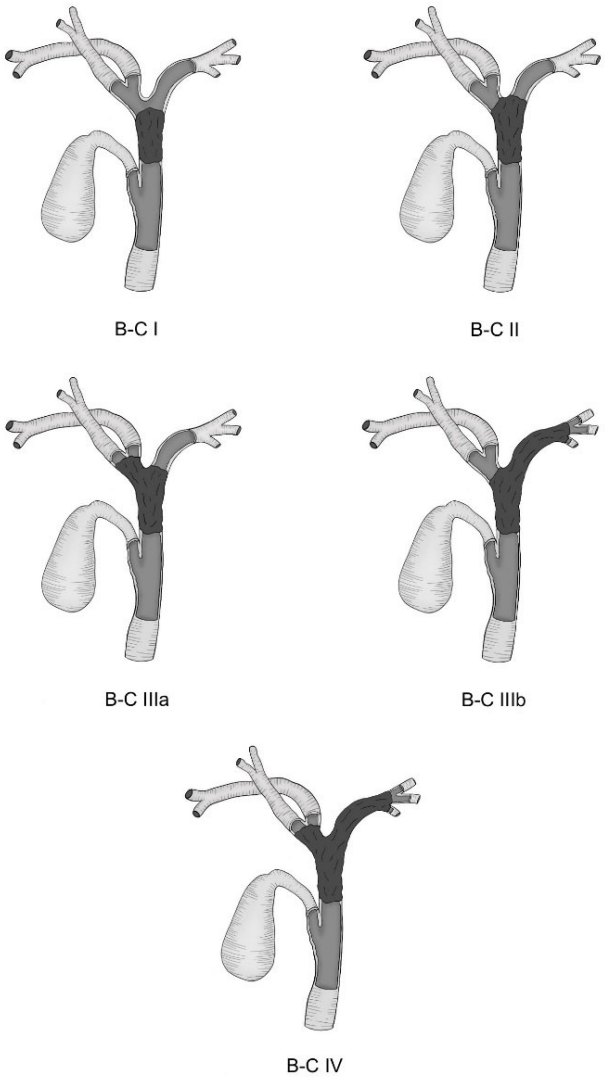
2.1.1 Biliary anatomy and physiology

In the most commonly encountered anatomy of the biliary tree (56%, type 1), the right anterior sectoral duct (draining segments 5 and 8) combines with the right posterior sectoral duct (draining segments 6 and 7) to form the short (1 cm) vertically orientated right hepatic duct which is prone to tumour involvement (**Figure 1**).[18,19] Confluence of the segmental ducts draining segments 2 and 3 form the left lateral sectoral duct at the umbilical fissure. This duct receives variable drainage from segment 4 to end in the left hepatic duct. The longer (3 cm) and horizontally orientated left hepatic duct runs in the peritoneal sheath of the hilar plate. The extrahepatic biliary tree is formed by the confluence of the left and right hepatic ducts to form the common hepatic duct, giving origin to the common bile duct after receiving drainage from the cystic duct. The most common variant (14%, type 2) involves a confluence of the right anterior and posterior sectoral ducts with the left hepatic duct, and with an absent right hepatic duct. Variable drainage of the two right-sided sectoral ducts into the left hepatic duct and common hepatic duct have been described as types 3 (20%) and 4 (10%) respectively.

It is known that the liver is drained by the right hepatic duct (55-60%), the left hepatic duct (30-35%) and tributaries from the caudate lobe (10%). Computed tomography liver volumetry in patients undergoing imaging for unrelated disease has established that, in general, the right liver contributes two thirds to total liver volume and the left liver one third.[20] In 75% of patients segments 2 and 3 together contributed less than 20% of total liver volume. Although proportionally the right liver usually contributes more to total liver volume, it is important to note that considerable variation is found between individuals. The right liver contribution ranges between 49%-82% and the left liver between 17%-49%.

2.1.2 Definitions and classification

There has been more than one attempt at defining the distal extrahepatic bile duct. Some authors refer to the distal third (intrapancreatic portion only), while the Japanese Society of Hepato-Biliary-Pancreatic Surgery refers to the distal half.[21,22] The recent international Asia-Pacific Consensus Meeting defined a distal stricture as “an abnormal narrowing of the distal half, which includes the distal third, of the extrahepatic bile duct”.[23]



Regarding anatomical classification of the proximal extrahepatic bile duct, the Bismuth-Corlette (B-C) classification system was originally developed in 1975 to assist the operating surgeon in deciding on the degree of biliary tree involvement in order to plan the location for anastomosis after resection for malignant disease in the hepatic hilum (**Figure 4**).[24] The classification system, in its original and modified format, refers to the most distal extent of normal biliary mucosa available for anastomosis.[25] With reference to malignant stricture classification, the loss of communication between the left and right liver (hilar block) is classified as a B-C II subtype. Bismuth-Corlette IIIa and IIIb indicate extension of the tumour into the right and left hepatic ducts respectively but without clarity on whether sectoral ducts are communicating.

Figure 4. *The Bismuth-Corlette classification system.*

Since the introduction of the B-C classification system, it has been applied as the starting point for anatomical reference to the hepatic hilum in many clinical scenarios, most notably strictures encountered after iatrogenic bile duct injury (**Table 1**).[26] In this setting, and in contrast to its use in malignant stricture classification, B-C I-III strictures allow for communication between the left and right liver, with separation indicating a B-C IV stricture. Several authors (eg, Strassberg, McMahon, and Way) have developed adaptations to include accompanying injuries, to stratify severity and to describe mechanism of injury. Costamagna et al., in a modification of the B-C classification system, attempted to marry B-C types to drainage strategy by indicating the theoretical number of stents required for drainage of 100% of liver volume.[27] Their approach assumes a hilar block for B-C II types and a right- and left-sided sectoral duct block for B-C IIIa and IIIb types, respectively, but does not account for the 40% of patients with an aberrant right-sided sectoral duct that drains into the left hepatic duct or common bile duct.

Table 1. The evolution of the Bismuth-Corlette classification system and its application in hilar pathology.

	Bismuth-Corlette Classification					
	I	**II**	**IIIa**	**IIIb**	**IV**	**V**
Bismuth-Corlette[24] 1975	Non obstructed primary confluence	Obstruction limited to primary confluence	Primary confluence obstructed with extension to right or left secondary confluence		-	-
Modified Bismuth-Corlette[25] 1992	Lesion confined to bile duct confluence but not involving the superior aspect	Lesion involving superior aspect of confluence, no communication between right and left	Lesion involves superior aspect of biliary confluence and extends into the right hepatic duct	Lesion involves superior aspect of biliary confluence and extends into the left hepatic duct	Lesion involves secondary bile ducts or hepatic parenchyma bilaterally, or main trunk of the hepatic artery or portal vein	-
Bismuth-Corlette[26] **bile duct injury** 2001	Common hepatic or main bile duct stump ≥ 2 cm	Common hepatic duct stump > 2 cm	Ceiling of the biliary confluence is intact; right and left ductal systems communicate		Ceiling of the confluence is destroyed; bile ducts are separated	Stricture of an isolated right duct is present
Costamagna[27] **modification and application** 2004	Stricture does not interrupt the main hepatic confluence	Stricture interrupts the main hepatic confluence	Stricture interrupts the main and the right secondary hepatic confluence	Stricture interrupts the main and the left secondary hepatic confluence	Primary and both, right and left, secondary hepatic confluences are interrupted	-
Number of stents for complete drainage	1	2	3	3	4	

2.2 DISEASES OF THE BILIARY SYSTEM

2.2.1 Gallstones

Most gallstones are cholesterol (90%) or pigmented stones (10%). Pigmented stones can be either 'black' bilirubinate stones or 'brown' infected stones. Cholesterol and bilirubinate stones form primarily in the gallbladder (cholecystolithiasis) but can find their way to the bile duct (secondary choledocholithiasis), while brown pigmented stones form in infected bile ducts (primary choledocholithiasis).[28] Gallstones that migrate from the gallbladder into the bile duct can pass through the ampulla of Vater spontaneously. This process may be asymptomatic, or gallstones may become lodged in the bile duct leading to obstruction. Most bile duct stones (90%-95%) are successfully removed by means of ERCP with biliary sphincterotomy (endoscopic division of the sphincter of Oddi) and balloon extraction, with the term 'difficult' bile duct stone assigned to the 5%-10% of stones resistant to removal by 'conventional' ERCP techniques.[29] There are several techniques that can be utilised for the endoscopic removal of "difficult" stones. Endoscopic papillary large balloon dilation (EPLBD) entails the insufflation of a 12-20 mm balloon inside the

ampulla of Vater to facilitate the passage of larger stones. Mechanical lithotripsy allows for the crushing of large stones by closing a wire basket over a captured stone.

There are currently more than 15 available society/consensus guidelines regarding the treatment of cholelithiasis, all with varying definitions of a 'difficult' bile duct stone and 'conventional' methods for stone removal. Stone attributes that render simple balloon extraction difficult include size (> 1.5 cm), number (multiple), shape (barrel-shaped), anatomical location (intrahepatic or in the cystic duct) or stones that have become impacted due to narrowing or angulation of the bile duct. Some guidelines include EPLBD and mechanical lithotripsy as conventional methods for stone removal, but most agree that intraductal treatment by employing cholangioscopy constitutes advanced therapy.[30] Either hydraulic or laser lithotripsy can be performed at the time of cholangioscopy, and although no comparable studies are available, success rates are similar in reported observational studies.[31]

2.2.2 Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic autoimmune disease resulting in progressive intra- and/or extrahepatic bile duct fibrosis and widespread structuring, with a lifetime risk of developing CC of up to 30%.[32] A dominant stricture is cholangiographically defined as a stricture of ≤ 1.5 mm in the common bile duct and ≤ 1 cm in the right or left hepatic duct.[33] The presence of a dominant stricture carries a high risk for subsequent development of CC (particularly perihilar). An indeterminate stricture is generally defined as one where radiological imaging and conventional ERCP fail to definitively determine the benign or malignant nature of the stricture.

2.2.3 Cholangiocarcinoma

The Asia-Pacific region has the highest prevalence of CC.[34] However, the incidence in Europe and the United States has increased over the past few years.[3,35,36] After hepatocellular cancer, CC is the most common hepatic malignancy, and after pancreatic adenocarcinoma, it is the most common cause of malignant distal biliary obstruction.

Many classification systems exist, with the most universal being the anatomical classification of intrahepatic, perihilar (most common) and distal.[37] Perihilar CC is defined as originating from cholangiocytes above the cystic duct and below second-order bile ducts (sectoral ducts) and can be morphologically subclassified according to growth pattern into mass forming, periductal infiltrating (most common) or intraductal types.[38] Pathological classification recognises three distinct subtypes: sclerosing (70%), nodular (20%) and papillary (5%–10%). Risk factors for the development of CC are chronic biliary inflammation associated with Hepatitis B and C infection, PSC, Caroli's disease, liver fluke infestation, hepatolithiasis and bilio-enetric anastomotic

reconstruction.[39] Patients usually present with painless obstructive jaundice (90%) and rarely cholangitis (10%). Computed tomographic and magnetic resonance imaging provide confirmation of an underlying biliary stricture and assist in staging. The diagnostic challenge lies in confirming whether the underlying stricture is malignant. Tumour markers (CA19-9 and CEA) can be falsely elevated or negative (10%), brush cytology at the time of ERCP is confirmatory in less than 40% of cases, and the addition of fluoroscopically guided biopsies or fluorescent in situ hybridization (FISH) increases sensitivity to no higher than 60%.[37,40] Up to 40% of patients remain with diagnostic uncertainty, risking unnecessary hepatectomy. Based on observational studies, current guidelines support the use of SOCP for intrinsic strictures, while endoscopic ultrasound-guided fine-needle aspiration is suggested for lesions where external compression or a mass lesion is present.[41]

There are currently two staging system in use for perihilar CC. The Memorial Sloan Kettering Cancer Centre (MSKCC) system considers B-C classification (tumour extent), portal vein involvement and the presence of lobar atrophy.[42] The American Joint Committee on Cancer (AJCC) staging system takes the size and extent of the tumour as well as lymph node and distant metastasis into consideration.[43] This assists with determination of resectability. Surgical resection is the only option for cure, however, most patients (60%-80%) presenting to specialised centres are diagnosed at an advanced stage and qualify for palliative biliary drainage rather than resection or transplantation.[42] Treatment goals are specific to the preoperative or palliative setting, with palliation consisting largely of biliary drainage.[44]

2.3 ERCP ASSOCIATED ADVERSE EVENTS

2.3.1 Pancreatitis

In a 2007 meta-analysis of 21 studies, Andriulli et al. determined an overall adverse event rate after ERCP of 6.9%, with pancreatitis the most common at a rate of 3.8%.[17] Seventy-six percent of pancreatitis cases were graded as mild to moderate and 24% as severe. The associated mortality rate was 3%. The origin of the current definition of pancreatitis dates back to a 2007 consensus meeting and has been widely accepted in clinical practice (Suppl. Table 1).[45] Pancreatitis is defined as a serum amylase or lipase of at least 3 times above the upper limit of normal, 24 hours post-procedure, accompanied by new onset abdominal pain consistent with pancreatitis, symptoms severe enough to require a hospital stay (or extend stay if already hospitalised) and/or abdominal computerised tomography scan consistent with the diagnosis of acute pancreatitis. It is postulated that pancreatitis is triggered by an ERCP induced event leading to pancreatic ductal hypertension by means of direct mechanical, chemical, thermal, hydrostatic, enzymatic or microbial injury to the pancreatic ductal epithelium. Although results from

observational studies differ somewhat, patient and procedure-related risk factors for the development of pancreatitis have been identified in two recent systematic reviews evaluating seven and eighteen risk factors, respectively.[46,47] A large multicentre randomised controlled trial (RCT) investigated the administration of rectal non-steroidal anti-inflammatories (NSAIDs) post-ERCP in high-risk cases.[48] The authors found that in 602 patients, rectal indomethacin reduced the incidence of pancreatitis from 16.9%-9.2%. These results have been confirmed in subsequent RCTs and 27 meta-analyses and currently form part of most guidelines as part of chemoprevention (also for average-risk patients in whom no contra-indication exist).[16,49] Aggressive hydration and sublingual nitrates are options in patients with a contraindication to NSAIDs, while prophylactic pancreatic stenting is reserved for high-risk patients (pancreatic wire passage or contrast injection).[16]

Updated European Society of Gastrointestinal Endoscopy (ESGE) guidelines suggest defining additional ERCP-related adverse events according to the 2010 American Society for Gastrointestinal Endoscopy (ASGE) lexicon and cholecystitis according to the revised 2018 Tokyo guidelines (Suppl. Table 1).[16,45,50]

2.3.2 Cholangitis

Cholangitis is defined as a temperature above 38°C for more than 24 hours in the presence of cholestasis. The incidence of post ERCP cholangitis is low (1%).[16] As a result of a landmark publication in 2008, there has been a move away from routine administration of antibiotic prophylaxis prior to ERCP.[51] For some time, incomplete drainage has been known to be a risk factor for the development of cholangitis.[52] Patients with PSC are at increased risk for cholangitis with reported rates ranging from 2.4%-4.0%.[53,54] One recent retrospective, single centre report on 4324 patients aimed to identify independent risk factors for the development of cholangitis.[55] Hilar obstruction, age $\geq$ 60 years and a history of previous ERCP were listed as significant risk factors. The investigators did not include patients in whom cholangioscopy was added to the ERCP procedure. Evidence regarding the relationship between cholangioscopy and cholangitis risk will be explored later in this chapter. Incomplete biliary drainage (hilar obstruction and PSC) and the addition of cholangioscopy is currently recognised as risk factors for post ERCP cholangitis.[16] Prophylactic antibiotics are advocated in cases where incomplete drainage is anticipated, in immunocompromised patients or in cases where cholangioscopy is added to the ERCP procedure.

2.3.3 Grading

Universal grading of adverse events assists with comparison of research results and is constantly evolving. A grading system for the common ERCP associated adverse events has been suggested where: grading of pancreatitis is according to the Atlanta classification for pancreatitis, grading of cholangitis and cholecystitis according to the 2018 Tokyo guidelines, and grading of other ERCP-related adverse events remain according to the 2007 ASGE lexicon.[16,45,50,56,57]

2.4 SINGLE OPERATOR CHOLANGIOPANCREATOSCOPY

Since the first bench simulations and feasibility studies reported by Chen et al. in 2007, SOCP in its second-generation digital format has evolved to become the most widespread system currently in use.[58,59] Although many applications for SOCP have been described, established indications include the treatment of 'difficult' bile duct stones and the diagnosis of indeterminate strictures.[60]

2.4.1 Therapeutic single operator cholangioscopy

For treatment of the 5%-10% 'difficult' bile duct stones not removed by means of conventional ERCP, SOCP has been combined with electrohydraulic and laser lithotripsy since the late 1980's.[31] Ongoing reports on SOCP use in the primary treatment of large stones (> 1 cm), and its ability to diagnose 'hidden' stones escaping detection at ERCP and non-invasive imaging, promise continuous possible benefit in both simple and complex cases.[61–63]

A 2015 meta-analysis, reviewing 49 studies (33 addressing difficult bile duct stones and 29 addressing indeterminate strictures), reported an estimated overall stone clearance rate of 88% for all types of cholangioscopy assisted stone removal.[64] More recent pooled and multicentre studies report SOCP single-session stone clearance rates between 70%-80%, with 94% eventual stone clearance and the pooled number of sessions to stone clearance as 1.26.[65,66] Temporary endoscopic stenting between SOCP treatment sessions allows friction to be generated between the stent and stones, and can assist with stone fragmentation.[67,68] The requirement for additional treatment sessions, however, remains a limitation.

Guidelines regarding an approach to 'difficult' bile duct stones currently suggest the use of endoscopic sphincterotomy and EPLBD as first-line treatment for stones not removed with initial simple balloon sweep, and mechanical lithotripsy or SOCP assisted lithotripsy if EPLBD fails or is contraindicated.[29] Guidelines are based on randomised comparisons of SOCP with both EPLBL and mechanical lithotripsy.[69–71] These studies report superior or similar stone clearance rates, with significantly shorter procedural times favouring conventional ERCP techniques. Surgery is reserved for when endoscopic intervention fails or is not available.

2.4.2 Diagnostic single operator cholangioscopy

Specificity and sensitivity of ERCP brush cytology and fluoroscopic-guided biopsy can reach up to 60%, however, SOCP has received considerable attention as a means to avoid the 7%-25% unnecessary resections performed for undiagnosed benign pathology.[72,73] It can assist in definitive diagnosis of indeterminate biliary strictures in one of two ways: firstly, by means of visual inspection, and secondly, by means of tissue acquisition with directed biopsies.

No standardised classification system exists to guide image interpretation when visually assessing indeterminate strictures and reports on its accuracy vary. In observational studies, the accuracy of visual inspection ranges from 83%-91%, while the accuracy for SOCP targeted biopsies range from 79%-96%.[64,74] Despite the expectation that these statistical measures would improve over time due to evolving technology, a recent large Japanese multicentre study reported lower overall accuracy for SOCP biopsies (70.7%).[75] Attempts at on-site vs. off-site processing of these small tissue samples and the use of cell-block technology has little impact on accuracy.[76,77] Two recent meta-analyses reporting on the accuracy of SOCP biopsies and including 539 and 356 patients, respectively, found the pooled sensitivity and specificity to be 72%-74% and 98%-99%.[78,79] Single operator cholangiopancreatoscopy application in patients with PSC not only aids in confirmation of the nature of the stricture but also assists in traversing otherwise inaccessible strictures, enabling dilation and/or establishment of adequate drainage.[80]

2.4.3 Single operator pancreatoscopy

Compared to the bile duct, maneuvering of the cholangioscope into the pancreatic duct is more challenging. Nonetheless, reports on the role of SOCP in pancreatic stone treatment and the management of intraductal papillary mucinous neoplasms (IPMN) are promising. Limited small prospective studies (none randomised) report successful pancreatic stone clearance rates of between 37%-100%, with an adverse event rate of 0%-30%.[81,82] Single operator cholangiopancreatoscopy has special application in patients with suspected IPMN and has recently been incorporated into consensus guidelines.[83] It assists with differentiation of IPMN from chronic pancreatitis and determines the extent of main duct involvement pre- or intraoperatively. Evaluation of 44 patients with IPMN undergoing pre-operative SOCP found the diagnostic accuracy to vary from 76% (main duct type) to 78% (branch duct type).[84] The promise of pre-operative diagnostic confirmation was, however, offset by a post-ERCP pancreatitis incidence of 17%. A more recent retrospective series spanning reported combined visual impression and SOCP-guided tissue sampling accuracy between 90%-95%, with an adverse event rate of 12%.[85] Reports on the use of SOCP in the pancreatic duct are, however, from high-volume centres and experienced operators, and therefore efficacy figures might be overestimated.

2.4.4 Clinical value of single operator cholangiopancreatoscopy

Whereas clinical *utility* of a novel procedure can be measured by effectiveness such as calculation of a stone clearance rate or diagnostic accuracy estimation, these measures speak to procedure performance. Quantifying the clinical *value or impact* that a new procedure contributes to patient care is more complex. Reports on the clinical value of SOCP are limited. An early retrospective multicentre series reported successful provision of treatment in 87% of patients with stone disease and modification of treatment in 69% of patients with indeterminate strictures.[86] The authors failed to provide methodological details of how the diagnostic impact of SOCP was assessed. In the first multicentre report on the use of SOCP, Chen at al. reported a change in patient management in 64% of patients, as assessed by the attending investigator.[87]

Three recent studies comprising relatively small sample sizes, assessed the impact of SOCP on patient management in cases of indeterminate strictures.[88–90] The first report evaluated 13 SOCP procedures with a change in patient management after the procedure as a secondary outcome.[88] The authors indicated that SOCP permitted exclusion of malignancy and, as such, avoided surgery in 9 patients (69%). Prat et al., in their multicentre study on the impact of SOCP use on patient management, included 61 patients and calculated the percentage of patients in whom SOCP changed outcomes favourably.[89] For each patient the investigators established: (a) planned management before SOCP vs. management after definitive diagnosis, and (b) planned management after SOCP vs. management after definitive diagnosis. Based on predefined criteria for adequacy between diagnosis and management, two teams (investigators and independent experts) rated all patients. They found that the addition of SOCP changed management in 60% of patients. De Vries et al. estimated the impact on patient management in 77 patients undergoing SOCP for evaluation of an indeterminate stricture.[90] The author reviewed records and classified management of patients into one of three categories: changed (17%), confirmation of planned management (51%) or no influence on management approach (32%). Forty percent of the patients had PSC, where the pretest probability for malignancy is known to be < 5%, likely explaining the lower impact in this study.[91]

Regarding the clinical value of SOCP application in the pancreatic duct, reports are from small patient samples. Single operator cholangiopancreatoscopy used to guide intra-operative extent of surgical resection in patients with IPMN has been reported in 21 patients.[92] Occult disease was diagnosed in eight and operative strategy was altered in five (23.8%). The value of SOCP in planning the extent of surgical resection was evaluated in 18 patients with IPMN.[93] Four patients (31%) had more extensive surgery, and 4 patients (31%) had less extensive surgery after SOCP examination than was initially planned.

2.4.5 Adverse events after single operator cholangiopancreatoscopy

Most publications on SOCP outcomes reflect efficacy studies from single, high-volume tertiary centres, complicating interpretation of reported adverse events. A multicentre study from the United States (available only in abstract format) included 224 SOCP procedures.[94] The primary outcome was adverse events. Pancreatitis, cholangitis, bleeding and perforation were reported in 3.9%, 1.4%, 3.1% and 3.9% of patients, respectively. A more recent retrospective review of multicentre data revealed adverse events in 13.2% of patients after SOCP, with cholangitis rates decreasing from 12.8% to 1% when prophylactic antibiotics were administered.[95] In the raw data from the meta-analysis by Korrapati et al. (including 49 observational studies) adverse events after cholangioscopy applied in the treatment of stone disease ranged between 0% and 25%, with cholangitis being the most common.[64] Pancreatitis was relatively rare likely due to the presence of a previous sphincterotomy in many cases. A more recent aggregate review and meta-analyses reported adverse event rates after cholangioscopy of between 6.1%-9.4%, and adverse event rates after pancreatoscopy between 0%-35%.[65,74,81,96]

Only two previous studies report on adverse events associated with the addition of SOCP at the time of ERCP.[97,98] Sethi et al. found an increase in the rate of adverse events from 2.9% to 7% when cholangioscopy was added to ERCP (OR 2.50; 95% CI [1.56-3.89]).[97] A significant difference in rate, particularly in terms of cholangitis, was determined (0.2% to 1%), however, adverse event rates remained comparable for pancreatitis (1.3% vs. 2.2%). Their report was a single centre study including 3475 ERCP procedures and 402 SOCP and 'mother-baby' procedures and was based on data from a prospectively maintained database. Limitations included an inability to establish pre-determined definitions of adverse events and that data was dependent on endoscopist self-reporting (without subsequent validation). Hammerle et al., in a single centre comparison of 1918 ERCP procedures and 169 SOCP procedures, found an overall adverse event rate of 7.7% and rates for pancreatitis, cholangitis, bleeding and perforation of 2.2%, 1.1%, 2.1% and 0.8%, respectively.[98] After multivariate analysis, they found no increase in adverse events if SOCP was added to ERCP (OR 1.43, 95% CI [0.77–2.65]). The authors relied on data from patient charts and laboratory reports, and referral centre reporting of delayed adverse events.

When considering the introduction of a new technology, associated cost, learning curve, clinical gain and adverse events need to be considered by the clinician. The main aim of study I was to define the clinical gain of SOCP when added to ERCP in a large patient sample. Study II was designed to describe the nationwide integration of SOCP and the extent to which adverse events are influenced when SOCP is added to ERCP.

2.5 ENDOSCOPIC STENTING

The motivation for stenting in patients with malignant biliary strictures is twofold; on the one hand, it provides *preoperative* drainage as a 'bridge-to-surgery' in tumours deemed resectable but where there is a specific indication for drainage; on the other hand, it provides *palliative* drainage when tumours are irresectable or metastatic, or when patient functional reserve precludes curative surgery. Most patients presenting with malignant biliary obstruction are candidates for palliative stenting, with curative treatment being the exception.

The treatment goal differs for patients undergoing preoperative vs. palliative drainage although minimising adverse events and the number of interventions is universal. The main aim of palliative drainage is relief of jaundice to improve quality of life (appetite, pruritis and general well-being) as part of end-of-life care. The treatment goal in *palliative* drainage is thus to achieve and maintain drainage of enough liver volume to allow for symptomatic control and to facilitate administration of oncological therapy. Preoperative drainage is a contentious issue and not universally advocated as infective perioperative complications are increased in such patients, demanding a risk vs. benefit calculation. The goal in the *preoperative* setting is to primarily drain the future liver remnant in selected patients only, mainly to limit perioperative complications.

2.5.1 Approach to distal drainage

Options for palliative distal drainage include surgical bypass (hepatico-, choledocho- and cholecystojejenostomy), ETP drainage, PTH drainage and more recently, endoscopic ultrasound-guided drainage (EUS-GD). Due to easy endoscopic access to the distal biliary tract and success and morbidity rates of > 95% and < 5%, respectively, ETP stenting is the most common approach for palliative drainage in patients with obstructing distal cancer.[23] Surgery is reserved for tumours deemed irresectable at the time of operative exploration and PTH drainage for cases of failed ERCP. Two meta-analyses of five available RCTs comparing surgery to ETP drainage consistently found surgery to provide longer-lasting relief of jaundice.[99,100] Notably, findings in terms of rates of morbidity and mortality were contradictory between the aforementioned meta-analyses. The analysis performed by Lima et al. highlighted the many biases involved and found lower procedure-related morbidity and 30-day mortality in patients treated with endoscopy.[100] All five above-mentioned RCTs reported 30-day mortality in absolute numbers with a low risk of bias demonstrated.

PTH drainage is often performed as a two-stage procedure, with initial percutaneous internal-external catheter (PIEC) or external catheter (pigtail) placement, followed by stenting. Technical challenges to a transhepatic approach are encountered in patients with minimal biliary dilation,

ascites or multiple liver metastases. In practice, the decision between an ETP and PTH approach is often dependent on local expertise and accessibility. Combination approaches, either simultaneous or sequential, can also be employed. The first EUS-guided cholangiopancreatography was performed by Wiersema in 1996, soon followed by the first EUS-GD procedure by creation of a choledochoduodenostomy.[101,102] The role of EUS-GD is rapidly expanding to include creation of a hepaticogastrostomy as well as combination and antegrade biliary stenting techniques.

The choice between PTH drainage and EUS-GD for salvage after failed ERCP depends on local expertise, and while PTH drainage is more widely available, there has been a recent rise in reports on the use of EUS-GD. The first published meta-analyses favour EUS-GD above a PTH approach as first choice after failed endoscopic stenting due to less complications and reinterventions, and guidelines advise accordingly.[103–107] The use of EUS-GD as primary drainage approach 'in lieu of' ETP stenting in patients with distal malignant obstruction has been evaluated in 3 RCTs and a single meta-analysis.[108–111] Similar findings in terms of technical- and therapeutic success rates and risk of stent occlusion were reported, but with a decreased risk of post-procedure pancreatitis after EUS-GD (RR 0.22, 95% CI [0.05-1.02]). In recent meta-analyses comparing EUS-GD with both ETP and PTH drainage, EUS-GD had equivalent technical and therapeutic success and total adverse events rates.[112–114] Reports on EUS-GD are, however, mostly from selected highly skilled EUS operators and published technical success rates (44%-100%) and adverse event rates (3%-34%) are difficult to replicate in wide clinical practice.

2.5.2 Distal stenting - stent type

When comparing SEMS to PS performance in the distal bile duct for palliative distal drainage, four previous meta-analyses and a recent fifth (including 1713 patients) found SEMS to have improved patency and decreased re-intervention rates, most notably 3-4 months after first stent placement.[115–119] Cost appears to be similar (even in patients with a life expectancy of < 3 months), while quality of life is better after SEMS placement.[120,121] The first comparisons of cSEMS vs. uSEMS did not uniformly support the anticipated increased patency of cSEMS, likely as decreased ingrowth is balanced out by increased migration.[122–124] More recent meta-analyses, with contrasting inclusion criteria and outcomes, have all failed to show clear superiority for cSEMS vs. uSEMS.[125–128] Plastic stent use is considered in cases where imaging is yet to be completed and a management plan (curative vs. palliative) yet to be finalised, and in patients scheduled to undergo biliary radiofrequency ablation.[129]

2.5.3 Preoperative distal drainage

Multiple meta-analyses have confirmed worse operative outcomes if preoperative drainage is employed in patients with distal malignant obstruction.[130–132] Indications for preoperative drainage are limited to patients presenting with cholangitis or intense severe pruritis, to those that will undergo neo-adjuvant therapy and to those in which surgery is delayed.[23,133] As with palliative distal stenting, evidence, consensus and guidelines suggest an endoscopic approach (lower seeding and recurrence risk) with SEMS placement (longer patency) as preferred options.[16,23,134] The performance of uSEMS and cSEMS is similar.[135] Plastic stent use might be prudent to limit artefact on cross sectional imaging (compromising future diagnostic certainty) when stricture nature has not yet been confirmed.[131]

In summary, evidence is almost unanimously in support of endoscopic SEMS placement for drainage in distal malignant obstruction. The situation for patients with MHO is less clear.

2.5.4 Hilar stenting

Endoscopic retrograde cholangiopancreatography in patients with MHO is technically more challenging as it is pathophysiologically and anatomically more complex. Patients with MHO often require drainage of more than one obstructed area, and a lack of adequate drainage (from an isolated segment) at the same setting predisposes to cholangitis.[136] The anatomical angles formed by the confluence of the left and right hepatic ducts begs for controlled and directed actions. However, the area of intervention is anatomically further away from the endoscopist, affording less maneuverability/pushability when compared to distal stenting. There is debate as to how much of the liver volume needs to be drained to achieve sufficient decompression after palliative drainage. There is evidence for 25%-30% representing adequate treatment, whereas, particularly in B-C types III and IV, drainage of > 50% (requiring bilateral or bisectoral stents) is associated with improved survival.[137,138] As lobar atrophy can be found in patients with MHO, computerised tomography or magnetic resonance imaging targeted drainage of functional volume may be more important than absolute liver volume drained.[139,140]

2.5.5 Approach to hilar drainage

The best surgical option for drainage of MHO is the segment III cholangiojejenostomy due to the high rates of morbidity (51%) and mortality (27%) associated with intra-operative transtumoural tube/stent placement, right sectoral duct bypass and palliative resection.[141] Retrospective series report superior patency, a better quality of life and increased survival when surgical drainage is compared to both ETP and PTH drainage, but inclusion is marred by selection bias, with frail patients never reaching the operating room.[142,143] Even in the absence of RCTs comparing surgery

with ETP/PTH approaches, non-operative treatment is considered the treatment of choice in most centres. Moreover, surgical drainage is often not possible in patients with extensive left-sided hepatic metastasis or atrophy, or when direct tumour spread or portal hypertension precludes safe open access to the left hepatic duct.

Non-surgical options for hilar drainage include ETP drainage, PTH drainage and EUS-GD. An endoscopic approach is not always the approach of choice for MHO, unlike for distal malignant obstruction. There are five RCTsthat compare an ETP with a PTH approach in patients with MHO (**Table 2**).[144–148] Three older studies are difficult to interpret due to inclusion of distal and hilar tumours, failure to control for stent type or evaluation in patients with gallbladder cancer only.[144–146] The two more recent RCTs were both closed prematurely due to higher-than-expected mortality in the PTH group in one study, and slow accrual due to referring clinician bias in the other.[147,148] Of 17 available retrospective studies, eight evaluated preoperative drainage and nine evaluated palliative drainage, making comparative analyses challenging.[149–165]

The reviewed meta-analyses are somewhat heterogenous, with some restricted to patients undergoing preoperative drainage and others including patients undergoing preoperative and/or palliative drainage for both distal and hilar cancers.[166–168] The two most recent meta-analyses that compared an ETP with a PTH approach in malignant biliary obstruction (both distal/hilar and preoperative/palliative) reported similar findings and comparable technical and therapeutic success, overall complications and mortality.[167,168] Cholangitis and pancreatitis rates were higher after an ETP approach, while bleeding rate was increased after a PTH approach. The pooled analysis by Moole et al. in 2016 is the only publication that exclusively addresses *palliative* drainage of MHO, and included 546 patients.[103] The author found higher odds for successful drainage after a PTH approach (pooled OR 2.53, 95% [CI 1.57–4.08]), with similar complications reported for both approaches.

Table 2. Randomised control trials comparing endoscopic transpapillary (ETP) and percutaneous transhepatic (PTH) approaches for drainage of malignant hilar obstruction.

	No. of patients Type of cancer Setting	**Stricture location (%)**	**Technical success**		**Therapeutic success**		**Salvage (%) Crossover (%) No. of procedures (mean or %)**	**Overall adverse events (%)**	**Recurrent biliary obstruction (%)**	**Mortality (%) Survival (months)**
			Definition	**(%)**	**Definition**	**(%)**				
Speer et al.[144] 1987	75 Hilar Palliative	Distal 61 Hilar 39	Radiological position across stricture	ETP 89 PTH 76	TB fall > 20% during initial admission	ETP 81 † PTH 61 †	NA	30-day: ETP 19 PTH 67	ETP 15 PTH 6	30-day mortality: ETP 15 PTH 33
Pinol et al.[145] 2002	54 Hilar Palliative	Distal 41 B-C I 30 B-C II 19 B-C III 9 B-C IV 1	Not stated	ETP 58 PTH 75	Decrease in TB > 20% of the preprocedure value	ETP 42 † PTH 71 †	NA	Initial admission: ETP 35 PTH 61	ETP 54 PTH 43	Median survival: ETP 2.0 † PTH 3.7 †
Saluja et al.[146] 2008	54 Gallbladder Palliative	B-C II 44 B-C III 56	Stent insertion	ETP 82 PTH 92	TB < 50% pretreatment value in 7 days	ETP 41 † PTH 89 †	Salvage procedure: ETP 11 PTH 0	30-day: ETP 52 † PTH 18 †	ETP 39 PTH 32	Procedure-related mortality: ETP 8 PTH 4
Coelen et al.[147] 2018	54 Hilar Preoperative	B-C I 2 B-C II 7 B-C IIIa 41 B-C IIIb 20 B-C IV 30	Achievement of internal biliary drainage of the future liver remnant segments	ETP 74 PTH 93	Normal calibre bile ducts in future liver remnant on US and a decrease in TB of at least 20% at day 7	ETP 63 PTH 78	Crossover: ETP 56 † PTH 4 † Single procedure: ETP 15 † PTH 33 †	Preoperative: ETP 67 PTH 63 Postoperative: ETP 55 PTH 65	Early closure	Preoperative mortality: ETP 0 PTH 11 All-cause mortality: ETP 11† PTH 41†
Elmunzer et al.[148] 2020	13 Hilar All ††	B-C II 39 B-C III-IV 61	NA	NA	50% reduction (or improvement to ≤ 2.5 mg/dL) in the TB level within 3 weeks without additional intervention	ETP 50 PTH 40	No. of procedures: ETP 2.3 PTH 2.6	ETP 75 PTH 80	Early closure	Early closure

†Statistically significant, ††All suspected malignant strictures (excluded B-C I). ETP, Endoscopic transpapillary; PTH, percutaneous transhepatic; B-C, Bismuth-Corlette; TB, total bilirubin; US, ultrasound; NA, not applicable.

There are four available meta-analyses exclusively including patients undergoing *preoperative* drainage of MHO (with emphasis on perioperative complications).[169–172] All four reported equivalent technical success for the two approaches but higher cholangitis and pancreatitis rates after an ETP approach, with the most recent reporting a higher bleeding rate after a PTH approach. Concern remains regarding the risk for later development of seeding metastases after a PTH approach, which is higher compared to an ETP approach (22.0% vs. 20.5%).[173] Due to the limitations in evidence, guidelines currently support PTH drainage for palliative stenting of B-C types III and IV.[133,174]

Despite equivalent technical and therapeutic success rates, and decreased rates of pancreatitis reported for both rescue and primary EUS-GD when compared to ETP drainage in patients with distal malignant obstruction, data on EUS-GD in MHO is limited.[112] There are currently 88 published cases with a reported technical success rate of 98% and a therapeutic success rate of 77%.[175] All of the reports are from specialised centres where procedures are performed by highly skilled operators. Besides the evident advantages in patients with altered anatomy (Roux-and-Y gastric bypass) and failed access (cannulation), the transluminal (gastro- or duodenohepatic) drainage established at the time of EUS-GD obviates the need for bridging of the stenosis. Although possible to overcome, a major disadvantage is limited access to the right liver.

2.5.6 Hilar stenting – stent type

In the palliative treatment of MHO, the performance of metal stents, in particular uSEMS, has consistently been better in RCTs and subsequent meta-analyses, due to a superior drainage rate, decreased early adverse events, longer survival, increased patency, and a resultant decreased cost compared to PS.[116,176–178] Superior patency might reflect decreased blockage of segmental branches by the mesh network of uSEMS.[179] In a recent large propensity score matched retrospective series, multiple PS use was inferior to single SEMS placement in terms of therapeutic success and cholangitis rates.[180] As is the case with distal stenting, PS placement may still be indicated when treating indeterminate strictures or in patients scheduled to undergo biliary radiofrequency ablation.[129]

2.5.7 Hilar stenting – extent of drainage

Unilateral stenting achieves drainage in up to 97% of patients, and sustained attempts at achieving placement of bilateral stents can increase cholangitis and liver abscess rates due to retained contrast in undrained segments.[178,181,182] Bilateral stent placement, on the other hand, is associated with improved cumulative patency and survival in retrospective studies, particularly in patients with CC.[180,183] Reported technical success rates for bilateral stenting are contradictory and

evolving (ranging from 76.9% to 95.5%), most likely due to heterogeneity in endoscopist skill.[181,184] A recent RCT found higher therapeutic success rates and lower reintervention rates after bilateral stenting in B-C III-IV types.[184]

Two systematic reviews comparing uni- to bilateral stenting were published in 2013, with a third and fourth added more recently.[116,185–187] The analysis by Ashat et al. included the two available RCTs and five retrospective studies, and found a lower reintervention rate for bilateral stenting, with equivalent rates for technical success, early- and late adverse events and stent malfunction .[178,184,186] Meybodi et al. included 18 studies (10 retrospective and 8 prospective, of which two randomised) and reported a higher weighted pooled rate of technical success for unilateral stenting vs. bilateral stenting (97% vs. 89%, p=0.003), with equivalent functional success (p=0.481) and adverse events.[187] A recent systematic review of reports comparing unilateral and bilateral drainage using an exclusively PTH approach found no differences in technical and therapeutic success, nor early or late adverse events.[188]

If bilateral hilar stenting is employed, either a stent-in-stent (SIS) or side-by-side (SBS) configuration is possible, both with advantages and disadvantages.[189] SIS deployment fits the innate anatomy of the biliary tree better, places less pressure on the surrounding bile duct wall and allows for stent additions, the main challenge being to get the wire through the mesh network of the already deployed stent. SBS deployment is technically more straightforward if bile duct dilatation allows enough space for two stents in parallel. The fear that the combined radial force exerted on the bile duct and portal structures can lead to choledochal perforation or portal vein thrombosis, has not been borne out in evidentiary reports. Evidence, in the form of retrospective series and a single RCT, suggests comparable technical and therapeutic success and adverse event rates.[190,191] In practice, endoscopists should be able to employ both techniques as individual anatomy and tumour pathology require.

In summary, continued improvements in instrumentation and technical proficiency ensures a constant flow of reports on bilateral and trisectoral SEMS placement in the hilum. Current evidence suggests that treatment should be targeted based on pre-procedure non-invasive imaging, and the emphasis should be to attain drainage of at least 50% of liver volume (whether uni- or multisectoral, or uni- or bilateral).[174] For B-C types II-IV, especially after bilateral upstream contrast opacification, this would most likely imply bilateral stent placement.[192] In patients where a non-dominant or atrophic lobe was drained initially (or inadvertently opacified at the time of stenting), bilateral stenting becomes critical.

2.5.8 Hilar stenting - distal stent position

Reports on both PS and SEMS placement above the sphincter of Oddi (suprapapillary) hold promise for decreasing the occurrence of pancreatitis and cholangitis, and prolonging time to recurrent obstruction due to the hypothesized decreased risk of enteric content gaining entry to the stent.[193,194] The decreased risk for cholangitis has, however, not been replicated in subsequent reports.[195] A recent large retrospective study revealed an equivalent adverse event rate and patency period, while endoscopic revision success rate was higher in patients with distal stent location in the duodenum (transpapillary).[196] In the prevailing environment where multidisciplinary and multimodality treatment of MHO is increasing survival and the need for reintervention, deliberate suprapapillary placement of hilar stents is not currently supported by evidence.

2.5.9 Preoperative hilar drainage

A recent meta-analysis including 16 retrospective studies confirmed increased morbidity for preoperative drainage, with poor outcomes most obvious in patients with lower serum total bilirubin (TB) values.[197] There is no consensus regarding indications for preoperative drainage in MHO. It has been suggested in scenarios associated with high postoperative liver failure rates, such as cholangitis or a predicted postoperative future liver remnant of < 30%-50%.[133,198] As previously discussed, there is no definitive evidence to recommend an ETP or PTH approach for preoperative drainage in MHO. It is still unclear whether PS, PIEC, SEMS or nasobiliary catheters perform best in this setting, and guidelines refrain from suggesting SEMS due to a lack of available evidence.[133,199] As is the case with distal malignant obstruction, plastic stents and catheters limit artefact if imaging is yet to be performed.[200]

2.5.10 Adverse events after endoscopic stenting

It is well established that routine sphincterotomy before biliary stent placement is not advocated.[16] However, little research has been conducted to elucidate the extent to which hilar stenting influences the risk for adverse events. Reknimitr et al., in an analysis of 61 patients undergoing hilar stenting, did not find an increased risk of pancreatitis but reported an increased cholangitis risk.[201] The authors reported the rate for cholangitis for B-C I, B-C II and B-C III-IV at 4%, 10% and 58%, respectively. In more recent retrospective studies, cholangitis rates vary between 29%-46%.[202,203] Xia et al., in a 2019 retrospective review of 502 patients with MHO, reported a cholangitis rate of 22% after hilar stenting and identified PS use and B-C IV types as independent predictors for the development of cholangitis.[204] The authors reported nine procedure-related deaths, of which five were due to cholangitis and subsequent septic shock. Results from RCTs on

unilateral vs. bilateral stenting are conflicting. In initial reports, patients had a significantly higher rate of cholangitis after attempted (but failed) bilateral drainage.[181] The most recent RCT comparing uni- and bilateral stenting substantiated the idea that bilateral stenting affords limited protection against cholangitis As no diff in cholangitis rates between the two groups were found (4.7% vs. 9.1%, p=0.323).[184]

2.5.11 Recurrent biliary obstruction

Stent specific complications, such as obstruction and migration, are viewed in current literature as causes of recurrent biliary obstruction rather than adverse events. Recurrent biliary obstruction is defined as the recurrence of jaundice and/or cholangitis following stent insertion.[23,205] Causes can be classified as non-tumour related (66%), such as migration, kinking, sludge formation and food impaction, or tumour related (34%), such as ingrowth or overgrowth.[206] Non-occlusion cholangitis occurs when a temperature above 38°C is recorded for more than 24 hours in the presence of cholestasis but in the absence of dilated bile ducts or a confirmed cause for recurrent biliary obstruction.[205]

Randomised trials report 6- and 12-month patency rates after distal stenting for malignant obstruction between 68%-78% and 32%-55%, respectively.[118,207] Mean patency after hilar stenting using SEMS in retrospective studies vary between 201-546 days according to bilateral or unilateral stent placement and RCTs report patency rates at 6- and 12-months of 30% and 17% respectively.[177,178,202,206] A prospective study found more durable stent patency after bilateral stenting, with B-C type not affecting patency on multivariate analysis.[184] A retrospective review found lower hilar SEMS patency in patients with gallbladder carcinoma, after left-sided SEMS placement and in cases where preprocedural cholangitis was present.[202] A meta-analysis of nine small observational studies on the use of biliary radiofrequency ablation hold promise for its future use, with a pooled weighted mean difference in stent patency of 50.6 days being determined.[208]

The extent to which outcome is worse in patients drained for MHO compared to distal malignant obstruction is not well-defined. Furthermore, there is no consensus in terms of patients with MHO regarding the optimal approach to gaining biliary access, number of stents to be utilized and extent of drainage to be persued.[133,174,192] This paucity in knowledge is particularly apparent regarding specific B-C locations in the biliary hilum. Study III aimed to investigate adverse events and patency rates after distal and hilar stenting in the different B-C locations of the biliary tree, while study IV was designed to compare ETP and PTH approaches and explore how approach type (ETP and PTH) relate to outcomes in different B-C types.

3 RESEARCH AIMS

The aims of this thesis are:

- To determine the clinical value, both therapeutic and diagnostic, of SOCP when added to ERCP

- To address the nationwide integration of SOCP and to determine to what extent adverse events are influenced when SOCP is added to ERCP

- To compare adverse events and reintervention rates after endoscopic stenting for MHO to stenting for malignant distal obstruction

- To compare outcomes after ETP stenting with outcomes after PTH stenting in the palliative drainage of patients with MHO

4 MATERIALS AND METHODS

4.1 PAPER I

Study design

Study I was a retrospective review of all SOCP procedures performed between March 2007 and December 2014 at a tertiary high-volume endoscopy unit.

Procedures

All patients were discussed at a multidisciplinary team (MDT) meeting and, according to unit protocol, received prophylactic antibiotics but no NSAIDs prior to SOCP procedures. An endoscopic sphincterotomy was completed in all patients and procedures were performed using the first-generation SpyGlass system. Electrohydraulic lithotripsy was performed using a 1.9-Fr coaxial electrode (Olympus, Sweden) or a bipolar biliary probe (Northgate Technologies, USA). All PSC patients received brush cytology and flow-cytometry while SOCP-guided biopsies were obtained at the discretion of the endoscopist. For the visual diagnosis of malignant biliary strictures, the presence of dilated, tortuous or irregular vessels was noted and for the diagnosis of IPMN, previously defined criteria were used.[209]

Determination of clinical utility

Each SOCP procedure's therapeutic value and diagnostic yield was evaluated using a predefined 4 graded scale as depicted in **Table 3**. A single independent reviewer assigned a grade to each procedure by reviewing the impact that treatment delivered at the time of the procedure had on patient management (therapeutic procedure), or the impact that information obtained at time of the procedure had on the final MDT decision (diagnostic procedure). In cases where it was difficult to ascertain the relative contribution that other treatment or diagnostic efforts lent to the final management plan, cases were graded as grade 2. Regarding the diagnostic value of SOCP in assessment of indeterminate strictures the following examples applied: grade 1 – SOCP in no way contributed to the diagnosis, grade 2 – SOCP provided contributory information to sway the diagnosis towards benign or malignant but definitive diagnosis remained elusive, grade 3 – SOCP provided confirmation of a previous diagnosis of benign or malignant, and grade 4 – SOCP yielded a tissue diagnosis of malignancy where previous sampling was benign.

Table 3. Grading scale to estimate the clinical value of single operator cholangiopancreatoscopy.

	Clinical utility of a single operator cholangiopancreatoscopy procedure		
Grade	**Therapeutic value**	**Diagnostic Yield**	
1	No value	No yield	No significant clinical gain
2	Did not alter clinical course	Did not impact clinical decision making	
3	Assisted subsequent disease management	Impacted on clinical decision making	Great clinical significance
4	Solved the clinical problem requiring no further therapeutic actions	Essential and critical for clinical decision making	Pivotal clinical importance

Definitions

Baseline physical status was defined according to the American Society of Anesthesiologists (ASA) classification system with: I – a normal healthy patient, II – mild systemic disease, III – severe systemic disease, and IV – systemic disease that is a constant threat to life. Complex cholelithiasis was defined as either 'difficult to remove' common bile duct stones or intrahepatic stones. 'Difficult to remove' common bile duct stones were defined as stones not removed by conventional means (sphincterotomy and balloon extraction) and indeterminate strictures as strictures where conventional means (brush cytology and flow-cytology) did not lead to a definitive diagnosis as benign or malignant. Adverse events were defined and graded according to the ASGE lexicon (Suppl. Table 1).[45]

Statistical analyses

Descriptive statistics were used to analyze results with frequencies (proportions and percentages), means (normally distributed data), medians (non-normally distributed data) and ranges reported. To explore risk factors for the occurrence of adverse events, subgroup analysis was performed considering the following risk factors: pancreatoscopy (vs. cholangioscopy) and a non-dilated pancreatic duct (vs. dilated pancreatic duct).

4.2 THE GALLRIKS REGISTRY

The GallRiks registry is the Swedish Registry for Gallstone Surgery and ERCP and was the source of data for studies II and III. It is a prospective population-based registry conceived in May 2005 by three Swedish Societies: the Swedish Surgical Society, the Swedish Society of Upper Abdominal Surgery and the Swedish Society of Laparoscopic Surgery. It has as its aim to record all endoscopic, laparoscopic and open interventions in the gallbladder and biliopancreatic ductal system. GallRiks uses an internet platform (www.ucr.uu.se/gallriks) for online data

registration and running cost is covered by the Swedish National Board of Health and Welfare (Socialstyrelsen). Its strengths lie in wide national participation and systematic validation.

Coverage

To assess participation, annual cross-referencing of the International Classification of Diseases (ICD) codes is performed between the Swedish National Inpatient Register and patients/procedures entered into GallRiks, and results are made public to stimulate ongoing engagement. Since its start in 2007, participation in the GallRiks registry has steadily increased from 75% of ERCP's registered in 2007 to 87% registered in 2009. From 2009 onwards it is considered nationwide with more than 90% of all cholecystectomies and ERCP's performed in Sweden currently registered in GallRiks.[210] The registry includes procedures from all University Hospitals, county/district hospitals and most private units in Sweden.

Validity

The validity of a national registry encompasses two dimensions; namely, completeness and correctness. Regarding the construct of GallRiks, clinicians enter initial data including baseline patient characteristics, choice of intervention, indication, technical success and adverse events. During the first two years of GallRiks coming into use, entered variables were adjusted to maximise captured data while at the same time minimising participant effort, and so increasing compliance. The GallRiks board meets on an ongoing annual basis to adjust the dataset as needed. Outcomes at 30 days after the procedure are completed by an independent local non-physician coordinator that compare registry data with local patient records. Independent external audit of the registry is furthermore carried out at 3-yearly intervals. Validation takes place through a random selection of 50 patients from a participating unit in whom data is correlated with medical records. The 30-day follow-up frequency after cholecystectomy and ERCP in GallRiks is 96% and 95% respectively.[210] A 2018 report confirmed the increased adverse events seen in units with a more complete 30-day follow-up, underscoring the importance of participant diligence.[210] External audit results are published annually on the website (http://www.ucr.uu.se/gallriks/index.php/arsrapporter) and discussed with GallRiks appointed surgeons and Heads of Department at each unit. For the GallRiks registry, a validity above 98% has been reported regarding completeness and correctness of data.[211]

This national registry has a function not only in quality control but also in improved health care policies. Research questions where conduction of a RCT will be costly and extend over several years have successfully been addressed by GallRiks-based studies.[212–215]

4.3 PAPER II

Study design

Study II was a nationwide case-control study nested within the cohort of ERCP procedures, with- or without SOCP and registered in the GallRiks registry between January 2007 and December 2012.

Selection of patients

Patients where cholangiopancreatoscopy was performed with the mother-baby system or where follow-up was incomplete, were excluded from the study. Only patients where 30-day follow-up was complete and where cholangiopancreatoscopy was performed with the single operator (SpyGlass) system, were included in the final analysis (**Figure 5**).

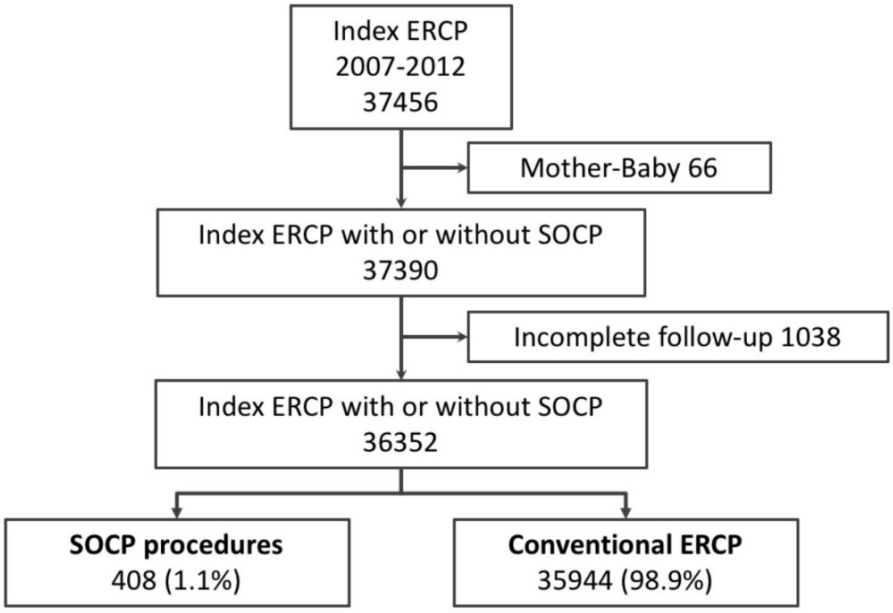


Figure 5. *Endoscopic retrograde cholangiopancreatography (ERCP) and single operator cholangiopancreatoscopy (SOCP) procedures included in Study II*

Definitions

Common indications for SOCP or ERCP were defined as common bile duct stones, obstructive jaundice or malignancy. Conventional ERCP was defined as ERCP without the addition of cholangiopancreatoscopy. Endoscopic retrograde cholangiopancreatography specific adverse events were defined according to the internationally accepted ASGE lexicon (Suppl. Table 1) and baseline physical status according to the ASA classification system.[45] Intraprocedural adverse events were defined as any occurrence that led to premature termination of the procedure.

Postprocedural adverse events were defined as complications occurring in the first 30 days after the procedure and requiring medical or surgical intervention.

Statistical analyses

Descriptive statistics and graphical methods were used to describe data, with Pearson's chi-squared test used for comparisons in contingency tables. A p-value of ≤ 0.05 was deemed significant. For the analysis of the impact of SOCP on adverse events, ERCP-specific adverse events were analysed individually and grouped as intra- or postprocedural adverse events. Univariate and multivariate logistic regression was performed with the following hypothesized risk factors taken into account: age (> 71 years and ≤ 71 years (median)), sex (female or male), ASA classification (ASA I-II or ASA III-IV), urgent or elective, native or postsphincterotomy papilla, pancreatic duct cannulation (yes or no), indication (common or uncommon) and sedation method (conscious sedation, propofol or general anesthesia). The models were tested for effect modification and were finally assessed for the goodness of fit. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Lastly, a subgroup analysis was performed with stratification of SOCP procedures into bile duct or pancreatic duct investigations.

4.4 PAPER III

Study design

Study III was a nationwide population-based cohort study including all patients undergoing ERCP for malignant biliary obstruction and prospectively entered in the GallRiks registry from January 2010 to December 2017. Date of death was determined by cross-referencing with the Swedish Central Death Register and patients were followed until December 2018.

Selection of patients

All patients that underwent ERCP and were entered into the GallRiks registry were considered for inclusion in the study (**Figure 6**). Endoscopic retrograde cholangiopancreatography procedures that were not index procedures and patients where the indication was for reasons other than malignant biliary obstruction according to histological/cytological confirmation, MDT decision or the ICD-10 coding system were excluded from further study. Likewise, patients were excluded if a stent could not be placed due to failed cannulation or unsuccessful bridging of the stricture with a guidewire (complete stenosis), or where a stent was placed but the position of the stricture or stent was unclear (missing data). Only patients that underwent stenting for confirmed malignant biliary obstruction were included for the analysis of adverse events. For determination and comparison of stent failure, patients that received a PS, a combination of PS and SEMS, or

multiple SEMS were excluded, so that only patients where a single SEMS was placed were analysed.

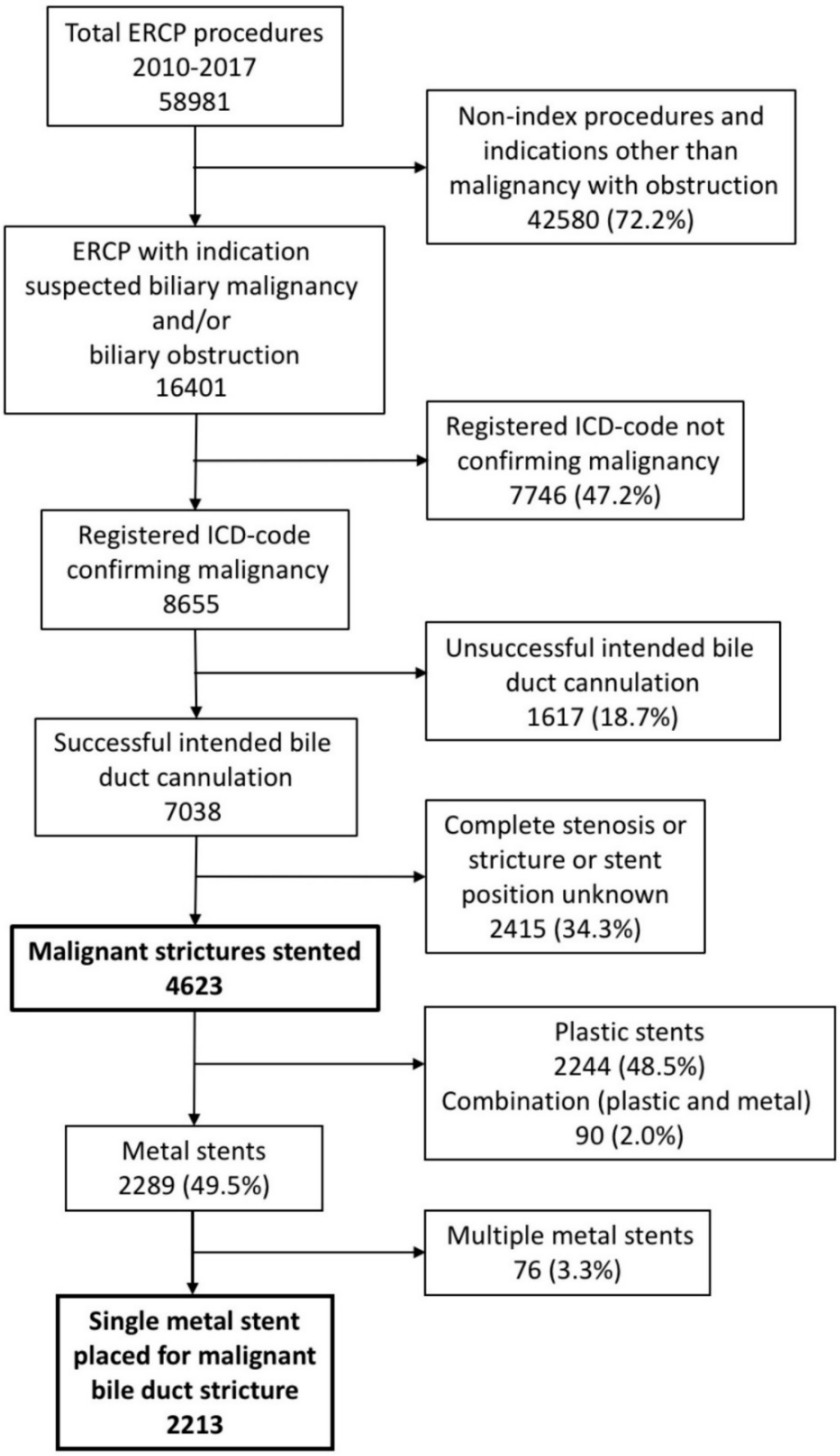


Figure 6. *Flowchart of included ERCP procedures in Study III.*
ERCP, cholangiopancreatography; ICD, International Classification of Diseases.

Definitions

An index procedure was defined as the first ERCP procedure performed. Baseline physical status was defined according to the ASA classification system. Proximal stricture extent was used as reference point for grouping of strictures into distal or hilar strictures. A *distal stricture* was defined as located in the ampulla of Vater or common bile duct with the proximal extent situated distal to the junction of the cystic duct to the bile duct. A *hilar stricture* was defined as involving or located above the cystic duct common bile duct junction with proximal extent in the common, left or right hepatic ducts. Hilar strictures were further subdivided according to the modified B-C classification system and B-C I-II subtypes were grouped as extrahepatic strictures while B-C III-IV were grouped as intrahepatic strictures.[25] Total procedure time was defined as time from endoscope insertion to endoscope withdrawal. Adverse events were defined according to the ASGE lexicon and grouped as intraprocedural and 30-days postprocedural (Suppl. Table 1).[45] Stent failure/patency was defined as the time to the need for endoscopic reintervention regardless of the cause for recurrent obstruction and according to the Tokyo criteria for reporting on transpapillary stenting.[205] The time point of recurrent biliary obstruction was defined as the point at which symptoms associated with obstruction necessitated reintervention.

Statistical analyses

Descriptive statistics were used for demographic and procedural data as well as adverse events. For within-group analyses, the Pearson's chi-squared test was used for the comparison of categorical data and the Student t-test for comparison of continuous data. For time to event statistical modelling, Kaplan-Meier analysis was employed. Endoscopic reintervention was considered a terminal event, whereas death or reaching the end of the study period with a functioning stent were treated as censored events. Cox proportional hazard models were utilised to calculate the risk for recurrent biliary obstruction according to age > 75 years (vs. < 75 years), male sex (vs. female sex), ASA class I-II (vs. ASA class I-II) and level of obstruction (hilar vs. distal), and hazard ratios (HR) and 95% CI were calculated.

4.5 PAPER IV

Study design

Analysis of the large population-based cohort in study III functioned as a platform for design of study IV which was a retrospective comparison of palliative ETP and PTH drainage approaches performed for MHO at two specialised referral centres from January 2015 to June 2020. Patients were identified from endoscopy and interventional radiology registries and entered in an online academic database.

Selection of patients

Consecutive index palliative drainage procedures performed for irresectable MHO were included for study. Patients in whom both ETP and PTH procedures were planned, whether simultaneous or sequential, were excluded. For comparison of the duration of therapeutic success, patients with lymphoma were excluded due to their expected better prognosis compared to primary hepatobiliary and metastatic cancers.

Procedures

All patients were discussed at MDT meetings and both endoscopic and percutaneous procedures were performed under conscious sedation with general anesthesia available for selected cases. Diagnoses were based on a combination of imaging, tumour markers and cytological or histological confirmation. The index approach and stent characteristics were at the discretion of the endoscopist or interventional radiologist after discussion with the treating physician. When an intended approach failed to achieve technical success, the decision to reattempt the initial approach or the alternative approach was up to the treating physician. Serum TB values were repeated only for patients planned for palliative chemotherapy, and biliary radiofrequency ablation was not utilised at either of the two centres during the inclusion period.

Data

Data included baseline demographics, comorbidities, Eastern Cooperative Oncology Group (ECOG) functional performance score, serum values, diagnosis (including method of diagnosis), as well as modified B-C classification type.[25] Stent characteristics included stent number, stent type (plastic vs. SEMS), stent position (internal PS/SEMS vs. PIEC) and the extent of intended drainage (unilateral, bilateral, trisectoral). For patients with B-C III strictures, unilateral stenting was described as ipsilateral or contralateral to segmental duct involvement. Procedure-related complications and severity grading according to the Modified Accordion Grading System (MAGS) for ETP and PTH approaches were documented and compared.[216]

Technical success

For ETP and PTH approaches access success (gaining entry to the bile duct), bridging success (guidewire crossing of stricture) and technical success (stent placement across stricture) were determined. For patients that crossed over from one drainage approach to another, the number of procedures before crossover were calculated. For patients that reached technical success, the number of procedures to stent placement was calculated for the successful approach, excluding procedures before crossover. Additionally, for patients that reached technical success, stent characteristics and extent of drainage achieved (represented by the total number of segments

drained and the estimated percentage of liver volume drained (dichotomised into 33.3% increments)) were documented. The extent of drainage achieved was assessed by a single reviewer after each drainage procedure and formal volumetric analysis was not performed on all patients.

Therapeutic success

Biochemically confirmed therapeutic success (TB value ≤ 40 µmol/L) was documented and compared for ETP and PTH approaches. Assuming a linear decrease in TB from first stent placement, the time point of calculated therapeutic success was taken where the serum TB value first crossed the 40 µmol/L line. Time to therapeutic success was defined as the time between the time points of achieving technical success and calculated therapeutic success. Time to therapeutic success was compared for ETP and PTH approaches independently, per B-C type, and as a function of stent characteristics and extent of drainage achieved. The influence of stent characteristics and extent of drainage on achievement of therapeutic success was explored regardless of which approach was used. Failure of therapeutic success (first TB value of ≥ 40 µmol/L) was documented and the duration of therapeutic success was compared for ETP and PTH approaches and per B-C type.

Definitions

Successful biliary access was defined as advancement of a catheter percutaneously or endoscopically into the bile duct, proximal and distal to the stricture, respectively. Successful bridging was defined as passage of a guidewire across the stricture. Technical success was defined as successful stent/PIEC placement across the stricture according to the Tokyo criteria for reporting on transpapillary stenting.[205] Biochemically confirmed therapeutic success was defined as a TB value of ≤ 40 µmol/L. Time to therapeutic success was defined as the time between the time points of achieving technical success and calculated therapeutic success. Failure of therapeutic success was defined as recurrent biliary obstruction regardless of cause with a TB value of ≥ 40 µmol/L. Duration of therapeutic success was defined as the time between the time points of therapeutic success and failure of therapeutic success. Complications were classified as intraprocedural (from entering the preparation area to leaving the endoscopy/radiology room) and early (≤ 14 days) or late (> 14 days) postprocedural. Endoscopic biliary drainage complications were defined according to ESGE guidelines and PTH drainage complications were defined according to the Society of Interventional Radiology (SIR) guidelines (Suppl. Table 1).[16,217]

Statistical analyses

Categorical variables (expressed as percentages) were compared by the Chi-squared or Fisher's exact test and continuous variables (expressed by means (SD) or median (IQR)) by means of the

two-samples t-test or Mann-Whitney U test. Within-group analyses were performed to explore outcomes for different B-C types and a p-value of ≤ 0.05 was regarded as significant. Multivariate logistic regression was performed to measure the influence of stent characteristics and extent of drainage achieved on eventual achievement of therapeutic success. For the analysis the following hypothesized risk factors were taken into account: B-C type (B-C I-IV), stent number (1 stent or > 1 stent), stent type (plastic or SEMS), stent position (internal PS/SEMS or PIEC), extent of intended drainage (unilateral, bilateral, trisectoral), total number of segments drained (dichotomized into <3, 3-6 and >6) and estimated percentage of liver volume drained (dichotomised into 33.3% and 50% increments). Odds ratios with 95% CI were calculated. Kaplan-Meier analysis was used to assess duration of therapeutic success and restricted mean survival time analysis was used to compare duration of therapeutic success between approaches and B-C types to supply clinically applicable estimates.

4.6 ETHICAL CONSIDERATIONS

Study I and II was approved by the Regional Research Ethics Committee in Stockholm and study III by the Regional Research Ethics Committee in Umeå, Sweden. Since these studies were purely retrospective in nature, informed consent from included patients was not required by the Review Boards. For conduction of study IV, ethics approval was obtained from the Regional Ethics Review Boards at both participating centres, the University of Stellenbosch and the University of Cape Town, South Africa. As the academic database developed for registration of all patients with MHO in the Western Cape would function as a prospective registry in future, it was in addition registered at the Human Research Ethics Committee, University of Cape Town as such. Included participants in study IV were entered in a retrospective manner, and thus informed consent was waived. Permission to use patient records was obtained from the Provincial Health Research Committee of the Western Cape. All study protocols complied with the ethical guidelines of the 1975 Declaration of Helsinki.

5 RESULTS

5.1 PAPER I

Over a 7.8-year period a total of 365 SOCP procedures were performed in 311 patients. In 71% of patients the bile duct was the main target of the procedure, in 24% the pancreatic duct, and in 5% both ducts. In 79.6% of cases the procedure could be performed in an outpatient setting. Patient demographics and indications for SOCP procedures are summarized in **Table 4**. Procedure time was a median of 99 min (range 50-275) and 15.9% of patients underwent a SOCP procedure for complex cholelithiasis, while 55.1% of patients underwent a SOCP procedure for indeterminate biliary stricture evaluation (non-PSC patient 32.6% and PSC patients 22.5%).

Table 4. Demographic data and indications for single operator cholangiopancreatoscopy (SOCP) procedures.

Patent demographic	n (%), median (range)	Procedure indication	n (%)
Patients undergoing a single procedure	273 (88)	Complex cholelithiasis	58 (15.9)
Patients undergoing multiple procedures	38 (12)		
Female sex	137 (44)	Indeterminate stricture (non-PSC patient)	119 (32.6)
Age (years)	64 (4-94)		
Referral from outside Stockholm	103 (33)	Indeterminate stricture (PSC-patient)	82 (22.5)
Duration of procedure (minutes)	99 (50-275)		
ASA classification		Cystic lesion of the pancreas (including IPMN)	64 (17.5)
ASA I	58 (16)		
ASA II	186 (51)	Chronic pancreatitis (+/- lithotripsy)	20 (5.5)
ASA III	121 (33)		
ASA IV	0 (0)	Miscellaneous	22 (6)

ASA, American Society of Anesthesiologists; PSC, primary sclerosing cholangitis; IPMN, intraductal papillary mucinous neoplasm.

Clinical utility

Single operator cholangiopancreatoscopy was found to be of pivotal clinical importance (grade 4) in 19% of cases and of great clinical significance (grade 3) in 44% of cases, while the procedure did not affect clinical decision-making or alter clinical course (grade 1 and 2) in 37% of cases (**Figure 7**). The largest number of grade 2 procedures were due to an inability to definitively ascertain the relative contribution of the information provided by the SOCP procedure, in the presence of multiple factors that ultimately affected the outcome (n = 54).

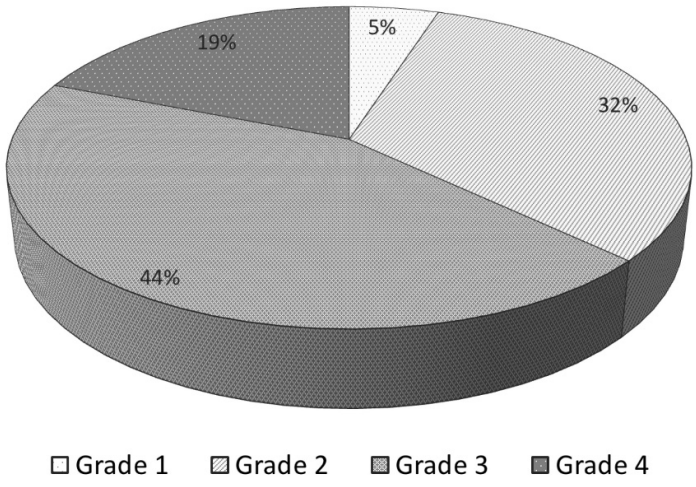


Figure 7. *The relative (%) distribution of therapeutic value and diagnostic yield as scored according to the predefined grade scale.*

Figure 8 is a representation of the assigned grades grouped as grade 1–2 or grade 3–4, according to the indications for a SOCP procedure. SOCP was found to be of significant clinical value (grade 3-4) in 79% of procedures performed for the treatment of complex bile duct stones, 66% of procedures performed as part of work-up for cystic pancreatic lesions, 57% and 56% of procedures performed for the evaluation of indeterminate biliary strictures in non-PSC and PSC patients, respectively, and in 45% of patients with chronic pancreatitis.

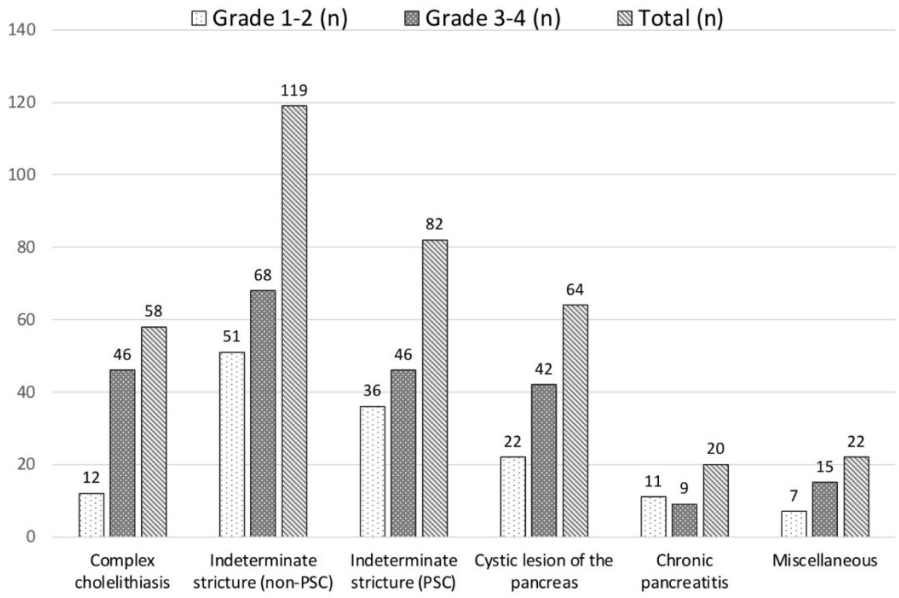


Figure 8. *Representation of the assigned grades (grouped as grade 1–2 or grade 3–4) according to the indication for single operator cholangiopancreatoscopy (SOCP). PSC, primary sclerosing cholangitis.*

Adverse events after single operator cholangiopancreatoscopy

The overall adverse event rate was 16.2% with the majority (96.6%) graded as mild to moderate. Pancreatitis was the most common (7.9%) and the cause for the single postprocedural mortality. In this patient a simultaneous EUS-guided cystic pancreatic lesion puncture was performed together with the SOCP procedure and severe necrotizing pancreatitis ensued that ended with multi-organ failure and death on day 101 post procedure. We could not demonstrate a change in pancreatitis risk over time. When analysing specific risk factors for the occurrence of postprocedural adverse events, we found that pancreatoscopy was associated with an overall adverse event rate of 19.8% as compared to 9.6% for cholangioscopy. In the pancreatoscopy group we furthermore found a non-dilated main pancreatic duct in 9/17 pancreatitis cases (53%).

5.2 PAPER II

Over a 6-year period a total of 37456 ERCP procedures were registered in GallRiks with 66 cholangiopancreatoscopy procedures performed with the mother-baby system and 408 with the single operator (SpyGlass) system (**Figure 5**). From 2007 onwards the number of SOCP procedures increased progressively from 16 in 2007, to 89 in both 2011 and 2012. An opposing decrease was seen in the number of mother-baby procedures (14 in 2007 to 6 in 2012). SOCP was utilised at 10 units in Sweden (mainly University Hospitals) with 69% of procedures performed at a single high-volume centre (**Figure 9**).

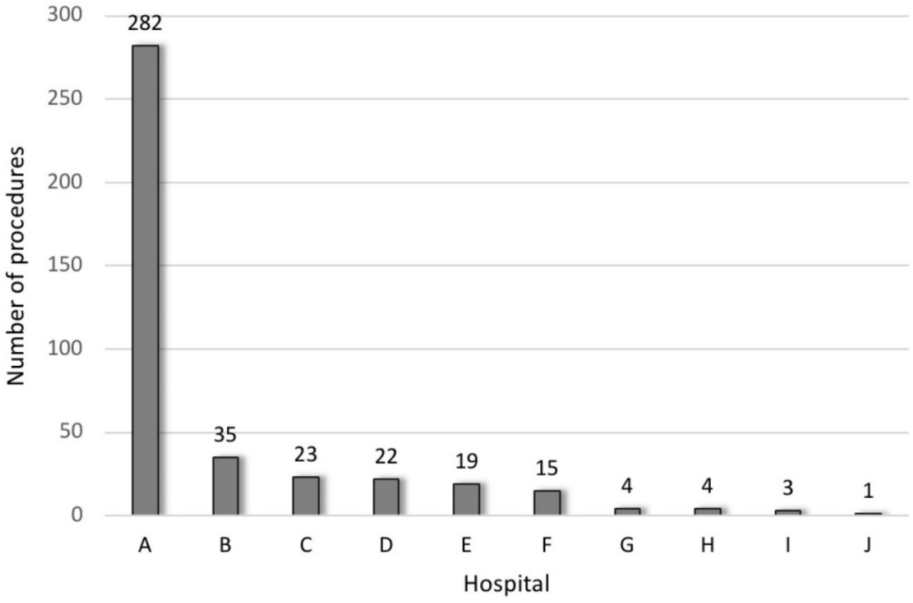


Figure 9. *Single operator cholangiopancreatoscopy (SOCP) procedures per hospital during a 6-year period. Hospital A is the Karolinska University Hospital.*

Suspected or known common bile duct stones, obstructive jaundice and malignancy was the indication for intervention in 16.9%, 2.9% and 12.3% of SOCP procedures respectively while 26.7% of procedures were performed in patients with PSC. Patients in the SOCP group were younger healthier males, undergoing more elective procedures under general anesthesia. SOCP procedures, when compared to conventional ERCP procedures, were associated with less native papillae (48.0% vs. 78.4%, p<0.0001), a higher cannulation rate (99.2% vs. 91.9% p<0.001), a lower rate of EPLBD or sphincterotomy (44.6% vs. 63.4%, p<0.001), more pancreatic duct interventions (31.4% vs. 23.3% p<0.001) and a lower rate of common bile duct stone clearance (58.2% vs. 71.6%, p=0.001).

Adverse events

Postprocedural adverse events, including pancreatitis and cholangitis, were more common in the SOCP group compared to the conventional ERCP group (19.1% vs. 14.0%, p=0.003, 7.4% vs. 3.9%, p<0.001 and 4.4% vs. 2.7%, p=0.003 respectively). Postprocedural adverse events were higher in the early period compared to the later period (25.3% vs. 15.7 %; p=0.017). The increase in postprocedural adverse events seen when SOCP is added to conventional ERCP was present in the early period (25.3% vs. 13.4%, p<0.001) but disappeared in the later period (15.7% vs. 14.5%, p=0.602). On univariate analysis, the risk of postprocedural adverse events, pancreatitis and cholangitis was increased for SOCP (**Table 5**). After adjustment, the risk for both intraprocedural and postprocedural adverse events were increased, while the risk for pancreatitis and cholangitis disappeared.

Table 5. Odds ratios and 95% confidence intervals for the risk of adverse events among patients undergoing single operator cholangiopancreatoscopy (SOCP) compared with conventional endoscopic retrograde cholangiopancreatography (ERCP).

Adverse events	SOCP versus Conventional ERCP			
	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Intraprocedural	1.52	0.90 - 2.40	2.25	1.31 - 3.61
Postprocedural	1.45	1.13 - 1.85	1.35	1.04 - 1.74
Pancreatitis	1.98	1.33 - 2.83	1.48	0.98 - 2.15
Cholangitis	1.67	1.00 - 2.61	1.38	0.82 - 2.18
Bleeding	1.19	0.61 - 2.07	1.82	0.93 - 3.21
Perforation	2.15	0.66 - 5.10	1.66	0.51 - 3.98

SOCP, single operator cholangiopancreatoscopy; ERCP, endoscopic retrograde cholangiopancreatography; OR, odds ratio; CI, confidence interval.

After stratification into procedures where bile or pancreatic duct cannulation was performed, there was an increased risk for intraprocedural adverse events after bile duct cannulation, even

after adjustment for confounders (**Table 6**). The increased risk for postprocedural adverse events and pancreatitis after pancreatic duct cannulation that was present on univariate analysis, disappeared after adjustment for confounders.

Table 6. Odds ratios and 95% confidence intervals for the risk of adverse events among patients undergoing single operator cholangiopancreatoscopy (SOCP) compared with conventional endoscopic retrograde cholangiopancreatography (ERCP) stratified according to bile duct or pancreatic duct cannulation.

Adverse events	Bile duct cannulation				Pancreatic duct cannulation			
	Univariate		Multivariate		Univariate		Multivariate	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Intraprocedural	2.05	1.05 – 3.59	3.01	1.52 – 5.36	1.25	0.49 – 2.62	1.77	0.68 – 3.83
Postprocedural	1.34	0.97 – 1.82	1.29	0.92 – 1.76	1.58	1.04 – 2.35	1.40	0.91 – 2.09
Pancreatitis	1.52	0.78 – 2.66	1.50	0.76 – 2.65	2.03	1.20 – 3.25	1.50	0.87 – 2.44
Cholangitis	1.87	1.06 – 3.05	1.48	0.83 – 2.45	1.03	0.25 – 2.76	0.88	0.21 – 2.37
Bleeding	1.22	0.52 – 2.41	1.69	0.71 – 3.40	1.23	0.37 – 2.95	2.25	0.67 – 5.71
Perforation	2.05	0.34 – 6.52	1.51	0.25 – 4.89	2.65	0.43 – 8.66	2.68	0.43 – 8.83

OR, odds ratio; CI, confidence interval.

5.3 PAPER III

Over a 7-year period a total of 58981 ERCP procedures were registered into GallRiks with 4623 of these performed for stenting of malignant biliary obstruction (**Figure 6**). Seventy and a half percent of patients (n=3259) had a distal stricture and 29.5% a hilar stricture (n=1364), of which 76.5% were extrahepatic (B-C I-II) and 23.5% intrahepatic (B-C III-IV) (**Figure 10**).

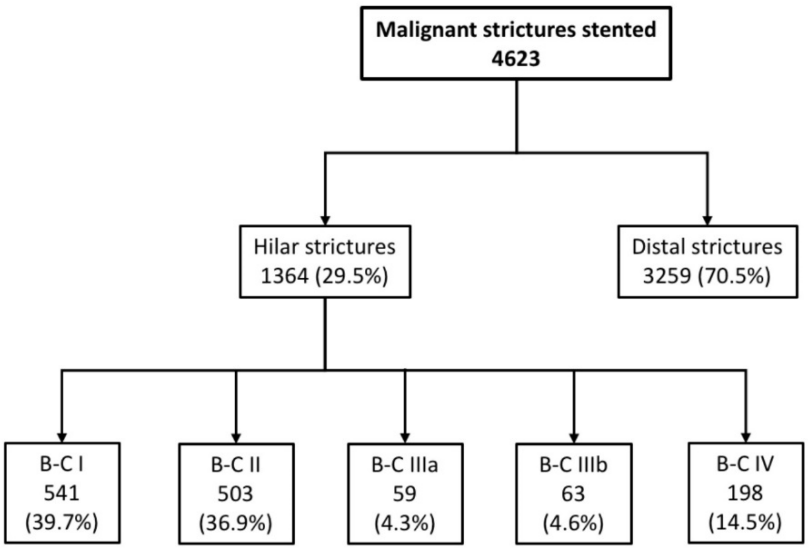


Figure 10. *Flowchart indicating the position of strictures in Study III. B-C, Bismuth-Corlette.*

Demographic details and adverse events

Patients undergoing hilar stenting were more often female, younger and in a higher ASA class compared to patients undergoing distal stenting, while time from scope insertion to withdrawal was longer **(Table 7)**. Hilar compared to distal stenting was associated with a higher total adverse event rate (19.2% vs. 14.2%, p<0.001) mostly attributable to increased postprocedural adverse events (17.2% vs. 12.0%, p<0.001). Both pancreatitis and cholangitis rates were increased after hilar stenting compared to distal stenting (6.6% vs. 4.0%, p<0.001 and 4.1% vs. 2.8%, p=0.024 respectively). When comparing B-C I-II with B-C III-IV strictures, patients with more advanced B-C types were younger (68.8 years vs. 72.3 years, p<0.001) and procedure time was longer (65.9 min vs. 47.6 min, p<0.001). Intraprocedural and postprocedural adverse events did not differ significantly between extrahepatic and intrahepatic stenting.

Table 7. Demographic and procedural details and adverse events comparing endoscopic transpapillary stenting for distal versus hilar strictures as well as extrahepatic hilar strictures (B-C I-II) versus intrahepatic hilar strictures (B-C III-IV).

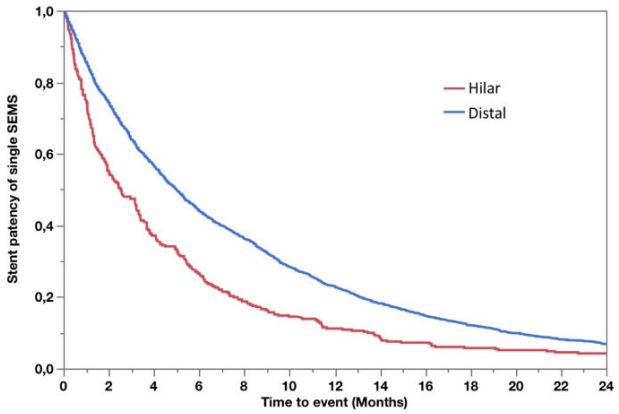
	Distal n=3259 n (%) or mean (SEM‡)	**Hilar n=1364 n (%) or mean (SEM‡)**	**p-value**	**Extrahepatic (BC I-II) n=1044 n (%) or mean (SEM‡)**	**Intrahepatic (BC III-IV) n=320 n (%) or mean (SEM‡)**	**p-value**
Demographic details						
Female	1670 (51.2)	750 (55.0)	0.020†	594 (56.9)	156 (48.7)	0.010†
Male	1589 (48.8)	614 (45.0)		450 (43.1)	164 (51.3)	
Age (years)	72.5 (0.2)	71.4 (0.3)	0.005††	72.3 (0.4)	68.8 (0.7)	<0.001††
ASA I-II	1938 (59.5)	638 (46.8)	<0.001†	503 (48.2)	135 (42.2)	0.060†
ASA III-IV	1321 (40.5)	726 (53.2)		541 (51.8)	185 (57.8)	
Procedure time (min)	36.9 (0.4)	51.9 (0.8)	<0.001††	47.6 (0.9)	65.9 (2.1)	<0.001††
Adverse Events						
Total	462 (14.2)	262 (19.2)	<0.001†	208 (19.9)	54 (16.9)	0.359†
Intraprocedural	71 (2.2)	28 (2.1)	0.788†	23 (2.2)	5 (1.6)	0.480†
Bleeding requiring intervention	6 (0.2)	0 (0)	0.113†	0 (0)	0 (0)	
Extravasation of contrast	37 (1.1)	12 (0.9)	0.439†	11 (1.1)	1 (0.3)	0.214†
Other intraprocedural complication	28 (0.9)	16 (1.2)	-	12 (1.1)	4 (1.3)	-
Postprocedural (30-day)	391 (12.0)	234 (17.2)	<0.001†	185 (17.7)	49 (15.3)	0.318†
Pancreatitis	129 (4.0)	90 (6.6)	<0.001†	74 (7.1)	16 (5.0)	0.188†
Cholangitis	92 (2.8)	56 (4.1)	0.024†	44 (4.2)	12 (3.8)	0.714†
Perforation	9 (0.3)	3 (0.2)	0.732†	2 (0.2)	1 (0.3)	0.686†
Bleeding requiring intervention	26 (0.8)	13 (1.0)	0.599†	9 (0.9)	4 (1.3)	0.532†
Other postprocedural complication	135 (4.1)	72 (5.3)	-	56 (5.4)	16 (5.0)	-

†Pearson's chi-squared test, ††Student t-test. SEM, standard error of mean; B-C, Bismuth-Corlette; ASA, American Society of Anesthesiologists.

Reintervention

Figure 11 is a representation of the need for endoscopic reintervention in months after hilar and distal single metal stent placement. At 6 months 56% of distally located stents required reintervention compared to 73% of hilar stents, while at 1 year 77% of distal stents and 89% of hilar stents required reintervention (p<0.001, p<0.001).

The time to need for endoscopic reintervention according to different B-C types (B-C I-IV) is represented in **Figure 12**. Six months after single metal stent placement, reintervention was required in 56%, 70%, 76%, 90%, 87% and 86% of patients with distal and B-C I through to IV types respectively (p<0.001).

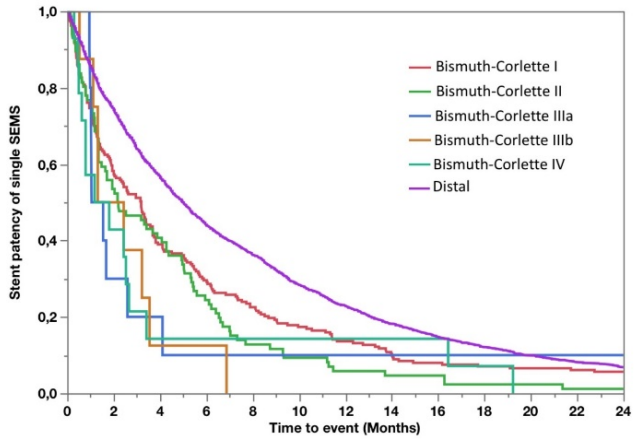


	Distal		Hilar		
Stent patent	n	%	n	%	p
6 months	830	44.1	88	26.6	**<0.0001**
12 months	430	22.9	37	11.2	**<0.0001**
18 months	227	12.1	19	5.7	**0.0007**
24 months	129	6.9	14	4.2	0.0733
p = Pearson's chi-square test					

Figure 11. *Need for endoscopic reintervention in months after hilar and distal single metal stent placement.*

(Log-Rank: ChiSquare 47.07 Prob>ChiSq <0.0001

Wilcoxon: ChiSquare 66.13 Prob>ChiSq <0.0001)



	Distal		BC I		BC II		BC IIIa		BC IIIb		BC IV		
Stent patent	n	%	n	%	n	%	n	%	n	%	n	%	p
6 months	830	44.1	63	29.6	21	24.4	1	10	1	12.5	2	14.3	**<0.0001**
12 months	430	22.9	29	13.6	5	5.8	1	10	0	0	2	14.3	**<0.0001**
18 months	227	12.1	15	7.0	2	2.3	1	10	0	0	1	7.1	**0.0212**
24 months	129	6.9	12	5.6	1	1.2	1	10	0	0	0	0	0.2654
p = Pearson's chi-square test													

Figure 12. *Need for endoscopic reintervention in months after single metal stent placement for the Bismuth-Corlette types (B-C I-IV).*

(Log-Rank: ChiSquare 58.85 Prob>ChiSq <0.0001

Wilcoxon: ChiSquare 74.04 Prob>ChiSq <0.0001)

Multivariate analysis taking into account sex, age, ASA class and level of obstruction revealed male sex and hilar stricture location were significantly associated with the risk for reintervention. Patients with a hilar stricture had a three times higher risk of requiring reintervention after single hilar metal stent placement compared to distal metal stent placement (HR 3.47, 95% CI [2.01-6.00], p<0.001) (**Table 8**).

Table 8. Univariate and multivariate analyses of the risk for reintervention after single metal stent placement.

	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio† (95% Confidence Interval)	p-value	Hazard Ratio† (95% Confidence Interval)	p-value
Hilar stricture	3.26 (1.89-5.59)	<0.001	3.47 (2.01-6.00)	<0.001
Male sex	1.85 (1.12-3.07)	0.017	1.97 (1.18-3.27)	0.009
Age > 75 years	0.98 (0.60-1.62)	0.951	1.08 (0.65-1.78)	0.775
ASA III-IV	1.05 (0.63-1.73)	0.860	0.94 (0.56-1.56)	0.804

†Cox proportional hazard analysis

5.4 PAPER IV

Over a 5.5-year period, 293 patients underwent an index drainage procedure as palliation for MHO, 153 (52.2%) with an intended ETP approach and 140 (47.8%) with an intended PTH approach. Although patients in the two intended approach groups had a similar distribution of diagnoses and B-C types, patients in the ETP group more often had a confirmed tissue diagnosis. Eastern Cooperative Oncology Group performance score of 0, 3 and 4 were more common compared to the intended PTH group. Additionally, patients in the intended ETP group were older, had more chronic obstructive pulmonary disease, had a lower median serum alkaline phosphatase and a higher median serum haemoglobin level.

A total of 263 patients (89.8%) reached technical success, 117 (44.5%) in the ETP group and 146 (55.5%) in the PTH group. Comparison of the ETP and PTH technical success patient cohorts revealed similar diagnoses but more patients with B-C IV types in the ETP group. There were more patients with 0 or 3 comorbidities, more patients with chronic obstructive pulmonary disease and a higher median serum haemoglobin level in the ETP group.

Thirty-four patients crossed over from an ETP to a PTH approach in order to reach technical success and 4 patients crossed over from a PTH to an ETP approach in order to reach technical success. Patients that crossed over from an ETP to a PTH approach were mostly B-C I types, and

when compared to patients that reached technical success via an intended PTH approach, crossover patients were older (Suppl. Tables 2-3).

Technical success

In total, 158 ETP approaches were attempted, 153 (96.8%) as the intended approach and 5 (3.2%) after crossover from the PTH group (**Figure 13**). A PTH approach was attempted in 179 patients, in 140 (78.2%) as the intended approach and in 39 (21.8%) after crossover from the ETP group. In the total technical success patient cohorts (intended approach and crossover) ETP vs. PTH access success was achieved in 83.5% and 97.2% respectively (p<0.001), bridging success in 90.2% and 84.5% respectively (p=0.199) and technical success in 98.3% and 99.3% respectively (p=0.854).

The number of procedures to reach technical success for the approach that ultimately achieved technical success were significantly less after an ETP approach, with 32.9% of patients requiring two procedures to achieve successful stent placement after a PTH approach (p=0.021). Bismuth-Corlette subgroup analysis revealed that 100% of patients with B-C IIIa types reached technical success after a single procedure undergoing an ETP approach, compared to 55.2% of patients after a PTH approach (p<0.001).

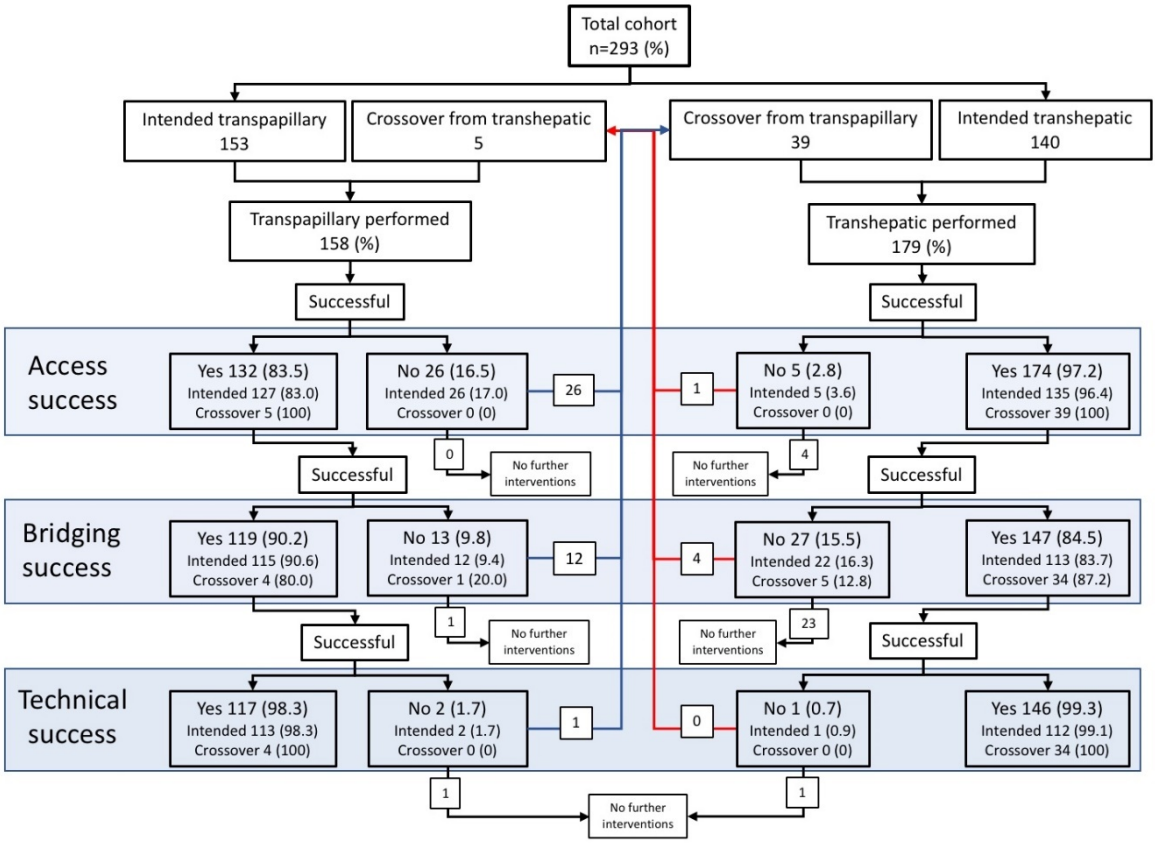


Figure 13. *Access success, bridging success and technical success for endoscopic transpapillary and percutaneous transhepatic approaches.*

Regarding number of procedures before crossover, patients that crossed from an ETP to a PTH approach had a median of two (range 1-3) procedures before crossover, while patients that crossed from a PTH to an ETP approach had a median of one (range 1-2) procedures before crossover (p=0.024).

Comparison of stent characteristics at technical success revealed PIEC placement in 31.5% of patients after a PTH approach and similar rates of plastic stent/catheter and SEMS placement between ETP and PTH approaches. Patients in the ETP group, however, received more two stent and bilateral stent placements compared to patients in the PTH group (p=0.001, p<0.001). Bismuth-Corlette subgroup analysis revealed more bilateral and trisectoral stent placement after an ETP approach, most significant in B-C IIIa types (p<0.001).

The extent of drainage achieved at technical success for ETP and PTH approaches revealed a similar total number of segments and estimated percentage of liver volume drained (p=0.968, p=0.209). B-C subgroup analysis indicated a trend towards a higher total number of segments and higher estimated percentage of liver volume drained in more advanced B-C types after an ETP approach, reaching statistical significance in B-C IIIa types (p=0.003, p=0.002).

In the ETP group, SEMS were placed in 16 patients (13.7%) after initial technical success with a PS (stent exchange), at a median of 24 days (range 7-43). In the PTH group, SEMS were placed in 19 patients (13.0%) after initial technical success with a PIEC (internalisation), at a median of 10 days (range 2-62) (p=0.875, p=0.851). Six patients in the ETP and PTH groups each required an additional SEMS placed to achieve therapeutic success.

Therapeutic success

Analysis of 146 patients in whom serum TB levels were serially performed revealed therapeutic success in 58 (81.7%) and 55 (73.3%) patients after an ETP and PTH approach respectively (p=0.242) (**Table 9**). Likewise, the median time to therapeutic success after ETP and PTH technical success was 30.5 days (range 1-345) and 28.0 days (range 1-83) respectively (p=0.577), with 54.9% of patients reaching therapeutic success regardless of approach within 29 days after successful stent placement (**Figure 14**). Similarly, on B-C subgroup analysis there was no difference between the two groups in the median time to achievement of therapeutic success and, due to small numbers, the influence of stent characteristics and extent of drainage achieved were not analysed further.

Table 9. Successful achievement of therapeutic success following endoscopic transpapillary (n=71) versus percutaneous transhepatic (n=75) technical success for the different Bismuth-Corlette types and the total cohort followed up.

	Achieved therapeutic success proportion (%)			
Bismuth-Corlette type	**Endoscopic transpapillary n=71**	**Percutaneous transhepatic n=75**	**p-value**	**Total n=146**
I	31/33 (93.9%)	28/39 (71.8%)	0.029	59/72 (81.9%)
II	10/12 (83.3%)	14/20 (70.0%)	0.676	24/32 (75.0%)
IIIa	9/14 (64.3%)	6/9 (66.7%)	1.000	15/23 (65.2%)
IIIb	2/3 (66.7%)	5/5 (100%)	0.375	7/8 (87.5%)
IV	6/9 (66.7%)	2/2 (100%)	1.000	8/11 (72.7%)
Total	58/71 (81.7%)	55/75 (73.3%)	0.242	113/146 (77.4%)

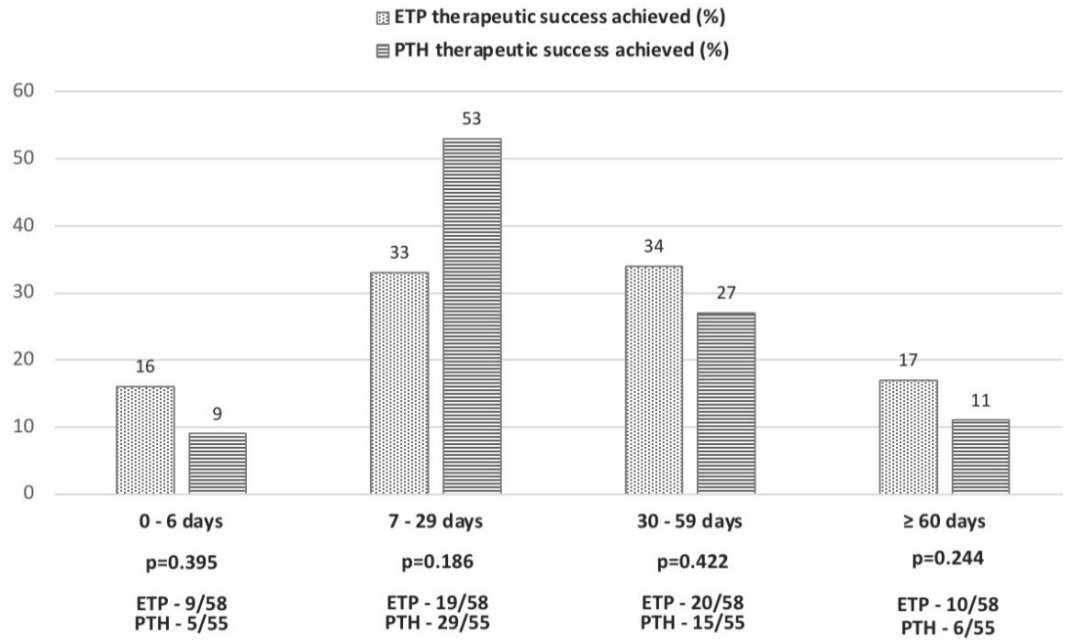


Figure 14. *Time to successful achievement of therapeutic success following endoscopic transpapillary (n=58) versus percutaneous transhepatic (n=55) technical success for all Bismuth-Corlette types. ETP, endoscopic transpapillary; PTH, percutaneous transhepatic.*

The association of stent characteristics on the achievement of therapeutic success regardless of approach is represented in **Table 10**. Within-group analysis revealed that SEMS vs. plastic stent/catheter placement and internal stenting (PS/SEMS) vs. PIEC use were positively associated with the achievement of therapeutic success ($p<0.001$, $p<0.001$). In patients with B-C IIIa and IIIb types bilateral or contralateral stent placement vs. ipsilateral placement was significantly associated with the achievement of therapeutic success ($p=0.049$, $p=0.018$).

The association of the extent of drainage achieved on the achievement of therapeutic success is represented in **Table 11**. Within-group analysis revealed a trend towards more segments and a larger percentage of liver volume drained to be associated with the achievement of therapeutic success, but this was statistically significant only in patients with B-C IIIb types ($p=0.018$).

On multivariate logistic regression modelling adjusted for B-C type, SEMS placement (vs. plastic stent/catheter placement) and internal stenting (vs. PIEC placement) had a higher odds for achievement of therapeutic success (OR 1.72, 95% CI [0.23-0.88], $p=0.020$ and OR 2.42, 95% CI [1.11-5.29], $p=0.026$). Regarding extent of drainage achieved, draining $\geq$ 50% of liver volume (vs. < 50%) had a higher odds for achievement of therapeutic success while draining $\geq$ 30% did not reach statistical significance (OR 2.60, 95% CI [1.47-4.60], $p=0.001$ and OR 1.7, 95% CI [0.55-5.84], $p=0.331$).

Table 10. The association of stent characteristics with the achievement of therapeutic success per Bismuth-Corlette type regardless of approach.

	Bismuth-Corlette type - therapeutic success achieved proportion (%)											
	I 59/72 (81.6)	p-value	II 24/32 (75.0)	p-value	IIIa 15/23 (65.2)	p-value	IIIb 7/8 (87.5)	p-value	IV 8/11 (72.7)	p-value	Total 113/146 (77.4)	p-value
Stent number												
1	52/64 (81.3)	1.000	17/22 (77.3)	0.695	5/11 (45.5)	0.089	5/5 (100)	0.375	3/4 (75.0)	1.000	82/116 (70.7)	0.634
2	7/8 (87.5)		6/8 (75.0)		10/12 (83.3)		2/3 (66.7)		5/7 (71.4)		30/38 (78.9)	
3	-		1/2 (50.0)		-		-		-		1/2 (50.0)	
Stent type												
Plastic	11/18 (61.1)	0.014	5/9 (55.6)	0.176	3/6 (50.0)	0.621	2/2 (100)	1.000	0/3 (0)	0.006	21/38 (55.3)	<0.001
SEMS	48/54 (88.9)		19/23 (82.6)		12/17 (70.9)		5/6 (83.3)		8/8 (100)		92/108 (85.2)	
Stent position												
Internal PS/SEMS	56/62 (90.3)	<0.001	23/28 (82.1)	0.039	14/20 (70.0)	0.269	7/8 (87.5)	-	8/11 (72.7)	-	108/129 (83.7)	<0.001
PIEC	3/10 (30.0)		1/4 (25.0)		1/3 (33.3)		-		-		5/17 (29.4)	
Extent of intended drainage												
Unilateral	54/66 (81.8)	1.000	17/23 (30.4)	1.000	5/11 (45.5)	0.089	6/7 (85.7)	1.000	4/5 (80.0)	1.000	86/112 (76.8)	0.819
Bilateral	5/6 (83.3)		7/9 (77.8)		10/12 (83.3)		1/1 (100)		4/6 (66.7)		27/34 (79.4)	
Trisectoral	-		-		-		-		-		-	
Extent of intended drainage in cases of unilateral stenting for Bismuth-Corlette IIIa and IIIb types												
Ipsilateral	NA	-	NA	-	2/7 (28.6)	0.049	0/1 (0)	0.018	NA	-	NA	-
Contralateral	NA		NA		3/4 (75.0)		6/6 (100)		NA		NA	
Bilateral	NA		NA		10/12 (83.3)		1/1 (100)		NA		NA	

SEMS, self-expanding metal stent; PS, plastic stent; PIEC, percutaneous internal-external catheter; NA, not applicable.

Table 11. The association of the total number of segments and estimated percentage of liver volume drained with the achievement of therapeutic success per Bismuth-Corlette type regardless of approach.

	Bismuth-Corlette stricture type - therapeutic success achieved proportion (%)											
	I 59/72 (81.6)	p-value	II 24/32 (75.0)	p-value	IIIa 15/23 (65.2)	p-value	IIIb 7/8 (87.5)	p-value	IV 8/11 (72.7)	p-value	Total 113/146 (77.4)	p-value
Total number of segments drained												
2	-	-	-	0.804	2/7 (28.6)	0.103	0/1 (0)	0.018	4/5 (80.0)	0.855	6/13 (46.2)	0.082
3	-		5/6 (83.3)		3/4 (75.0)		-		2/3 (66.7)		10/13 (76.9)	
4	-		12/17 (70.6)		1/1 (100)		6/6 (100)		2/3 (66.6)		21/27 (77.8)	
5	-		-		9/11 (81.8)		1/1 (100)		-		10/12 (83.3)	
8	59/72 (81.6)		7/9 (77.8)		-				-		66/81 (81.5)	
Estimated percentage liver volume drained												
< 33%	-	-	5/6 (83.3)	0.804	5/11 (45.5)	0.141	0/1 (0)	0.018	4/5 (80.0)	0.382	14/23 (60.9)	0.084
33%-67%	-		7/9 (77.8)		2/2 (100)		1/1 (100)		2/2 (100)		71/86 (82.6)	
> 67%	59/72 (81.6)		12/17 (70.6)		8/10 (80.0)		6/6 (100)		2/4 (50.0)		28/37 (75.7)	

Duration of therapeutic success was significantly longer after an ETP approach compared to a PTH approach (p=0.009) (**Figure 15a**). After an ETP approach there was a 3-month gain in duration of therapeutic success over the first 400 days of follow-up adjusted for B-C type I vs. II-IV (95% CI [26-160], p=0.006) (**Figure 15b**).

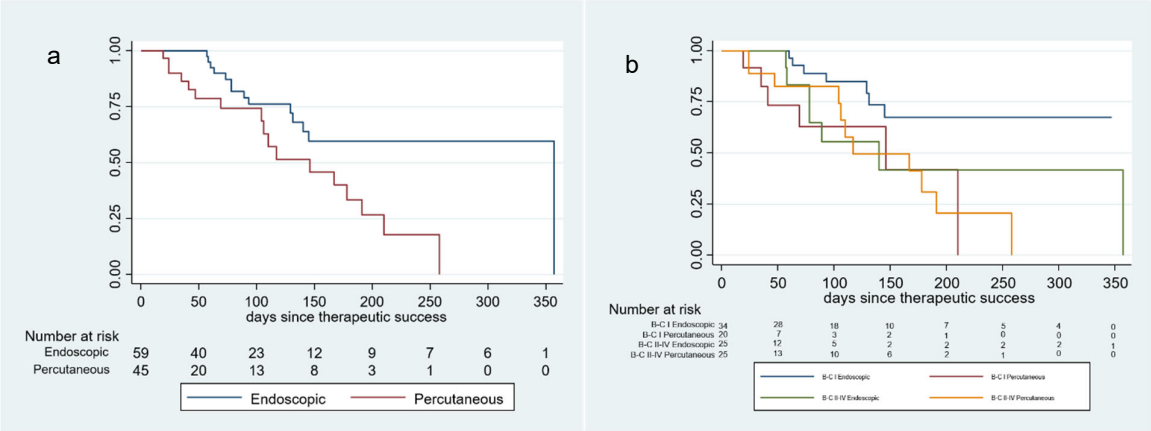


Figure 15. ***a)*** *Duration of therapeutic success following achievement of therapeutic success after an endoscopic transpapillary and percutaneous transhepatic approach.* ***b)*** *Duration of therapeutic success following achievement of therapeutic success after an endoscopic transpapillary and percutaneous transhepatic approach per Bismuth-Corlette type (B-C I vs. B-C II-IV).*

Duration of therapeutic success decreased progressively for B-C types I through to III, with duration shortest in B-C IIIa types (p=0.096) (**Figure 16a**). There were 7 patients with B-C IV types that were followed up, with only 1 failure of therapeutic success. After grouping into B-C I and B-C II-IV, a significant difference in duration of therapeutic success was observed between B-C I vs. B-C II-IV types (p=0.023) (**Figure 16b**).

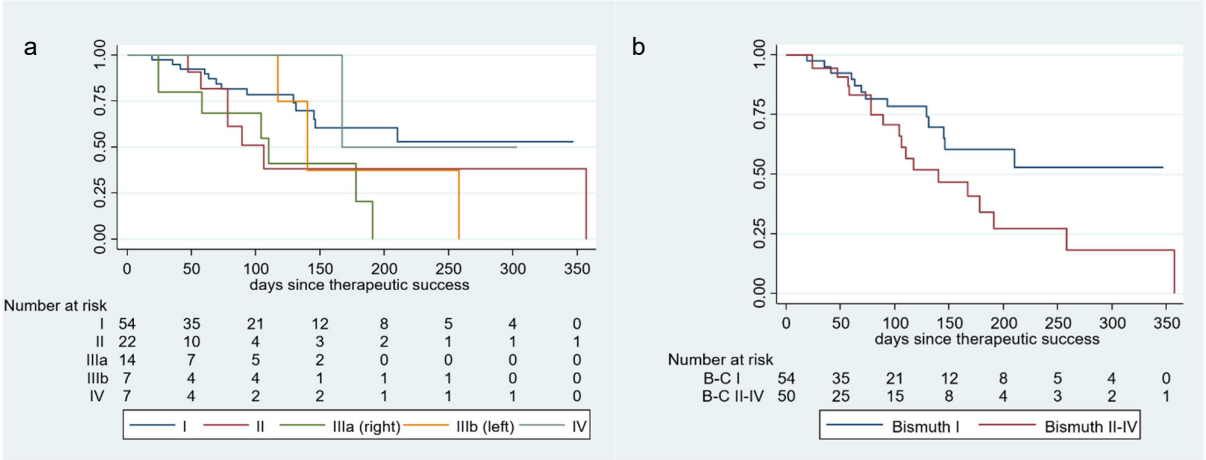


Figure 16. ***a)*** *Duration of therapeutic success following achievement of therapeutic success per Bismuth-Corlette type.* ***b)*** *Duration of therapeutic success following achievement of therapeutic success per Bismuth-Corlette type (B-C I vs. B-C II-IV).*

Complications

There were more intraprocedural penetrations (unintended penetration beyond the mucosa or duct) in the PTH group (4.8% vs. 0%, p=0.018) but similar severity grading between the two groups. Within 14 days from drainage, pancreatitis occurred in 9.4% of patients after an ETP approach while cholangitis rates were similar between the two groups (21.4% vs. 24.7%, p=0.530). There were more postprocedural deaths (MAGS grade 6) in the PTH group (15.8% vs. 7%, p<0.001) of which most were sudden deaths where the exact cause of death could not be established definitively. Postprocedural complications > 14 days after drainage were similar between the two groups.

Supplementary Table 1. Definition and grading of endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography related adverse events.

Endoscopic Retrograde Cholangiopancreatography (ERCP) related adverse events **European Society of Gastrointestinal Endoscopy (ESGE) Guidelines[16] 2020**		
Complication	**Reference, year**	**Definition**
Pancreatitis	ESGE Guidelines[16] 2020	New or worsened abdominal pain combined with > 3 times the normal value of amylase or lipase at more than 24 hr after the procedure and requirement of admission or prolongation of a planned admission.
Bleeding	ASGE Lexicon[45] 2010	Hematemesis and/or melena or hemoglobin drop > 2 g/dL
Cholangitis	ASGE Lexicon[45] 2010	Temperature of > 38°C for > 24 hr with cholestasis
Cholecystitis	Tokyo Guidelines[50] 2018	A) Local signs of inflammation etc. (1) Murphy's sign, (2) Right upper quadrant mass/pain/tenderness B) Systemic signs of inflammation etc. (1) Fever, (2) elevated C-reactive protein, (3) elevated white cell count C) Imaging findings characteristic of acute cholecystitis Suspected diagnosis: One item in A and one item in B Definite diagnosis: One item in A and one item in B and C
Perforation	ASGE Lexicon[45] 2010	Evidence of air or intraluminal content outside of the gastrointestinal tract.
Penetration	ASGE Lexicon[45] 2010	Visual or radiographic evidence of unintended penetration beyond the mucosa or duct, without perforation
Sepsis of unknown origin	ASGE Lexicon[45] 2010	Temperature of > 38°C for > 24 hr without an obvious cause
Cardiovascular	ASGE Lexicon[45] 2010	Hypotension - < 90/50 mm/Hg or down 20%, Hypertension > 190/130 mm/Hg or up 20%, Dysrhythmia – must specify
Pulmonary	ASGE Lexicon[45] 2010	Hypoxia – O_2 Saturation < 85%
Thromboembolic	ASGE Lexicon[45] 2010	Deep vein thrombosis, Pulmonary embolism
Instrumental	ASGE Lexicon[45] 2010	Impaction – Unable to remove instrument or device, Malfunction
Adverse event	ASGE Lexicon[45] 2010	An adverse event is an event that prevents completion of the planned procedure and/or results in admission to hospital, prolongation of existing hospital stay, another procedure (needing sedation/anesthesia), or subsequent medical consultation.
Incidents	ASGE Lexicon[45] 2010	Incidents are unplanned events that do not interfere with completion of the planned procedure or change the plan of care, (ie, do not fulfil the stated criteria for AEs). Examples include bleeding that stops spontaneously or with endoscopic therapy and transient hypoxia that resolves with or without reversal agents, supplemental oxygen, or bagging.
Timing of adverse events	ASGE Lexicon[45] 2010	Events can occur pre-procedure, intra-procedure (from entering the preparation area through leaving the endoscopy room), post-procedure (up to 14 days), and late (any time after 14 days).
Attribution	ASGE Lexicon[45] 2010	Definite, probable, possible, unlikely.
Reporting of adverse events	ASGE Lexicon[45] 2010	When reporting complication rates, only definite and probably attributable events occurring within 14 days should be included. Rare adverse events that occur after 14 days and are clearly attributable can be recorded as a separate category. Examples include a proven nosocomial infection or stent migration causing a new clinical problem, not just failure of the original treatment goal.
Percutaneous transhepatic cholangiopancreatography related adverse events **Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Quality Assurance Document and Standards for Classification of Complications: The CIRSE Classification System[218]**		
Complication	**Reference, year**	**Definition**
Complication or adverse event	CIRSE Classification System[218] 2017	Defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

Continuation of Supplementary Table 1.

Percutaneous transhepatic cholangiopancreatography related adverse events **Quality Improvement Guidelines for Percutaneous Transhepatic Cholangiography, Biliary Drainage, and Percutaneous Cholecystostomy**[217]		
Complication	**Reference, year**	**Definition**
Intraprocedural sepsis	Quality Improvement Guidelines[217] 2010	-
Intraprocedural hemorrhage	Quality Improvement Guidelines[217] 2010	-
Intraprocedural inflammatory or infectious	Quality Improvement Guidelines[217] 2010	Abscess, peritonitis, cholecystitis, pancreatitis
Intraprocedural pleural	Quality Improvement Guidelines[217] 2010	-
Intraprocedural death	Quality Improvement Guidelines[217] 2010	-
Postprocedural catheter discontinuation	Quality Improvement Guidelines[217] 2010	Requiring de novo procedure, death and/or surgery
Grading of complications - The Accordion Severity Grading System of Surgical Complications[219]		
Complication	**Reference, year**	**Definition**
Grade 1	Accordion Classification[219] 2009	Mild complication. Requires minor invasive procedure that can be done at the bedside such as insertion of intravenous lines, urinary catheters, and nasogastric tubes, and drainage of wound infections. Physiotherapy and antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy are allowed.
Grade 2	Accordion Classification[219] 2009	Moderate complication. Requires pharmacologic treatment with drugs other than such allowed for minor complications, for instance antibiotics. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Accordion Classification[219] 2009	Severe: invasive procedure without general anesthesia (endoscopic or interventional procedure / re-operation† without GA).
Grade 4	Accordion Classification[219] 2009	Severe: requires management by an operation under GA.
Grade 5	Accordion Classification[219] 2009	Severe: organ system failure††.
Grade 6	Accordion Classification[219] 2009	Death. Postoperative death.
Definitions of organ failure for the Accordion classification system†††		
Cardiac	Accordion Classification[219] 2009	Need for any of the following medications in the following doses: Norepinephrine > 0.1 $\mu g/kg^{-1} \cdot min^{-1}$, Epinephrine > 0.1 $\mu g/kg^{-1} \cdot min^{-1}$, Dopamine > 15 $\mu g/kg^{-1} \cdot min^{-1}$
Central nervous system	Accordion Classification[219] 2009	Glasgow coma scale equal to or less than 6.
Hematologic	Accordion Classification[219] 2009	Platelet count less than 20 x 10^9/L.
Liver	Accordion Classification[219] 2009	Liver: Need for FFP to correct INR in patient with serum bilirubin > 12 mg/dL (205 mMol/L) OR INR > 2.5 in patient with serum bilirubin > 12 mg/dL (205 mMol/L).
Renal	Accordion Classification[219] 2009	Need for dialysis in patient not on dialysis preoperatively.
Respiratory	Accordion Classification[219] 2009	Need for mechanical ventilation for greater than 24 hr in a patient who requires reintubation after surgery OR need for mechanical ventilation of greater than 72 hr in a patient who is not extubated on the day of surgery. Does not include patients already on a mechanical ventilator for respiratory failure.

†An example would be a wound re-exploration under conscious sedation and/or local anaesthetic. ††Such complications would normally be managed in an increased acuity setting but in some cases patients with complications of lower severity might also be admitted to an intensive care unit. †††The definitions used here for failure in cardiac, central nervous system, and hematologic systems are derived from definitions of "score 4" in the sequential organ failure assessment (SOFA) scale.[220] The definition for liver failure is derived in part from the SOFA scale, which uses bilirubin > 12 mg/dL as the sole criterion. The definitions for renal and respiratory failure rely on the need for dialysis and mechanical ventilation in keeping with the basic concept of T92 that the severity is reflected by the treatment. ESGE, European Society of Gastrointestinal Endoscopy; ASGE, American Society for Gastrointestinal Endoscopy; CIRSE, Cardiovascular and Interventional Radiological Society of Europe (CIRSE); GA, general anesthesia; INR, international normalised ratio.

Supplementary Table 2. Demographic and clinical characteristics, diagnoses and Bismuth-Corlette classification of the endoscopic transpapillary and percutaneous transhepatic intended versus 'crossover to' technical success patient cohorts.

	Intended transpapillary n=113 (%)	Crossover to transhepatic n=34 (%)	p-value	Intended transhepatic n=112 (%)	Crossover to transpapillary n=4 (%)	p-value
Demographics						
Female sex, n (%)	67 (59.3)	19 (57.6)	0.860	62 (55.4)	3 (75.0)	0.630
Age, years, mean (SD)	60.7 (12.4)	64.4 (12.9)	0.169	58.0 (13.1)	67.5 (14.4)	0.142
BMI, median (IQR)	26.3 (4.8)	22.9 (7.5)	0.112	26.3 (10.7)	-	0.338
Number of comorbidities, n (%)						
0	51 (45.1)	13 (38.2)	0.103	36 (32.1)	2 (50.0)	0.876
1	24 (21.2)	14 (41.2)		39 (34.8)	1 (25.0)	
2	26 (23.0)	7 (20.6)		29 (25.9)	1 (25.0)	
3	10 (8.8)	0 (0.0)		6 (5.4)	0 (0.0)	
4	2 (1.8)	0 (0.0)		2 (1.8)	0 (0.0)	
Comorbidities, n (%)						
Diabetes mellitis	21 (18.6)	6 (17.6)	0.902	14 (12.5)	0 (0.0)	1.000
Hypertension	51 (45.1)	16 (47.1)	0.843	47 (42.0)	2 (50.0)	1.000
COAD	9 (8.0)	1 (2.9)	0.454	2 (1.8)	0 (0.0)	1.000
IHD	8 (7.1)	1 (2.9)	0.685	9 (8.0)	1 (25.0)	0.306
HIV	7 (6.2)	4 (11.8)	0.279	9 (8.0)	0 (0.0)	1.000
ECOG performance score, n (%)						
0	11 (11.5)	4 (13.3)	0.289	3 (3.0)	0 (0.0)	0.635
1	50 (52.1)	13 (43.3)		59 (59.6)	2 (50.0)	
2	18 (18.8)	4 (13.3)		26 (26.3)	1 (25.0)	
3	13 (13.5)	9 (30.0)		11 (11.1)	1 (25.0)	
4	4 (4.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Baseline serum values, median (IQR)						
Urea (mmol/L)	4.6 (3.1)	4.3 (2.9)	0.534	4.1 (3.0)	3.0 (5.7)	0.225
Creatinine (µmol/L)	68.5 (33)	58.0 (31)	0.020	63.0 (30)	58.0 (30)	0.615
Total bilirubin (µmol/L)	293.0 (220)	354.5 (181)	0.222	300.0 (219)	331.0 (257)	0.737
Conjugated bilirubin (µmol/L)	237.0 (180)	262.0 (199)	0.256	258.0 (214)	286.0 (248)	0.831
Aspartate transaminase (U/L)	147.0 (142)	128.0 (136)	0.429	159.0 (131)	186.0 (-)	0.877
Alanine transaminase (U/L)	136.0 (130)	108.0 (81)	0.150	119.5 (129)	60.5 (112)	0.134
Alkaline phosphatase (U/L)	703.0 (730)	710.0 (488)	0.350	842.5 (876)	1171.0 (1675)	0.456
Gamma-glutamyl transferase (U/L)	791.0 (841)	555.5 (781)	0.115	575.0 (871)	997.0 (1404)	0.366
Haemoglobin (g/dL)	11.5 (2.5)	10.7 (2.65)	0.259	10.9 (2.7)	10.0 (3.0)	0.410
White Cell Count (10^9/L)	9.3 (4.4)	9.9 (6.4)	0.671	9.6 (5.2)	11.3 (20.1)	0.488
Albumin (g/L)	31.0 (11)	30.5 (6)	0.749	31.0 (9)	30.0 (7)	0.347
C-reactive protein (mg/L)	42.0 (91.7)	-	0.101	50.0 (62.5)	-	0.307
CA 19-9 (kU/L)	414 (2065)	691 (1737)	0.983	719 (3229)	4384 (-)	0.178

Continuation of Supplementary Table 2.

	Intended transpapillary n=113 (%)	Crossover to transhepatic n=34 (%)	p-value	Intended transhepatic n=112 (%)	Crossover to transpapillary n=4 (%)	p-value
Method of diagnosis, n (%)						
Imaging and tumour markers	43 (38.1)	13 (38.2)	0.147	48 (42.9)	2 (50.0)	1.000
Imaging and tissue sampling	47 (41.6)	9 (26.5)		31 (27.7)	1 (25.0)	
Imaging alone	23 (20.4)	12 (35.3)		33 (29.5)	1 (25.0)	
Diagnosis, n (%)						
Cholangiocarcinoma	80 (70.8)	20 (58.8)	0.467	68 (60.7)	3 (75.0)	1.000
Gallbladder carcinoma	20 (17.7)	10 (29.4)		19 (17.0)	0 (0.0)	
Hepatocellular carcinoma	4 (3.5)	1 (2.9)		3 (2.7)	0 (0.0)	
Metastatic disease†	9 (8.0)	3 (8.8)		22 (19.6)	1 (25.0)	
Bismuth-Corlette classification, n (%)						
I	45 (39.8)	23 (67.7)	0.024	43 (38.4)	1 (25.0)	0.347
II	24 (21.2)	4 (11.8)		33 (29.5)	1 (25.0)	
IIIa	22 (19.5)	5 (14.7)		24 (21.4)	1 (25.0)	
IIIb	7 (6.2)	2 (5.9)		8 (7.1)	0 (0.0)	
IV	15 (13.3)	0 (0.0)		4 (3.6)	1 (25.0)	

†Including lymphoma and neuroendocrine tumour. BMI, body mass index; COAD, chronic obstructive airway disease; IHD, ischaemic heart disease; HIV, human immunodeficiency virus; ECOC, Eastern Cooperative Oncology Group; CA, cancer antigen.

Supplementary Table 3. Demographic and clinical characteristics, diagnoses, and Bismuth-Corlette classification for endoscopic transpapillary and percutaneous transhepatic intended versus 'crossover from' technical success patient cohorts.

	Intended transpapillary n=113 (%)	Crossover from transhepatic n=4 (%)	p-value	Intended transhepatic n=112 (%)	Crossover from transpapillary n=34 (%)	p-value
Demographics						
Female sex, n (%)	67 (59.3)	3 (75.0)	0.648	62 (55.4)	19 (57.6)	0.822
Age, years, mean (SD)	60.7 (12.4)	67.5 (14.4)	0.285	58.0 (13.1)	64.4 (12.9)	0.010
BMI, median (IQR)	26.3 (4.8)	-	0.222	26.3 (10.7)	22.9 (7.5)	0.815
Number of comorbidities, n (%)						
0	51 (45.1)	2 (50.0)	1.000	36 (32.1)	13 (38.2)	0.657
1	24 (21.2)	1 (25.0)		39 (34.8)	14 (41.2)	
2	26 (23.0)	1 (25.0)		29 (25.9)	7 (20.6)	
3	10 (8.8)	0 (0.0)		6 (5.4)	0 (0.0)	
4	2 (1.8)	0 (0.0)		2 (1.8)	0 (0.0)	
Comorbidities, n (%)						
Diabetes mellitis	21 (18.6)	0 (0.0)	1.000	14 (12.5)	6 (17.6)	0.569
Hypertension	51 (45.1)	2 (50.0)	1.000	47 (42.0)	16 (47.1)	0.599
COAD	9 (8.0)	0 (0.0)	1.000	2 (1.8)	1 (2.9)	0.551
IHD	8 (7.1)	1 (25.0)	0.277	9 (8.0)	1 (2.9)	0.454
HIV	7 (6.2)	0 (0.0)	1.000	9 (8.0)	4 (11.8)	0.501

Continuation of Supplementary Table 3.

ECOG performance score, n (%)						
0	11 (11.5)	0 (0.0)	0.893	3 (3.0)	4 (13.3)	0.007
1	50 (52.1)	2 (50.0)		59 (59.6)	13 (43.3)	
2	18 (18.8)	1 (25.0)		26 (26.3)	4 (13.3)	
3	13 (13.5)	1 (25.0)		11 (11.1)	9 (30.0)	
4	4 (4.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Baseline serum values, median (IQR)						
Urea (mmol/L)	4.6 (3.1)	3.0 (5.7)	0.210	4.1 (3.0)	4.3 (2.9)	0.869
Creatinine (µmol/L)	68.5 (33)	58.0 (30)	0.363	63.0 (30)	58.0 (31)	0.089
Total bilirubin (µmol/L)	293.0 (220)	331.0 (257)	0.916	300.0 (219)	354.5 (181)	0.490
Conjugated bilirubin (µmol/L)	237.0 (180)	286.0 (248)	0.702	258.0 (214)	262.0 (199)	0.847
Aspartate transaminase (U/L)	147.0 (142)	186.0 (-)	1.000	159.0 (131)	128.0 (136)	0.356
Alanine transaminase (U/L)	136.0 (130)	60.5 (112)	0.087	119.5 (129)	108.0 (81)	0.543
Alkaline phosphatase (U/L)	703.0 (730)	1171.0 (1675)	0.384	842.5 (876)	710.0 (488)	0.039
Gamma-glutamyl transferase (U/L)	791.0 (841)	997.0 (1404)	0.449	575.0 (871)	555.5 (781)	0.529
Haemoglobin (g/dL)	11.5 (2.5)	10.0 (3.0)	0.087	10.9 (2.7)	10.7 (2.65)	0.487
White Cell Count (10^9/L)	9.3 (4.4)	11.3 (20.1)	0.410	9.6 (5.2)	9.9 (6.4)	0.801
Albumin (g/L)	31.0 (11)	30.0 (7)	0.421	31.0 (9)	30.5 (6)	0.640
C-reactive protein (mg/L)	42.0 (91.7)	-	0.210	50.0 (62.5)	-	0.102
CA 19-9 (kU/L)	414 (2065)	4384 (-)	0.111	719 (3229)	691 (1737)	0.636
Method of diagnosis, n (%)						
Imaging and tumour markers	43 (38.1)	2 (50.0)	0.836	48 (42.9)	13 (38.2)	0.805
Imaging and tissue sampling	47 (41.6)	1 (25.0)		31 (27.7)	9 (26.5)	
Imaging alone	23 (20.4)	1 (25.0)		33 (29.5)	12 (35.3)	
Diagnosis, n (%)						
Cholangiocarcinoma	80 (70.8)	3 (75.0)	0.504	68 (60.7)	20 (58.8)	0.230
Gallbladder carcinoma	20 (17.7)	0 (0.0)		19 (17.0)	10 (29.4)	
Hepatocellular carcinoma	4 (3.5)	0 (0.0)		3 (2.7)	1 (2.9)	
Metastatic disease†	9 (8.0)	1 (25.0)		22 (19.6)	3 (8.8)	
Bismuth-Corlette classification, n (%)						
I	45 (39.8)	1 (25.0)	0.920	43 (38.4)	23 (67.7)	0.044
II	24 (21.2)	1 (25.0)		33 (29.5)	4 (11.8)	
IIIa	22 (19.5)	1 (25.0)		24 (21.4)	5 (14.7)	
IIIb	7 (6.2)	0 (0.0)		8 (7.1)	2 (5.9%)	
IV	15 (13.3)	1 (25.0)		4 (3.6)	0 (0.0%)	

†Including lymphoma and neuroendocrine tumour. BMI, body mass index; COAD, chronic obstructive airway disease; IHD, ischaemic heart disease; HIV, human immunodeficiency virus; ECOG, Eastern Cooperative Oncology Group; CA, cancer antigen

6 DISCUSSION

6.1 FINDINGS AND IMPLICATIONS

6.1.1 Single operator cholangiopancreatoscopy

Study I reported on 365 SOCP procedures from a tertiary centre and is, to our knowledge, the largest to date to assess the clinical value of adding SOCP to ERCP. Single operator cholangiopancreatoscopy had significant clinical value in 63% of patients. Reviewing its application in the biliopancreatic ductal system revealed that 71% were cholangioscopy procedures, 24% were pancreatoscopy procedures, while in 5% of cases both the bile and pancreatic ducts were targeted. In 21.4% of cases the SOCP procedure was enlisted in the treatment of benign (mostly stone) disease (biliary 15.9% vs. pancreatic 5.5%), while in 72.6% of cases it was utilised to assist in distinguishing benign from malignant disease (biliary 55.1% vs. pancreatic 17.5%). This utilisation of SOCP is in line with reports from most tertiary endoscopy units and likely reflects the spread of complex diseases challenging clinicians in practice.[221] Eighty percent of procedures were successfully performed in an outpatient setting, emphasising the minimally invasive nature of the procedure.

Study II was an investigation of the nationwide integration of SOCP. Procedural adverse events in patients undergoing SOCP compared to conventional ERCP were higher. Similarly, overall, the incidence of postprocedural adverse events was 19.1% vs. 14.0% for the two procedures (SOCP vs. ERCP): pancreatitis (7.4% vs. 3.9%) and cholangitis (4.4% vs. 2.7%). These are important findings as previous studies from single centres and smaller patient samples reported lower adverse event rates when SOCP is added to ERCP (7.0%-7.7%).[97,98] The overall increase in SOCP procedures and accompanying decrease in mother-baby procedures observed in this report reflects the ease of use of the single operator system. Its predominant use at a single University Hospital is in keeping with its application in complex hepatobiliary diseases, underscored by the fact that 27% of SOCP procedures were performed in patients with PSC and 17% were performed for stones not removed at previous ERCP.[221]

Clinical utility of single operator cholangiopancreatoscopy

In scrutinising the impact of SOCP for specific indications, it was found to have most value in the treatment of complex bile duct stones (79% grade 3-4). This is in keeping with previous reports of its effectiveness regarding eventual complete stone clearance (70%-94%) and becomes especially relevant to patients who are poor operative candidates.[64,65] The long procedure time (mean of 99 min) restricts is use and demonstrates a limitation of the procedure.

The second largest clinical value of adding SOCP to an ERCP procedure was found to be in the evaluation of cystic pancreatic lesions (66% grade 3-4). This correlates with recent reports that note that SOCP findings altered the extent of surgical resection in 62% of patients with IPMN.[93] Although dependent on frozen sections, intra-operative pancreatoscopy avoids 'cannulation' associated complications and may be a safer approach when employing SOCP to guide the extent of resection.[92]

The clinical value of SOCP in the evaluation of indeterminate strictures graded as grades 3-4 ranged from 56%-57% in patients without and with PSC, respectively. This illustrates the difficulty encountered when trying to differentiate malignant from benign strictures in the bile duct. Cytological confirmation of malignancy is possible in only 40%-60% of cases.[37,40] The challenge in obtaining tissue for confirmatory diagnosis together with the increasing role of multimodality treatment, will likely drive clinicians to utilise SOCP in the evaluation of indeterminate strictures even in cases where the clinical yield is lower than for other indications. In study I, over half of patients (55%) underwent SOCP for indeterminate biliary stricture evaluation, demonstrating the aforementioned.

In contrast to its value in the treatment of biliary stone disease, SOCP appeared to have the least impact in the small subgroup of patients who underwent SOCP for chronic pancreatitis with or without pancreatic stone lithotripsy. This subgroup was the only group where more patients were graded as grades 1-2 (55%) rather than grades 3-4 (45%). However, given the small sample size, caution must be exercised when interpreting this finding. In light of an increased adverse event rate associated with pancreatoscopy determined in both studies I and III, together with previously reported stone clearance rates from as low as 37% in the pancreatic duct, larger prospective studies are needed to assess the value of SOCP in patients with chronic pancreatitis.[81]

Adverse events after single operator cholangiopancreatoscopy

As SOCP is mainly utilised in patients with complex disorders (difficult stones and indeterminate strictures), multiple confounding factors can influence adverse event rates and multivariate analysis is of paramount importance to provide context. Possible risk factors for pancreatitis (e.g., female sex, younger age, sphincterotomy and EPLBD) and cholangitis (PSC and older age) could be statistically adjusted for in study II. On multivariate analysis, the risk for pancreatitis and cholangitis became less relevant, an increased risk for intraprocedural adverse events became evident and statistically significant, and the risk for postprocedural adverse events remained.

Previous multicentre observational studies reported similar adverse event rates after SOCP and ERCP, while smaller comparative studies did not report an increased risk with the addition of SOCP (after adjusting for confounders).[94,98] Results from study II assist in placing previous

reports of increased risk into perspective.[97] Our results from a large and well-validated registry emphasise the caution that should be exercised when adding SOCP to an ERCP procedure and lend support to its use in high-volume centres. Comparing adverse events in patients undergoing SOCP in the first 3 years of study to the last 3 years of study suggested a definite learning curve, as the postprocedural adverse event rate after SOCP decreased from 25% to 16%.

Adverse events after pancreatoscopy are less well defined due mainly to the retrospective nature of reports on small patient numbers.[81,82,84,85] As wire passage into the pancreatic duct increases the risk for pancreatitis at the time of ERCP, the main concern would be the increased risk for pancreatitis particularly in patients with no previous history of pancreatitis or sphincterotomy. In our analysis of SOCP use in study I, pancreatoscopy was associated with an adverse event rate of 20% (vs. cholangioscopy 9.6%). Although numbers were too small to analyse comprehensively, 9/17 patients (53%) who developed pancreatitis after pancreatoscopy had a non-dilated pancreatic duct. In our exploration of adverse events after SOCP in study II, most confounders could be adjusted for, leading to the added risk for pancreatitis and cholangitis to diminish. After stratification into pancreatic and bile duct cannulation respectively, when the pancreatic duct was cannulated, the risks of postprocedural adverse events and pancreatitis were increased in the unadjusted analysis but this difference disappeared in the multivariate analysis.

6.1.2 Hilar stenting

Study III is, to our knowledge, the largest study to compare adverse events and reintervention rates after stenting of malignant biliary obstruction in different locations in the biliary tree. Adverse event rates when stenting takes place in the hilum compared to the distal biliary tree have not been well-defined in previous studies. The large sample size in study III allowed for increased power to detect statistically significant findings. Hilar stenting compared to distal stenting was associated with an increased total adverse event rate (19% vs. 14%), pancreatitis rate (6.6% vs. 4%) and cholangitis rate (4% vs. 3%).

Study IV was a comparative cohort study of ETP and PTH palliative drainage procedures performed for MHO and is, to our knowledge, the largest comprehensive comparison of the two approaches to date. The strengths and weaknesses of the two approaches were highlighted for B-C subgroups in terms of access, bridging and technical success, and achievement and duration of therapeutic success.

Adverse events after hilar stenting

Prior studies have not reported an increased risk of pancreatitis after hilar stenting and the high rates of pancreatitis observed in both studies III and IV (6.6% and 9.4%, respectively) may be

explained by the increased procedure time associated with hilar stenting (mean of 51.9 min). In addition, the non-dilated distal biliary tree, a well-known risk factor for pancreatitis, might contribute to increased rates. Our findings support current guidelines suggesting pancreatitis prophylaxis (rectal NSAIDs) for average-risk patients undergoing ERCP and emphasise this practice in patients undergoing hilar stenting.[16,49]

Cholangitis rates after hilar stenting observed in study III (4.1%) reflect rates reported in RCTs (5%-17%) and confirm the increased risk when compared to distal stenting (2.8%).[181,184] Cholangitis rates reported in study IV after ETP and PTH drainage approaches (21.4% and 24.7%, respectively) are more in line with reports from observational studies (30%-45%).[203] Interestingly, neither postprocedural adverse events nor cholangitis rates differed significantly between intrahepatic (B-C I-II) and extrahepatic (B-C III-IV) stenting in study III, contrasting with previous reports where more advanced B-C types predisposed to the development of cholangitis.[201,204] The inability to control for mitigating and risk factors such as periprocedural antibiotics and undrained segments, may have confounded results in this smaller subgroup analysis.

Hilar stent patency

The definition and classification of recurrent biliary obstruction and the reasons for reintervention/stent failure are not well defined in current literature, making direct comparison difficult.[23,205,206] In study III, 6-month patency rates for distal strictures compared to B-C I through to IV types were 44%, 30%, 24%, 10%, 12% and 14%, respectively. Reported 6-month patency rates for stenting of distal and hilar strictures in RCTs are 68%-78% and 25%-35%, respectively.[118,177,178,207] Study III is the first to describe triple the risk for requiring reintervention in patients receiving a single SEMS for MHO compared to those receiving a SEMS for distal malignant obstruction. The innate anatomy of the biliary tree allows for more proximal stent overlap when distal stenting is performed. High reintervention rates in hilar compared to distal strictures might be partly explained by tumour progression and resultant non-occlusive stent failure (with- or without cholangitis), where reintervention is performed for undrained segments even though an adequate decrease in bilirubin has been established. It is important to note that our results reflect the need for reintervention in the population at large.

Our finding of worsening patency in more advanced B-C types is in contrast to previous studies where B-C type was not associated with decreased patency.[184] Patency was lowest for B-C IIIa types in both studies III and IV, questioning previous reports where left-sided SEMS placement predicted lower patency.[202] This finding is most likely to be the effect of proximal disease progression around the short right hepatic duct, resulting in occlusion of segments that may be colonized, and requiring additional intervention.

Stent type and extent of drainage in the hilum

Results from study IV support the superiority of uSEMS for drainage in MHO.[116] The finding that B-C III types achieved therapeutic success more readily after bilateral stent placement substantiates bilateral drainage for more advanced B-C types. This topic is still under debate in current literature.[186,187,191] Our finding that B-C III types achieved therapeutic success more readily after *bilateral or contralateral* vs. *ipsilateral* stent placement merits further discussion. Based on functional volumes of liver segments, drainage of > 50% of liver volume requires right-sided or bilateral stenting in B-C II and IIIb types, and bilateral stenting in B-C IIIa and IV types.[20] The short right hepatic duct is predisposed to sectoral duct involvement (B-C IIIa and IV) and a single right-sided stent in this scenario will unlikely achieve and maintain drainage of > 50% of liver volume.

Approach when stenting the hilum

Study IV is the first to deconstruct access, bridging and technical success for ETP and PTH approaches, highlighting the strengths of each. An ETP compared to a PTH approach had inferior access success but superior bridging success, while technical success was similar. Most patients who crossed over from an ETP to a PTH approach did so after unsuccessful access (failed cannulation) and more procedures were required for eventual technical success via a PTH approach due to repeated attempts at bridging. Previous studies have not reported on reason for crossover or number of procedures required to reach technical success.

Study IV was also the first to compare stent characteristics and extent of drainage between ETP and PTH approaches at the time of technical success. One of the advantages of an ETP approach is the potential to place multiple stents from one access point. Results from study IV revealed more two stent and bilateral stent placement after an ETP approach in advanced B-C types, which resulted in more segments and a larger percentage of liver drained. This did not have an impact on achievement of therapeutic success or time to therapeutic success, which was similar between the two approaches, but likely contributed to the superior duration of therapeutic success that was found after an ETP compared to a PTH approach. The 2016 meta-analysis by Moole et al. (the only to specifically compare palliative ETP with PTH drainage of MHO) included 2 RCTs and 7 retrospective studies (546 patients).[103] Our results, with equivalent therapeutic success for ETP and PTH approaches, challenge their finding of superior successful drainage after a PTH approach in advanced B-C types. Results from study IV question the dogma that a PTH approach should be used in advanced B-C types.[133,201]

In study IV, B-C IIIa patients were more likely to receive bilateral stents and B-C IIIb patients were more likely to receive contralateral stents after an ETP approach. Liu et al., in a

retrospective analysis of 446 patients undergoing unilateral PS placement via a PTH approach found entry via the left lobe (compared to the right) associated with higher technical and therapeutic success, and decreased adverse events compared to a right-sided puncture.[222] It may be that, after MDT discussion, if a decision is made to prioritise right-sided drainage, an ETP approach should be pursued first. If left-sided drainage is prioritised, a PTH approach should be pursued first. Future studies should continue to explore outcome differences for ETP and PTH approaches for advanced B-C types.

Two recent meta-analyses reported similar overall complication and mortality rates, with pancreatitis and cholangitis rates higher after an ETP approach and bleeding rate increased after a PTH approach.[167,168] Theoretically, unsuccessful access (failed cannulation) after an ETP approach predisposes to pancreatitis, whereas unsuccessful bridging after a PTH approach allows for placement of an external catheter (pigtail) and so protecting against cholangitis. Study IV confirmed more patients developed pancreatitis after an ETP approach, mostly of MAGS grade 1-3, with a single pancreatitis-associated death (MAGS grade 6). Cholangitis rates between the two approaches were similar, likely due to more double/bilateral stent placement after ETP drainage. A recent RCT was prematurely closed after accrual of 54 patients due to a higher-than-expected mortality in the PTH approach group compared to the ETP group (41% vs. 11%) and, although not designed to compare survival, our study found more sudden deaths after a PTH approach (15.8% vs. 6.0%).[147]

Comparative patency duration has not been extensively explored for ETP and PTH approaches. In prospective studies a PTH approach appeared superior, although not statistically significant.[144,146] In retrospective reports earlier studies favoured a PTH approach, while more recent comparisons found equivalence or superiority for an ETP approach.[150,151,154,161] The longer duration of therapeutic success resulting in a gain of 3 months after an ETP approach seen in study IV is likely secondary to more bilateral stent placements and a larger volume of liver drained in especially advanced B-C types, as such safeguarding against future symptomatic recurrent obstruction.

As the goals for preoperative and palliative drainage differ, the first aiming to drain the future liver remnant to limit perioperative complications and the second to drain enough functional liver volume to afford symptomatic relief or administer oncological therapy, comparative analyses are challenging. Two recent meta-analyses, including distal and hilar malignant obstruction in patients undergoing both preoperative and palliative drainage, reported similar technical and therapeutic success rates, overall complications and 30-day mortality for ETP and PTH approaches.[167,168] The equivalence in technical success, therapeutic success and time to therapeutic success after ETP and PTH approaches found in study IV are in accordance with

these reports and again corroborate the philosophy that the two approaches are complementary rather than competitive.

6.2 METHODOLOGICAL ASPECTS

6.2.1 Paper I

In the absence of an available system to assess the impact on patient management when SOCP is added to ERCP, the grading scale used in study I had to be developed anew. To ensure content validity, the grading scale had to be:

1. Complex enough to measure all aspects of SOCP clinical value to allow differentiation between therapeutic and diagnostic intent.

2. Practical and simple enough to be applied to a large number of procedures (n=365).

It should be noted that the grading scale could not be correlated with previous scales, due to a lack of previously published scales. Criterion validity could not be calculated, and final validation will depend on future studies.

The single reviewer used in study I was not involved in the clinical care of included patients, but the absence of more than one reviewer meant that reproducibility (interobserver variation) could not be calculated. Repeatability (intra-observer reliability) was maximized by defining examples in each grade (therapeutic vs. diagnostic). In cases where it was difficult to ascertain the relative contribution that other treatment or diagnostic efforts lent to the final management plan, cases were graded as grade 2. To further minimise bias, the reviewer decision as to final grading of diagnostic value was measured utilising the final MDT meeting decision, with the benefit of extensive expert input.

The observer bias introduced when the endoscopists had access to all relevant clinical information at the time of visual assessment of biliary strictures or IPMN lesions, risks overestimation of the clinical value of SOCP. It is difficult from an ethical point of view to argue for withholding relevant information from the endoscopist. More importantly, incorporating clinical information (history, examination, serum markers and imaging) as the diagnostic process progresses (as new information becomes available), reflects everyday clinical practice.

Inherent in studies attempting to assess diagnostic accuracy or impact on management is the absence of the gold standard of diagnosis (histology of the resected specimen) in strictures diagnosed as benign. Under these circumstances the clinical course can be used as a substitute, and due to the retrospective nature of the current study, this benefit could be utilised.

6.2.2 The GallRiks Registry

Study II and III utilised prospective data from the nationwide Swedish Registry for Gallstone Surgery and ERCP (GallRiks). The main strength of both studies lies in the large sample sizes available for inclusion and comparison, minimising random errors and the effect of chance, and increasing statistical power of the studies.

An advantage of the registry, when reporting on both SOCP and ERCP associated adverse events, is that since its conception adverse events have been defined according to internationally accepted criteria.[45] This ensures reporting conformity and allows for comparison with previous reports. The population-based registry has nationwide participation (> 90% of hospitals in Sweden) thus minimising selection bias and increasing applicability to the population at large (high external validity). Selection bias is, however, inherent in self-reported registries where clinicians might be reluctant to declare undesirable outcomes. In the Gallriks registry this risk is minimised by the capturing and reviewing of 30-day adverse events by an independent non-physician coordinator. The 30-day follow-up frequency for GallRiks after cholecystectomy and ERCP is 96% and 95% respectively.[210]

Population-based registry studies reflect what takes place at the bedside (high external validity) but internal validity becomes vulnerable due to the presence of unaccounted confounders.[223] All possible variables that increase pancreatitis risk could not be accounted for (such as sphincter of Oddi dysfunction, a non-dilated bile duct and normal preprocedural liver function tests). Likewise, known factors that increase cholangitis risk (incomplete drainage in hilar obstruction) and bleeding risk (anticoagulant and antiplatelet use) could not be adjusted for. In both studies I and II, data on the use of known mitigating factors for pancreatitis (NSAIDs) and cholangitis (prophylactic antibiotics) was not available from the start of participant inclusion. In study III, important possible confounders regarding hilar stenting such as stricture number and length, the number of segments obstructed and subsequently drained, the volume of liver drained and the reasons for reintervention were not known, making definitive conclusions and comprehensive multivariate analysis problematic.

Coordinator review and regular external auditing of adverse event documentation allowed for minimal missing data in study II (2.7%). There might be a concern regarding missing data in study III (34.3%) regarding stricture location and stent position. This was, however, a result of an inability to definitively classify stricture/stent position from the images captured in GallRiks, in which case patients were excluded.

6.2.3 Paper II

Study II was a representation of the nationwide integration of SOCP, including data from 10 Swedish centres, but there might be a concern that 69% of procedures were performed at a single high-volume University Hospital. On subgroup analysis and comparison there was, however, no difference in adverse events between this centre and the other units included in the study.

National coverage of the registry between 2007 and 2009 saw an increase in participation from 73% to 90%. The increase in participation was mostly due to the addition of regions and not due to increased participation in units already making use of the registry. With reference to analysis of adverse events after ERCP it should be noted that completeness for GallRiks participating units during this time period varied between 97.2% and 98.2%.[211]

Both studies I and II included SOCP procedures performed with the first-generation SOCP system in use from 2007 to 2015. The digitalized second-generation system offers improved image quality and thus clinical value might be underestimated and adverse events overestimated when results from the current data is extrapolated to its future use.

6.2.4 Paper III

There might be concern for the different pathological processes and prognoses that are involved in distal and MHO. However, the focus in both studies III and IV was on anatomical and technical aspects of transpapillary stenting for malignant biliary disease such as approach, stricture and stent location, stent characteristics and patency. Because of differences in tumour biology regarding progression (ingrowth/overgrowth) and response to oncological therapy, survival was not addressed in either of the reports. Survival in patients with especially MHO is, however, limited.[44] Once a diagnosis of irresectable hilar malignancy is made, the main treatment goal is symptomatic relief with/without the administration of oncological therapy, with survival following thereafter.

The definition of a distal stricture used in study III (originating in the common bile duct below the cystic duct junction) does not consider the variability in cystic duct anatomy and can lead to misclassification of distal strictures as B-C I strictures and vice versa. The Asia Pacific consensus meeting in 2020 defined a distal stricture as an abnormal narrowing of the distal half of the extrahepatic bile duct and this definition will allow for consistency in future studies.[23]

To enable comparison of the need for reintervention in study III and to limit confounders, we included only patients in whom a single metal stent was placed. The superiority of metal over plastic stents regarding patency for both distal and hilar malignant strictures has already been

proven and was not the objective of this study.[116,119] We did not distinguish between the use of uSEMS or cSEMS in the current study as there is a lack of collaborating evidence showing a significant difference in outcomes between these two stent types for distal strictures.[128] Both stent types are predisposed to recurrent biliary obstruction albeit via different pathways (cSEMS migration and overgrowth, uSEMS ingrowth). The use of metal stents in the hepatic hilum has been restricted to uSEMS to prevent blockage of secondary intrahepatic biliary radicles.[133,179] A single stent establishes 100% drainage in distal and B-C I malignant strictures, while two stents is required in the hilum to drain more than 50% of the liver in more advanced B-C types (B-C IIIa and IV). There is ongoing robust debate as to the number of stents to be placed to achieve the treatment goal (safe resection, adequate symptom relief or administration of oncological therapy).[186,187]

Matching of the GallRiks registry with the Swedish Central Death Register allowed for complete mortality data in patients stented for malignant biliary obstruction. The registry does not, however, account for indications for reintervention (stent factors, tumour factors or non-occlusion stent failure/cholangitis) and thus the reason for the much higher reintervention rate after hilar stenting could not be explored further. The registry furthermore only account for endoscopic interventions and operative, percutaneous, EUS-guided and oncological interventions are not represented. This underestimates the number of stent failures, especially for advanced B-C types. An important statistical limitation of the study also warrant consideration. Reintervention rates were calculated from retrospective data in contrast to patency duration calculated in a prospective manner. Death without re-intervention was treated as a censored event, but actual stent patency at the time of death could not be confirmed, and random censoring and an occluded stent at time of death could not be excluded (underestimating stent failure).

The study has simplified and does not cover the whole spectrum of hilar stenting, having excluded patients treated with plastic or multiple stents and percutaneous or EUS-guided stents. Registries such as GallRiks, designed for ERCP and not specifically for hilar strictures, lack granular information on key variables, precluding in-depth analyses of important unanswered questions. However, the RCTs that have generated strong evidence regarding numerous issues concerning distal stenting, cannot be replicated in MHO.[147,148] Despite the inherent drawbacks encountered when a registry is used retrospectively, and due the challenges posed by selecting a prospective randomised study design in many instances, combining these two methodologies in future can draw on the strengths of each (as evidenced in previous publications).[224,225] Analyses of large population-based cohorts can be a platform for studies creating more robust data and the challenges encountered in study III could inspire the design of study IV.

6.2.5 Paper IV

The use of classification systems, definitions and grading scales allows for standardization and easy comparison between reports. The B-C classification, definition of therapeutic success and MAGS grading system used in study IV posed specific challenges but were chosen for specific reasons.

The B-C classification system was developed to guide the operating surgeon but has limitations when applied by the endoscopist or interventional radiologist.

1. It indicates hepatic duct (common, left and right) involvement but disregards strictures stretching beyond sectoral ducts and does not take into account the 40% of anatomical variants where aberrant intrahepatic drainage is present.

2. It does not account for functional liver volume proximal to strictures, whether healthy or atrophied, which is essential when planning drainage in more advanced stricture types.

3. It fails to standardise the definition of a hilar or sectoral block which can be dependent on the force of contrast injection at the time of intervention.

An ideal classification system to describe and guide hilar drainage is still lacking but should aim to reflect the functional state of the proximal liver parenchyma in addition to ductal topography.

The definition of therapeutic success (TB value of ≤ 40 µmol/L) is based on previous publications where populations are undergoing drainage mostly as a bridge-to-surgery.[152,155] It is less well suited as surrogate for the treatment goal in patients with irresectable or metastatic MHO where two groups are identified: those where TB values need to normalize before commencement of palliative oncological therapy and those with advanced disease where purely symptomatic relief is pursued. In accordance with end-of-life treatment goals, patients in study IV were not biochemically followed up beyond symptom resolution if symptomatic relief was the only intended outcome.[44]

As additional access to the biliary tract is allowed endoscopically, percutaneously, and recently via EUS, definition and grading systems for complications applicable across all access approaches are lacking. Internationally recognised definitions were chosen for endoscopic and radiological complications respectively (Suppl. Table 1).[16,217,218] An ideal grading system should be practical, easily clinically applied, general enough to reach across specialties and yet allow for a relatively detailed and accurate description of most eventualities. The Clavien classification system for post-surgical complications introduced the principle of grading according to the amount of effort required to reverse or manage a complication and was later modified by Dindo

(Clavien-Dindo) and Martin et al. (Memorial Sloan Kettering grading system).[226–228] The Accordion grading system was developed as an adaptation of previous classifications to be more universally applicable to large and complex studies and was the system chosen for this study, allowing for applicability across different biliary approaches.[219]

The retrospective nature of study IV meant that there was no control for random and institutional bias, e.g., selection of patients, biliary approach and stent type and number. Inclusion of patients from two centres with high-volume endoscopy and interventional radiology units (with independent functioning) mitigates this to some extent. Volumetric assessment was not performed on all patients and patients with no further interventions could not be accounted for. However, as the early closure of two recent RCTs demonstrates, comparison of ETP and PTH approaches is not easily performed prospectively.[147,148] This is mostly due to divergent institutional expertise and availability and/or clinician bias towards a specific approach. Many confounders that need to be considered complicate the construction of practical inclusion and exclusion criteria. Future studies will have to depend on large multi-institutional registries designed specifically to include the number of possible confounders that need to be considered in MHO.

For comparison of ETP and PTH approaches per B-C type in this study we focused on within-group comparisons, with the main drawback being that numbers become smaller after subgrouping, especially when controlling for multiple confounders. For comparison of time to therapeutic success between ETP and PTH approaches per B-C type, the Mann-Whitney U test was utilised due to a very skewed dependent variable. Comparisons were not likely to show significance due to wide ranges (and even interquartile ranges) with large overlap. When attempting to compare time to therapeutic success per B-C type and as a function of stent and drainage characteristics, numbers became too small for meaningful analyses.

7 CONCLUSIONS

This thesis provides results to support the following conclusions:

- Single operator cholangiopancreatoscopy, when added to ERCP, has significant clinical value in 63% of cases. In current endoscopic practice it is applied in the biliary tract (70%), pancreatic duct (25%) and both ducts (5%). Its clinical value lies firstly in the treatment of complex bile duct stones, and secondly as aid in the diagnosis of cystic pancreatic lesions and indeterminate biliary strictures.

- The SOCP system has replaced the performance of cholangiopancreatoscopy by the mother-baby system and there is clear learning curve when first introduced.

- Intraprocedural and postprocedural adverse events are increased when SOCP is added to an ERCP procedure.

- In patients with malignant biliary obstruction the risk for adverse events, including pancreatitis and cholangitis, is increased after hilar compared to distal stenting.

- Stent patency rates are lower for a single SEMS placed for MHO compared to distal malignant obstruction, with stenting for B-C IIIa types having the worst patency.

- In patients with MHO undergoing palliative biliary drainage, ETP and PTH approaches have distinct strengths and weaknesses. Technical and therapeutic success rates are similar, while therapeutic success durability is better after an ETP approach. The two approaches have similar overall adverse event and cholangitis rates, while pancreatitis is more common after an ETP approach and deaths more common after a PTH approach.

8 POINTS OF PERSPECTIVE

Although many reports on SOCP performance regarding stone clearance rates and the accuracy of visual inspection/biopsy is available, quantification of the clinical value/impact of SOCP is dated and limited.[86,87] Measurement of its clinical value was attempted in three small recent reports, restricted to the management of indeterminate biliary strictures.[88–90] The grading scale used in study I is the only of its kind that allows for simultaneous assessment of SOCP therapeutic and diagnostic value but requires validation. Inclusion of more than one blinded reviewer will allow for calculation of interobserver variation (reproducibility) and its use in future studies will allow for measurement of criterion validity.

Results from this thesis, highlighting the clinical value but also the increased risk for adverse events when SOCP is added to ERCP, corroborate the placement of SOCP in treatment algorithms in current guidelines for the treatment of 'difficult' bile duct stones and in the investigation of indeterminate strictures.[29,174] A demonstratable learning curve cautions for its continued use in specialised high-volume centres where staff are adequately trained to prevent, recognise and treat associated adverse events. Future meticulous documentation of investigations to generate more evidence is a prerequisite for the firm establishment of this important procedure in pancreaticobiliary endoscopy algorithms.

Although the robust data collected in the GallRiks registry (accounting for most confounders) allowed for comprehensive multivariate analysis of the risk of adverse events when SOCP is added to ERCP in study II, study III underscored the difficulties encountered in investigating stenting for MHO when making use of registry data. The GallRiks dataset is reviewed annually and adjustment of variables is performed accordingly, ensuring its continued excellence as data source in answering research questions pertaining to endoscopy in the hepatobiliary systems. Analysis of large population-based cohorts remains a platform for studies creating more robust data, as exemplified by the challenges encountered in study III leading to the creation of a multicentre registry dedicated to MHO in study IV. This registry currently offers analysis of outcomes after simultaneous or sequential combined ETP and PTH approaches, as well as mechanisms of recurrent biliary obstruction in the hepatic hilum. The combination of established national registries with a prospective randomised study design will increasingly in future make economic sense.

The B-C classification system was designed for the operating surgeon to indicate the most distal extent of normal biliary mucosa available for anastomosis after curative resection in patients with CC.[25] It is not optimal as a guide to the endoscopist or interventional radiologist as it does not give sufficiently detailed information on the extent of obstruction of sectoral ducts and does not

account for upstream liver functionality. A dedicated classification where not only the actual ductal topography is described, but in which functional parenchymal volumes beyond strictures are also quantified, would be of more value.

The definition of therapeutic success after MHO drainage in published literature is based on decreased TB values which is used as a surrogate for the goal of treatment. In patients with MHO the treatment goal differs for patients undergoing preoperative stenting, patients planned for palliative oncological therapy and those with advanced disease where purely symptomatic relief is pursued. These differences need to be considered in future study designs and when comparing results between different patient populations.

The definition and classification of recurrent biliary obstruction is not well defined in current literature.[23,205,206] Mechanisms of recurrent obstruction, reasons for reintervention and treatment options at the time of reintervention differ somewhat for distal and hilar obstruction. Future studies and classification systems should explore and consider these differences.

In study IV, patients with B-C IIIa types had 100% technical success after a single ETP procedure. They also had significantly more bilateral stents placed, a higher percentage of liver volume drained and trended towards a faster time to therapeutic success. The general dictum that B-C III-IV types should be drained via a percutaneous approach is challenged by our results showing ETP outperforming PTH in BC IIIa patients and being equal to PTH in BC IIIb and IV patients.[103,133,174] Although small numbers limited statistical power in some analyses (especially B-C IIIb and IV), our data suggest that ETP drainage might be more successful in selected advanced B-C types. Future studies should endeavor to increase patient numbers and explore outcome differences for advanced B-C types.

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10 REFERENCES

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