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NEW TECHNOLOGIES FOR THE FURTHER ADVANCEMENT OF ERCP

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New technologies for the further advancement of ERCP

Thesis for doctoral degree (Ph.D.)

By

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To Katarina, Judith and August

“I’ve never been certain whether the moral of the Icarus story should only be, as is generally accepted, ‘don’t try to fly too high,’ or whether it might also be thought of as ‘forget the wax and feathers, and do a better job on the wings.’”

Stanley Kubrick

ABSTRACT

Background The capabilities of conventional endoscopic retrograde cholangiopancreatography (ERCP) are hampered by several limitations. Newly developed adjunct technologies such as single operator peroral cholangiopancreatoscopy (SOPCP) and new imaging techniques could overcome some of these limitations, but their role in common clinical practice have not yet been established.

Aims To assess the diagnostic and therapeutic yield of SOPCP in the diagnosis and treatment of biliopancreatic disease. To investigate patient-related risk factors for post procedural pancreatitis (PPP) following single-operator peroral pancreatoscopy. To determine the feasibility and potential clinical yield of bimodal ERCP. To assess radiation dose in cone beam ERCP.

Methods In paper I, All SOPCP procedures performed at Karolinska University Hospital between March 2007 and December 2014 were included in this study and each procedure's diagnostic yield and therapeutic value was evaluated using a predefined 4 grade assessment scale. In paper II, all consecutive patients that underwent single operator pancreatoscopy (SOPP) at Karolinska University Hospital between April 2015 and Nov 2020 were included. The Swedish Registry for Gallstone Surgery and ERCP (GallRiks) was used to retrieve patient data and preprocedural imaging was reviewed in consensus by two senior radiologists. Pancreatic gland morphology and main pancreatic duct (MPD) diameter were evaluated as risk factors for PPP using uni- and multivariate logistic regression. In paper III, patients undergoing conventional ERCP had a previous T2-weighted magnetic resonance cholangiopancreatography (MRCP) sequence aligned and fused with the two-dimensional image generated from the fluoroscopy c-arm unit in real time and data regarding feasibility and clinical yield was retrieved. In paper IV, radiation exposure data from conventional ERCP procedures and cone beam ERCP (CB-ERCP) procedures performed between February 2016 and June 2017 at a tertiary high volume endoscopy unit was analyzed. CB-ERCP cases used either the standard exposure protocol 'DR' or the modified low dose exposure protocol'DR Care'.

Results During the study period in paper I, 365 SOPCP procedures were performed. SOPCP was found to be of pivotal importance (grade 4) in 19% of cases, and of great clinical significance (grade 3) in 44% of cases. SOPCP did not affect clinical decision-making or alter clinical course (grade 1 and 2) in 37% of cases. In paper II, Postprocedural pancreatitis occurred in 15 (23%) of patients during the 30-day follow up. Univariate analysis of risk factors for PPP showed a significant association with chronic pancreatitis (OR 0.28 95% CI 0.08-0.92), insertion of a pancreatic stent (OR 0.28; 95% CI 0.08-0.95) and the ratio between MPD and pancreatic gland thickness in the body of pancreas (OR 1.14; 95% CI 1.03-1.28). In a multivariate regression model, the association between an increased body MPD/gland ratio in pancreatic body and PPP remained significant (OR 1.26; 95% CI 1.06-1.57) after adjustments for confounders including chronic pancreatitis. In paper III, 13 patients underwent bimodal ERCP for bile duct stricture, complex cholelithiasis or ductal leakage. Bimodal ERCP was feasible in all 13 cases, and image quality was assessed as "good" in 11 patients (85%). Bimodal ERCP aided in visualizing the lesion of interest (77 %), assisted in understanding the 3D anatomy of the biliopancreatic ductal system (62 %), and aided in finding a favorable position for the c-arm (38%) for subsequent therapeutic intervention. In paper IV, 728 conventional ERCP procedures were performed and 42 cases utilized CB-ERCP. The median total dose area product (DAP) was 48.9 Gycm2 for CB-ERCP procedures

using the DR exposure protocol and 19.7 Gycm2 for CB-ERCP procedures using the DR care exposure protocol. The median total DAP was 6.5 Gycm2 when conventional ERCP was used. Conventional ERCP generated a significantly reduced total DAP compared to both CB-ERCP using the 'DR' exposure protocol ($U=908$, $p < 0.001$) and CB-ERCP using the 'DR care'exposure protocol ($U=3823$, $p < 0.001$).

Conclusions SOPCP has a high impact on management of patients with complex cholelithiasis, indeterminate biliary strictures and pancreatic cystic lesions in a tertiary care setting, but the procedure contributes to a considerable risk of adverse events. There is an association between the pancreatic gland thickness and MPD diameter in the pancreatic body with the risk of developing PPP after SOPP. Bimodal ERCP is feasible and can aid in understanding biliary anatomy and visualizing the lesion of interest. Its future area of use may lie in the assessment and treatment of complex intrahepatic biliary disease. Cone beam asssisted ERCP procedures are associated with higher total radiation doses than conventional ERCP procedures, but it is possible to decrease radiation doses to acceptable levels with adjustments of exposure protocols. These adjustments do not compromise the capabilities of cone beam ERCP to provide enhanced intraprocedural guidance.

LIST OF SCIENTIFIC PAPERS

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

II. **Preoperative imaging of the pancreas and risk of postprocedural pancreatitis after single operator peroral pancreatoscopy**
Marcus Reuterwall Hansson, Nikolaos Kartalis, Nelson Ndegwa, Aristeidis Grigoriadis, Matthias Löhr, Urban Arnelo and Erik von Seth
Manuscript

III. **Bimodal ERCP, a new way of seeing things**
Marcus Reuterwall Hansson, Alexander Waldthaler, Jeanne Lubbe, Nils Kadesjö, Raffaella Pozzi Mucelli, Marco Del Chiaro, Matthias Löhr and Urban Arnelo
Endoscopy International Open 2020 Mar;8(3):E368-E376

IV. **Radiation dose in cone beam CT guided ERCP**
Alexander Waldthaler, Marcus Reuterwall Hansson, Urban Arnelo and Nils Kadesjö
European Journal of Radiology 2020;123:108789

Related publications not included in the thesis

Preoperative biliary drainage by plastic or self-expandable metal stents in patients with periampullary tumors: results of a randomized clinical study.
Olsson G, Frozanpor F, Lundell L, Enochsson L, Ansorge C, Del Chiaro M, **Reuterwall Hansson M**, Shetye A and Arnelo U
Endoscopy International Open 2017;5(9):E798-e808.

Survival Analysis and Risk for Progression of Intraductal Papillary Mucinous Neoplasia of the Pancreas (IPMN) Under Surveillance: A Single-Institution Experience
Del Chiaro M, Ateeb Z, **Reuterwall Hansson M**, Rangelova E, Segersvärd R, Kartalis N, Ansorge C, Löhr Matthias J, Arnelo U and Verbeke C
Annals of Surgical Oncology 2017;24(4):1120-6.

Primary sclerosing cholangitis leads to dysfunction and loss of MAIT cells
von Seth E, Zimmer CL, **Reuterwall Hansson M**, Barakat A, Arnelo U, Bergquist A, Ivarsson M and Björkström N
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A biliary immune landscape map of primary sclerosing cholangitis reveals a dominant network of neutrophils and tissue-resident T cells
Zimmer CL, von Seth E, Buggert M, Strauss O, Hertwig L, Nguyen S, Wong AYW, Zotter C, Berglin L, Michaëlsson J, **Reuterwall Hansson M**, Arnelo U, Sparrelid E, Ellis ECS, Söderholm JD, Keita ÅV, Holm K, Özenci V, Hov JR, Mold JE, Cornillet M, Ponzetta A, Bergquist A and Björkström NK.
Science Translational Medicine 2021;13(599).

CONTENTS

LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
AER	Adverse event rate
ASA	American Society of Anesthesiologist
ASGE	American Society for Gastrointestinal Endoscopy
BH	Breath-hold
BMI	Body mass index
CB-ERCP	Cone beam ERCP
CBCT	Cone beam computed tomography
CI	Confidence interval
Co-MRCP	Co-registered MRI-derived cholangiopancreatogram
CP	Chronic pancreatitis
CT	Computed tomography
DAP	Dose area product
DICOM	Digital Imaging and Communications in Medicine
DWI	Diffusion weighted imaging
EHL	Electrohydraulic lithotripsy
ERCP	Endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
EUS	Endoscopic ultrasound
FB	Free-breathing
GRE	Gradient recalled echo

IPMN	Intraductal papillary mucinous neoplasm
MD-IPMN	Main duct-IPMN
MDCT	Multi-detector computed tomography
MDT	Multidisciplinary team
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PACE	Prospective acquisition correction navigator-triggered
PEP	Post-ERCP pancreatitis
POCP	Peroral cholangiopancreatoscopy
PPP	Post-procedural pancreatitis
PSC	Primary sclerosing cholangitis
RDSR	Radiation dose structured report
RFA	Radiofrequency ablation
SMV	Superior mesenteric vein
SOPCP	Single operator peroral cholangiopancreatoscopy
SOPP	Single operator peroral pancreatoscopy

1 INTRODUCTION

Diseases of the biliopancreatic ducts are challenging to diagnose and treat. The conditions the clinician should evaluate and treat in the relatively inaccessible biliopancreatic ducts range from trivial disorders to aggressive, difficult to treat and resource-demanding cancers (1-3). The increasing availability of advanced radiological imaging diagnostics has led to an increasing number of findings in the biliopancreatic tract with possible malignant potential that requires assessment and definitive management (4-6). Histopathological diagnosis is often lacking since representative tissue is frequently difficult to obtain. In many cases with suspected malignancy, the only potentially curative treatment option is surgical resection for early-stage disease, and the required major surgery is associated with considerable morbidity and mortality (7-9).

Conventional endoscopic retrograde cholangiopancreatography (ERCP) is a widely used minimally invasive tool in the diagnosis and treatment of biliopancreatic diseases. The basic technique of ERCP has remained largely unchanged since its introduction over 50 years ago. The diagnostic and therapeutic capabilities of ERCP are hampered by several limitations which include challenges in tissue acquisition, suboptimal and indirect visualization of the biliopancreatic ductal systems and adverse events associated with the procedure (10, 11). To overcome some of these limitations, new adjunct technologies have developed over the last decades. Although promising and interesting results have been seen with these new technologies, their role in common clinical practice have not yet been established (12-14). The overall aim of this thesis is to explore and contribute to the understanding of some of these new technologies.

2 BACKGROUND

2.1 CONVENTIONAL ERCP

Despite advances in endoscope design and instrument development, the basic principles of conventional ERCP have remained unchanged over the last four decades. A side viewing duodenoscope with a working channel is used to reach and visualize the papilla, and a number of different devices are used to gain access to the biliopancreatic ducts. After cannulation of the biliopancreatic ducts, a radiation source and a detector are used to visualize the contrast medium-filled ducts with fluoroscopy for subsequent diagnostic or therapeutic procedures (15, 16). Figure 1 illustrates the basic principles of conventional ERCP.

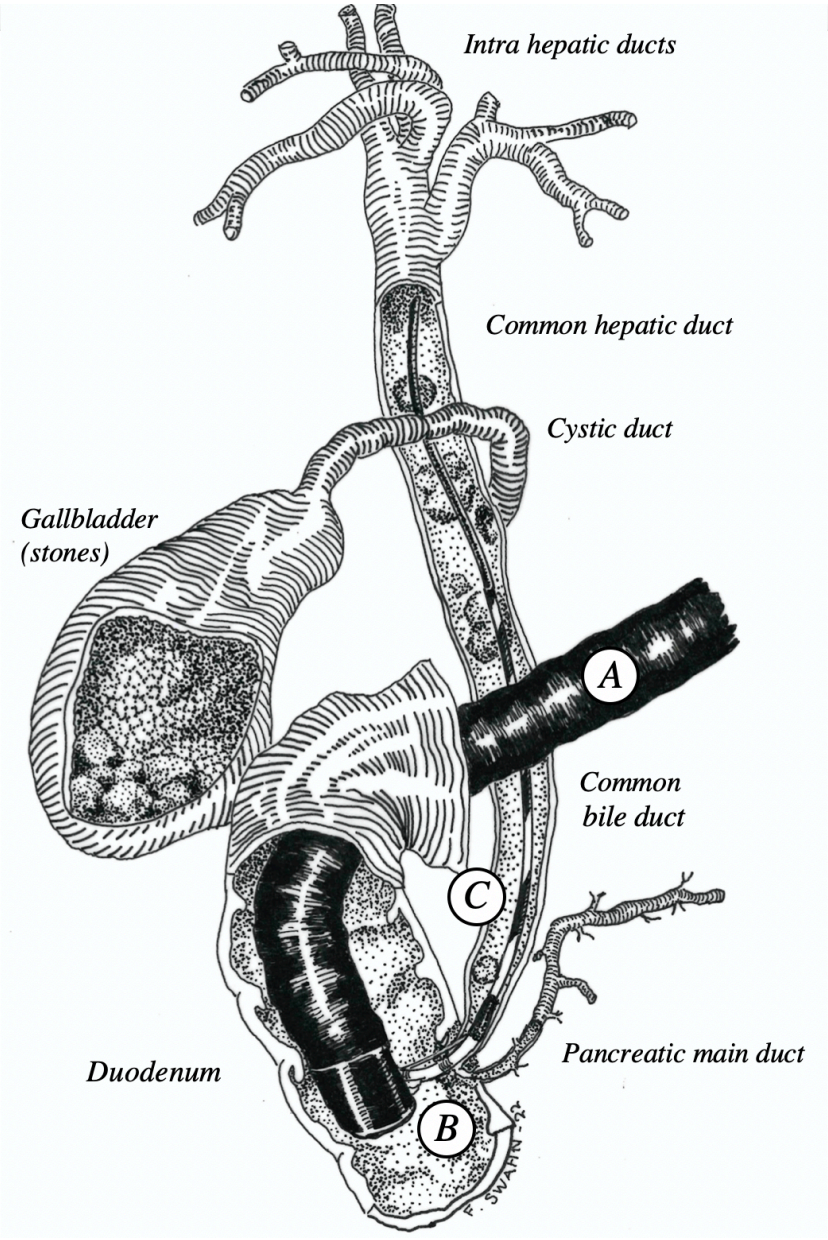


Figure 1 Conventional ERCP. The doudenoscope (A) with a sphincterotome catheter (B) passing (cannulation) the papilla of Vater and the sphincter of Oddi, into the bile duct with the help of a guide wire (C), in this case for the removal of bile duct stones. Illustration by Fredrik Swahn

2.1.1 A brief history of conventional ERCP

ERCP was described for the first time in 1968 (17) and has since spread rapidly as a mainly diagnostic tool for the investigation of diseases of the pancreas and biliary ducts. In Sweden, the first ERCP was performed by Lennart Wehlin in 1972 who had acquired knowledge about the technique during visits to colleagues in Japan (18). This was before the widespread use of advanced cross-sectional imaging techniques, when ERCP was one of the few ways to visualize biliopancreatic disorders (19, 20). Improvements in endoscope and device design, as well as the introduction of new techniques such as sphincterotomy in 1974 expanded the indications for ERCP. The early endoscopists borrowed ideas and instruments from adjacent image-guided disciplines such as endovascular surgery and urological endoluminal surgery. The introduction of plastic endoprothesis in 1980 and subsequently self-expanding metal endoprothesis, manufactured from shape memory alloys, led to an increase in the spectra of diagnoses and interventions available to the treating physician (21, 22). Although seen as a minimally invasive procedure, ERCP still carries the risk of adverse events. The use of ERCP gradually shifted from diagnostic to mainly therapeutic indications as advanced non-invasive imaging techniques with similar or higher diagnostic yield increased awareness surrounding adverse events associated with ERCP (23-25).

As a result, ERCP has now evolved to become the gold standard for palliative treatment of malignant jaundice, as well as definitive treatment for benign biliary strictures and biliary leakage, avoiding the need for open surgical procedures associated with considerable morbidity and mortality (26-28). Parallel to the growth of laparoscopic biliary surgery in the 1980s and 1990s, that saw an associated drop in open bile duct exploration for choledochal stones, ERCP gained popularity in the treatment of choledocholithiasis and is now generally accepted as the gold standard for the treatment of biliary ductal stone disease (29-32). In Sweden approximately 10000 ERCPs are performed every year (33).

2.1.2 Conventional ERCP and diagnostic yield

In the early days of ERCP enthusiastic reports (34) indicated that evaluation of the fluoroscopic appearance of a stricture in the biliopancreatic ductal system could aid in the determination of its nature, for example whether the stricture represented a malignant or a benign process. These findings later proved to be non-specific, and it is now commonly accepted that a benign stricture is indistinguishable from a malign by fluoroscopic appearance alone (35, 36). As a result, the addition of ERCP-guided tissue sampling techniques such as fluoroscopy guided forceps biopsies, brush cytology, and biliopancreatic juice sampling are now common practices in the management of suspected malignancy in biliopancreatic

system. Despite the advancement of instrument design and improved cytopathological diagnostic tools, the diagnostic yield of these sampling techniques has been disappointingly low, with sensitivity ranging from 15% to 80% (37, 38). When these sampling techniques are combined together, minor improvements in diagnostic accuracy have been observed (36, 39). The sensitivity and specificity of ERCP in the detection of choledocholithiasis is high, but it is not recommended for routine use in diagnosis of suspected choledocholithiasis due to its associated risk for adverse events. Magnetic resonance cholangiopancreatography (MRCP) has comparable diagnostic accuracy for the detection of choledocholithiasis and is now considered the primary investigation of choice (40, 41). With the development of new imaging modalities with comparable or better diagnostic yield in many cases, ERCP without therapeutic intent is generally justified only in selected cases (32).

2.1.3 Conventional ERCP and risk

The use of ERCP is hampered by serious adverse events, among which the most common is post-ERCP pancreatits (PEP) (10, 42). The most commonly used definition of PEP by Cotton et al. defines PEP as "clinical pancreatitis with amylase at least three times the upper limit of normal at more than 24 hours after the procedure, requiring hospital admission or a prolongation of planned admission" (43, 44). The incidence of PEP varies in different studies from 3%-10% (45-47). The majority of these cases are classified as mild, but severe cases occur in 11%, which emphasizes that this is an important clinical issue (45). The recognized risk factors for PEP can be divided into patient-related and procedure-associated. Sphincter of Oddi dysfunction, young age, female sex, previous PEP and normal bilirubin levels are patient-related factors that in several studies have shown to increase the risk of PEP. These risk factors are synergistic, and patients with several risk factors have a higher risk of PEP (42). Patients with chronic pancreatitis have a lower risk for PEP, presumably due to reduced exocrine functioning of the pancreas in this disease state. Procedure-associated factors that increase the risk of PEP include difficult cannulation (defined as prolonged and/or repetitive attempts to gain deep access to the biliopancreatic ductal system), sphincterotomy of the pancreatic sphincter, injection of contrast and/or insertion of a guide-wire into the pancreatic ductal system and large balloon dilatation of a native biliary sphincter (48-51). Whether precut sphincterotomy is an independent risk factor for PEP is controversial with conflicting results from heterogenous studies (49, 52-55). Questions has been raised whether the increased risk of PEP associated with precut sphincterotomy can be attributed to repeated attempts at the time of difficult cannulation, or whether early precut sphincterotomy actually reduces the risk of PEP by avoiding repeated wire/catheter probing of the ampulla (56). The

rendez-vous technique, which uses transcystic guidewires to facilitate cannulation during cholecystectomy, has been shown to reduce the risk of PEP (57, 58).

Numerous other attempts have been made to address and reduce the risk of PEP (59). Many pharmacological agents with possible prophylactic effects have been studied, among which rectal administration of nonsteroidal anti-inflammatory drugs (NSAID) seems to be the most efficient. Several well-designed studies suggest that rectal NSAID administrated before the procedure reduces both the incidence and severity of PEP (60-62). Pancreatic duct stenting with an indwelling 5F stent placed after manipulation of the pancreatic ductal system in selected patients can also reduce the risk of PEP (46, 63).

2.1.4 Conventional ERCP and ionizing radiation

The adverse health effects from ionizing radiation are well described for both patients and staff (64). The conventional fluoroscopy setup in ERCP, like in other image-guided interventional procedures, uses a c-arm with an x-ray tube which converts electricity into x-rays that are directed at the organ system of interest (65). Different organ systems exhibit varying degrees of absorption which creates contrast when displayed side-by-side. The remaining x-rays are collected via an image intensifier or flat panel detector before being transferred to a monitor for viewing (66). Injury from radiation can be stochastic (non-dose dependent) or deterministic (dose-dependent). Stochastic effects, such as cancer, can happen at any radiation dose level, and the severity of the effect is not dose dependent. However, when the radiation dose is elevated, the likelihood of stochastic effects will increase. Deterministic effects, such as skin burns and cataracts, will only occur if a radiation dose threshold is exceeded, and the severity of the effect is directly dependent on the radiation dose (66, 67).

Buls et al. (68) investigated the effective radiation dose exposure to staff during ERCP and compared it to staff in other image guided interventions. They found that ERCP procedures have the potential to cause high radiation doses to both staff and patients and concluded that this was partly related to an inattention to protective gear and equipment. They also noted that ERCP procedures are increasingly being performed by non-radiologist clinicians who receive less training in the safety issues surrounding radiation, and raised concerns regarding regulatory and educational aspects of radiation safety. The concept of keeping the radiation dose exposure “as low as reasonably achievable” has lately emerged and is now widely accepted (69).

2.2 MINI-ENDOSCOPES AND OTHER TECHNICAL ADJUNCTS TO CONVENTIONAL ERCP

2.2.1 Technical development of peroral cholangiopancreatoscopes

Technological achievements and enthusiasm among endoscopists and industry personnel has led to the emergence of miniaturized endoscopes as an answer to the diagnostic and therapeutic challenges posed by the inaccessible biliopancreatic ducts. Early fiberoptic peroral cholangiopancreatoscopes (POCP) were dual operator dependent, requiring an additional operator who controlled the mini-endoscope moving forward through the working channel of a duodenoscope into the biliopancreatic ductal system (70-72). The widespread adoption of these early systems was hampered by insufficient visualization, cumbersome handling, fragility of the instruments and cost. Subsequently, development in endoscope design allowing for single operator controlled peroral cholangiopancreatoscopes (SOPCP) and the advancement of digital visualization systems has markedly improved the diagnostic and therapeutic capabilities of POCP (73-77). Figure 2 illustrates the SOPCP technique when used in the main pancreatic duct. The qr code in Figure 3 links to a video clip where images of a main pancreatic duct obtained with a digital cholangiopancreatoscope are shown.

2.2.2 Clinical use and yield of peroral cholangiopancreatoscopes

POCP enables direct visualization of the biliopancreatic ductal system, intraductal therapy and targeted intraductal mini-biopsies which can enhance the diagnostic and therapeutic yield of conventional ERCP (77-79). POCP is increasingly used in the clinical workup of indeterminate biliary strictures, in the treatment of ‘difficult’ biliary stones when stone clearance with conventional methods have been inadequate, as well as in various pancreatic disorders (74, 76, 80-83). Evidence on the impact of POCP use on clinical management decisions consist of three relatively small studies (84-86) and few well-designed prospective studies on the clinical yield of POCP exist. Systematic reviews addressing the subject are limited by heterogeneity in study design and differences in definition of the outcome variables among the included studies (87). In addition, rapid technological development of mini-endoscopes with incremental improvement in steerability, tissue-acquisition capabilities and visualization systems makes analysis of pooled data from studies utilizing different mini-endoscope systems challenging.

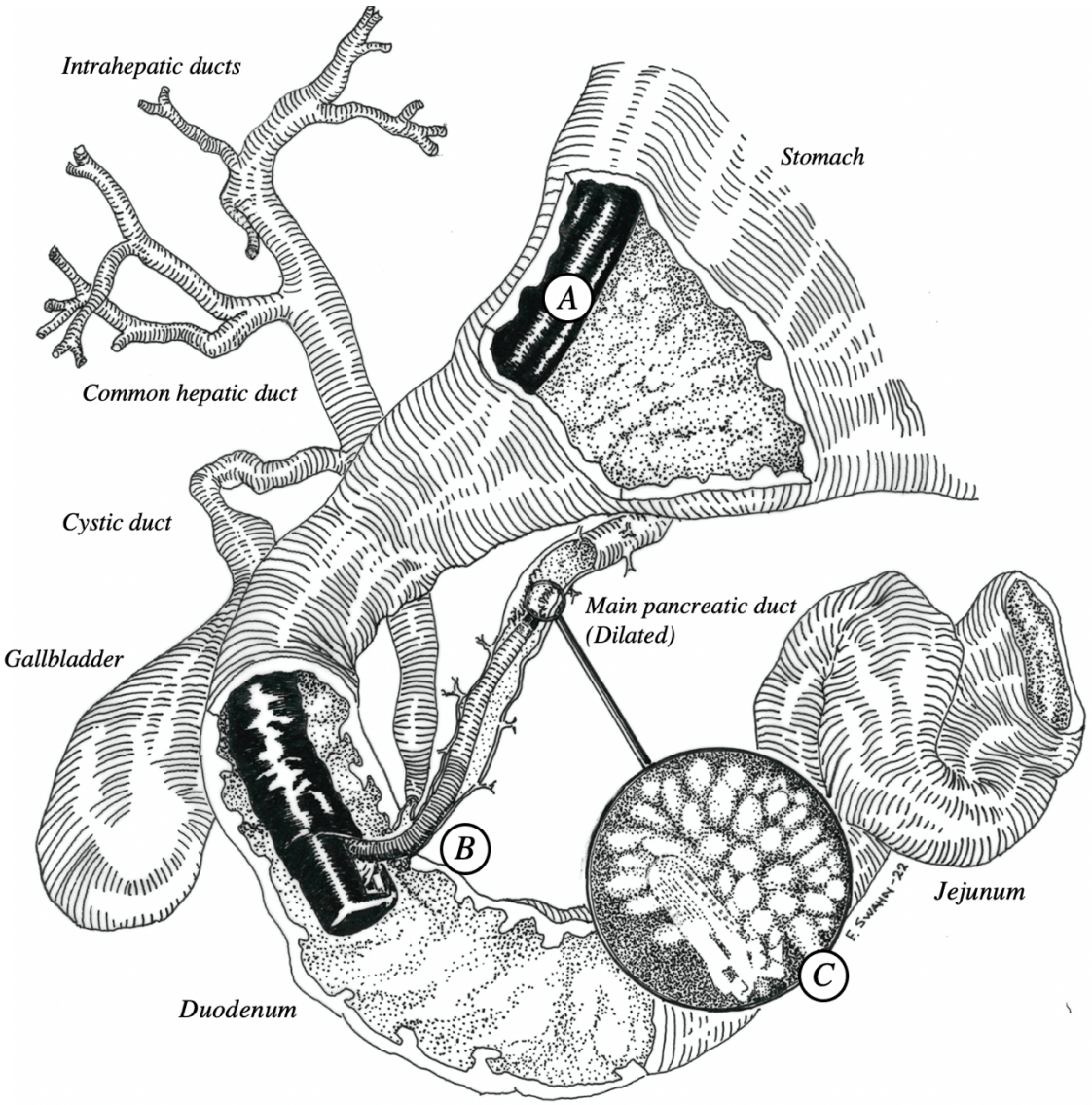


Figure 2 Single operator peroral cholangiopancreatoscopy. The duodenoscope (A) is positioned in the descending part of the duodenum facing the entrance (papilla of Vater) of the bile- and pancreatic duct. The cholangiopancreatoscope (B) is introduced into the main pancreatic duct. Lesions can be visualised and directed biopsies (C) can be obtained for histopathological evaluation. Illustration by Fredrik Swahn.

Figure 3 Qr code which links to a video clip where images of a main pancreatic duct obtained with a digital cholangiopancreatoscope are shown. Video clip provided by Niklas Fagerström.

2.2.2.1 Indeterminate strictures

Several definitions of indeterminate stricture of the bile duct have been proposed, but the most widely accepted is "when basic work-up, including transabdominal imaging and endoscopic retrograde cholangiopancreatography with routine cytologic brushing, are non-diagnostic" (88). It is important to correctly characterize an indeterminate stricture early in the course of the disease as benign or malignant, as long-term survival in cholangiocarcinoma clearly correlates with when it is detected (89). Conversely, properly classifying an indeterminate stricture as benign can facilitate the decision to abstain from major surgery which involves notable morbidity and mortality. In studies examining the sensitivity for cholangiocarcinoma with a legacy generation of SOPCP (Spyglass® fiberoptic system), it was observed that mini-biopsies had an average sensitivity of 68% (36, 77, 87, 90, 91) and macroscopic appearance had a sensitivity of 84%-95% (87, 92). Several attempts at a structured classification system of the macroscopic appearance of lesions in the bile duct have been made, but no system has gained widespread acceptance and interobserver reliability is modest (93, 94). A possible explanation for this discrepancy between histological and visual diagnosis may be that SOPCP-guided tissue sampling is limited by suboptimal maneuverability of the endoscope and insufficient size of the biopsy of the miniaturized forceps. In a recent systematic review comparing the diagnostic value of different generations of mini-endoscopes, it was concluded that the newer generations of SOPCP with video-chip visualization systems had better sensitivity and specificity both in terms of visual assessment and tissue acquisition in the diagnosis of indeterminate bile duct strictures (95). Regarding indeterminate strictures in patients with primary sclerosing cholangitis (PSC), Njei et al. (96) performed a systematic review including 4 studies evaluating the accuracy of SOPCP in this setting. The authors found that the pooled sensitivity and specificity of SOPCP for cholangiocarcinoma in patients with PSC were 65% and 95%, respectively. Whether SOPCP ultimately affects the longer-term outcome of patients with PSC is unclear, and its value in the management of patients with PSC remains controversial (84).

2.2.2.2 Difficult stones of the bile duct

The most widely adopted definition of a ‘difficult bile duct stone’ is when more than one of the following characteristics prevails: “largest stone diameter > 15mm, failed prior attempt at stone clearance, impacted stone, multiple stones, intrahepatic duct location or located above a stricture”(97) In these settings, cholangioscopy-assisted intraductal lithotripsy with either laser lithotripsy or electrohydraulic lithotripsy, has demonstrated high efficiency in complete clearance of stones in the bile duct (87, 98). Whether surgical exploration of the common bile

duct is a safer and more time- and cost-effective treatment option compared to endoscopic stone retrieval, remains a subject of discussion (99). In a systematic review including 31 studies, performed by Korropati et al. (100), the overall stone clearance rate using a variety of cholangioscopy-assisted techniques was 88%, with a tendency of higher efficiency for the later generations of single operator mini-endoscopes. In the 2019 guidelines from the European Society of Gastrointestinal Endoscopy (ESGE), it is recommended that cholangioscopy-assisted stone removal is used when conventional endoscopic techniques, including endoscopic papillary large-balloon dilatation, have failed (30).

2.2.2.3 Diagnostic and therapeutic application in pancreas

Parallel to the growing awareness and understanding of the malignant potential of pancreatic cystic neoplasms, there has been a surge in interest in the diagnostic capabilities of pancreatoscopy. Hara et al. (101) described the endoscopic appearance of main duct IPMN (MD-IPMN) in 2002 and concluded that findings of fish egg-like, prominent and villous mucosal protrusion predicts a final histological diagnosis of malignancy with a sensitivity of 68% and a specificity of 87%. In a study of 44 patients with IPMN where preprocedural characterization with cross-sectional imaging were considered insufficient, our group has previously shown that SOPCP correctly identified MD-IPMN in the majority of cases, and influenced the management in 76% of patients (102). These and other promising results regarding the diagnostic efficiency of SOPCP in the pancreatic duct (103-105) suggests that SOPCP, even though there is limited data regarding risks, may be included in the future work-up algorithms for IPMN. This is especially true when results from noninvasive diagnostic modalities are insufficient for deciding on a definitive management plan.

In the treatment of pancreatic ductal stones in patients with chronic pancreatitis, complete stone clearance rates and technical success with SOPCP and intraductal lithotripsy has been reported in 50%-100% of cases (106, 107). However, its role in the management of patients with chronic pancreatitis remains unclear, mainly due to scarce data regarding its impact on patient symptoms and quality of life (108).

2.2.2.4 Other

Several different areas of usage for SOPCP has been suggested in case reports and small case series. Its ability to visualize tight strictures in the biliopancreatic ductal system has been reported to aid in the process of traversing tortuous strictures with a guidewire for subsequent further intervention (109). Reports on its ability to aid in retrieval of proximally migrated

stents (110), assist in intraductal targeted radiofrequency ablation (111), and drainage of the gallbladder through the cystic duct (112) have also been presented.

2.2.3 Peroral cholangiopancreatoscopes and risk

The overall rate of adverse events with POCP is higher than with conventional ERCP, with post-procedural pancreatitis (PPP) when targeting biliary ducts ranging from 3.9% to 7.4% (74, 113, 114). These numbers have to be interpreted with caution however, as previous studies on POCP have focused mainly on clinical yield while concurrently reporting on adverse events in a retrospective setting. Reports are plagued by limitations in structured follow-up protocols, and thus the true incidence of adverse events following POCP is unknown. Cases of rare events such as air embolism fatalities has been reported (115) but clinically relevant adverse events remain pancreatitis, cholangitis, perforation and bleeding. In a large multicenter study by Adler et al. (116) including 282 POCP procedures, the authors presented rates of post-procedural pancreatitis (3.9%), post-procedural cholangitis (1.4%), bleeding (1%) and perforation (0.7%).The authors concluded that the incidence of adverse events following POCP were similar to those following conventional ERCP without additional adjunct techniques. Sethi et al. (113) reported higher rates of cholangitis when comparing cholangiopancreatoscopy procedures with conventional ERCP (1.0% vs 0.2%) and proposed that the volume and pressure of irrigated fluids used to increase visibility during the procedure may play an important role. Furthermore, in a study by Lubbe et al. (114), which included 408 cholangioscopy procedures performed between 2007-2012 in Sweden, higher rates of adverse events were reported (pancreatitis 7.4%, cholangitis 4.4%). In this study, which had adverse events as the primary outcome and included patients that were prospectively registered in the nationwide Swedish Registry for Gallstone Surgery and ERCP, the rate of adverse after POCP were approximately twice as much when compared to conventional ERCP.

Few studies have addressed the question of specific patient- or procedure related risk factors for PPP after POCP. When the pancreatic duct is the target for POCP, small and heterogenous studies report varying rates of PPP, with incidence ranging from 0%-17% (102, 117, 118). Individual risk factors for PPP after single operator peroral pancreatoscopy (SOPP) have been suggested by anecdotal reports, such as high intraluminal pressure of irrigation fluid, a small diameter main pancreatic duct and concomitant pancreatic sphincterotomy. However, our present understanding of PPP risk after SOPP remains limited.

2.2.4 EUS and confocal laser endomicroscopy

Endoscopic ultrasound (EUS) has since the 1990s rapidly evolved to become an important diagnostic and therapeutic tool for the biliopancreatic system. EUS enhanced by simultaneous fine needle aspiration is increasingly used to biopsy and stage solid lesions in the pancreas, and is considered the first line investigation in the evaluation of pancreatic cysts when conventional cross-sectional imaging is inconclusive (119-121). For the detection of biliary ductal stones, diagnostic accuracy of EUS is comparable or even superior to ERCP (122, 123). Therapeutic EUS has gained traction over the past decade with the introduction of new echoendoscopes and new accessories. In the treatment of peripancreatic fluid collections, EUS-guided drainage has largely replaced other invasive techniques, and its efficiency has been confirmed in several studies (124-126). Other therapeutic applications of EUS are described in multiple small studies indicating major therapeutic capabilities, but its role in biliopancreatic therapy has not yet been definitively established (127, 128). Probe based confocal laser endomicroscopy and other new techniques that allows direct intraductal histological analysis of indeterminate lesions has shown some promising results that are noteworthy, but unresolved questions regarding interobserver reliability and clinical yield has hampered its widespread use (129-131).

2.3 CONE BEAM COMPUTERIZED TOMOGRAPHY, FUSION IMAGING AND OTHER NEW IMAGING TECHNIQUES

The development of cross-sectional imaging such as magnetic resonance imaging (MRI) and multidetector computed tomography (MDCT) has markedly changed the way we diagnose biliopancreatic disorders. These imaging modalities have an unprecedented ability to produce three-dimensional (3D) images of the biliopancreatic ducts with a high diagnostic value. A large number of patients who present for ERCP would have undergone some type of preprocedural non-invasive imaging (132-134).

In conventional ERCP, fluoroscopy is used for intraprocedural image guidance. Fluoroscopy is restricted by two-dimensional representations of the three-dimensional biliopancreatic ductal system and expose the health staff and patient to relatively high radiation doses. The images produced by the c-arm in the conventional ERCP suite gives little information about the 3D nature of the biliopancreatic ductal system, nor does it give information about structures or lesions outside the contrast filled ducts (135-137).

2.3.1 Cone beam computed tomography guided ERCP

The cone beam computed tomography (CBCT) technique, which creates a 3D dataset from a single rotation of the c-arm, was developed in the 1990s and has the ability to provide 3D intraprocedural guidance in real time. In a CBCT scan acquisition, the C-arm which contains the x-ray generator and the detector makes a single spin around the target organ through approximately 200 degrees. During this rotation, which typically takes 5-40 s (depending on system used) hundreds of two-dimensional (2D) x-ray projections are acquired by the detector. This raw data is processed and reconstructed into a three-dimensional (3D) model by a computerized system which also transmits the 3D images to a monitor for viewing (138). Modern CBCT systems are able to produce 3D images with a high diagnostic value and an image quality equal to or even superior to conventional multislice computed tomography but with considerably lower radiation dose (139). It is reported that radiation doses are increased in individual cases when CBCT are used compared to cases when conventional fluoroscopy are used, but the study design in these reports are non-randomized, and the radiation dose might reflect the complexity of the procedures. There are authors (140, 141) that argue that total radiation dose decreases when the use of repeated fluoroscopy is avoidable owing to information gained from CBCT data sets. Figure 4 shows imaging equipment with a rotatable c-arm capable of producing CBCT images of the biliopancreatic ductal system as well as qr codes with links to video clips illustrating cone beam ERCP (CB-ERCP).

Initially CBCT was mainly used in dental applications and particularly in the planning of preoperative implant placement (142), but in recent years, we have seen a rapid expansion of clinical uses for CBCT. In endovascular surgery, CBCT capabilities are present in most modern hybrid operation theaters (143) and are increasingly used to guide endovascular surgeons in complex procedures such as endovascular aneurysm repair with fenestrated grafts (144). Numerous reports on CBCT advantages over conventional fluoroscopy with digital subtraction angiography in vascular applications have been presented: Tornquist et al. (145) and Schultz et al. (146) concluded that CBCT is superior to conventional fluoroscopy in detecting endoleaks after endovascular aortic repair. Biasi et al. (147) reported that there were fewer re-interventions in the group in which CBCT was used for intraprocedural guidance. Finally, in a review including 15 studies by Pung et al. (148) it was concluded that CBCT can increase the detection of tumors and feeding arteries in the setting of transcatheter arterial chemoembolization treatments of hepatocellular carcinoma.

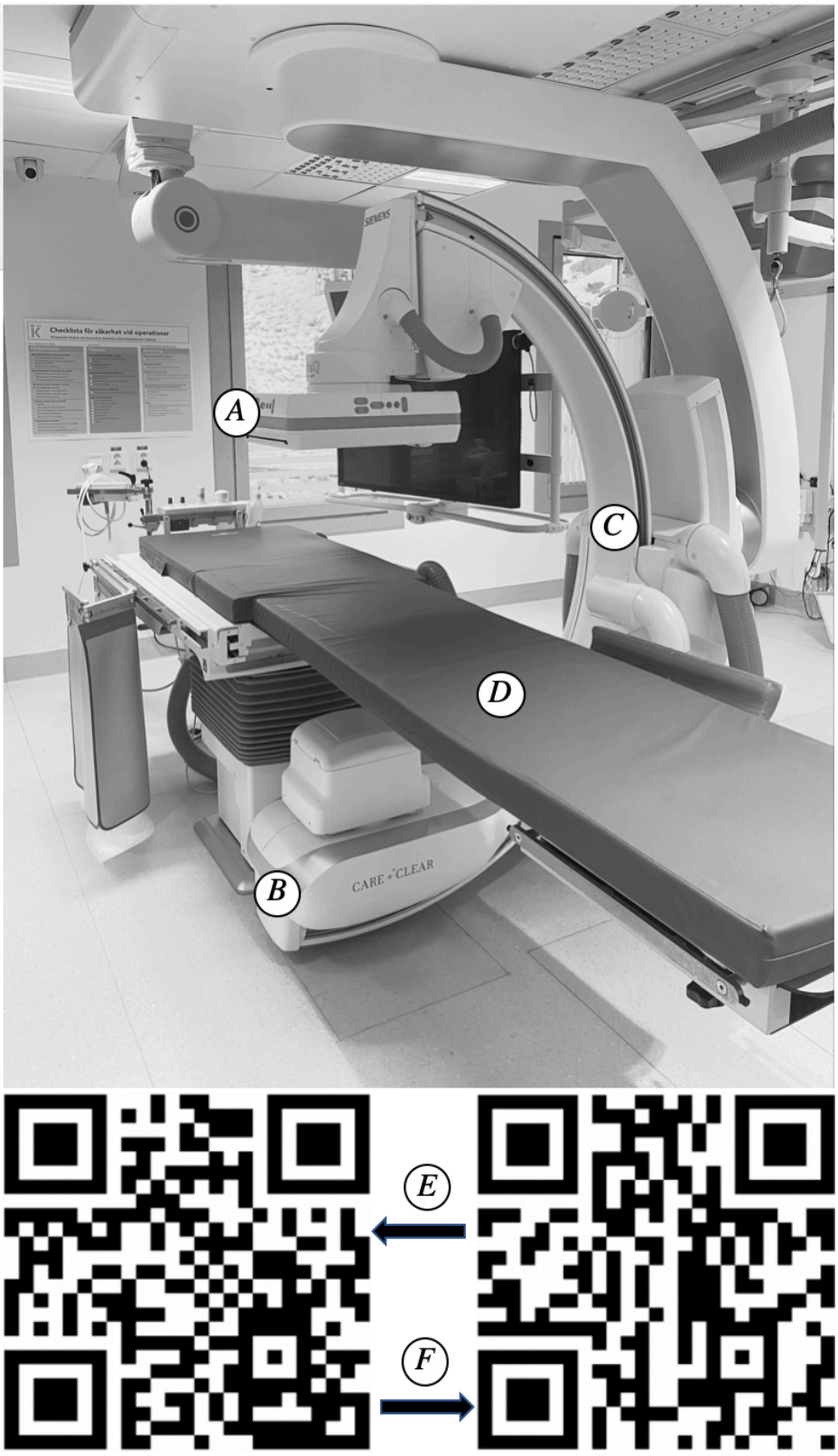


Figure 4 Imaging equipment capable of producing cone beam computed tomography images of the biliopancreatic ductal system. The flat panel detector (A) and x-ray source (B) are attached to a rotatable c-arm (C). Rotation of the system around the patient table (D) allows for acquisition of multiple 2D images which are processed and reconstructed to a 3D model. Qr code E links to a video clip showing processed and reconstructed cone beam images of the bile duct system and qr code F links to a video clip showing raw and unprocessed data. Photograph by Erik von Seth and video clips by Marcus Reuterwall Hansson.

In an attempt to define the contribution of CBCT in breast cancer diagnosis, Wienbeck et al. (149) reports that the sensitivity for non-contrast CBCT is higher compared to conventional 2D mammography in both high and low density breasts. Intraprocedural image guidance with CBCT has, in addition, recently seen a widespread use in neurovascular interventions and in the initial care of the trauma patients. Early reports indicates that the CBCT technique increases technical success and decreases procedure time (12, 150, 151). Flat panel detectors, with higher spatial resolution compared to conventional image intensifiers, has further advanced the clinical use of CBCT (152, 153). However, few reports exist on the use of CBCT technique when addressing the biliopancreatic system. Wallace et al. (143) suggested that CBCT-cholangiography using the percutaneous transhepatic route aids to delineate biliary anatomy and tumor abnormalities. As an adjunct to ERCP, this technique is largely unexplored, but in a case series with six patients by Weigt et al. (141), it was reported that CBCT provided additional valuable information to guide endoscopic biliary therapy.

2.3.2 Image fusion techniques in image guided interventional procedures

Fusion imaging techniques, where a preprocedural data volume from MRI or MDCT is used to build a 3D model that is later co-registered and linked with anatomical landmarks in images from live fluoroscopy, has gained widespread use in other image guided interventional disciplines (154). Albeit a new technology, promising results from various settings have shown that the technique can lead to decreased radiation dose, shorter procedure time and decreased volume of injected contrast medium (155, 156). Since the first report in 2011 of this technique in endovascular surgery by Djikstra et al. (144), it has become increasingly used mainly in complex endovascular and neurovascular procedures (157). In general, fusion imaging technique in the setting of image guided procedures involves linking or ‘fusing’ 3D datasets from a preprocedural computed tomography scan or magnetic resonance scan with the live conventional fluoroscopy image used in real time during the procedure (155). Figure 5 shows an example of a preprocedural MRCP fused with the conventional fluoroscopic image during ERCP. The resulting “roadmap”, with information on the 3D anatomy of the target organ, additionally contains information on tissue outside the contrast-filled ducts which is not accessible with conventional fluoroscopy. In a recent systematic review and meta-analysis of image fusion techniques used in endovascular aortic repair by Goudeketting et al. (157), it was concluded that this technique was associated with reduced volumes of injected contrast agent compared to conventional imaging with fluoroscopy, especially in complex cases. Secondary outcomes such as radiation dose, fluoroscopy time, and total operation time were similarly decreased, although further analysis

was restricted by limitations in research design among the included studies. Furthermore, in a study including 10 patients by Schwein et al. (155), it was demonstrated that patients with impaired renal function could undergo complex endovascular procedures with preserved postprocedural residual renal function when the volume of nephrotoxic contrast agents was reduced. This reduction in contrast agent volume was due to usage of preprocedural magnetic resonance angiography which was fused with images from conventional intraprocedural image guidance.

The direct access to preprocedural imaging fused with real time conventional image guidance has the potential to increase the diagnostic and therapeutic capabilities of ERCP but no studies on this technique as an adjunct to ERCP exist at present.

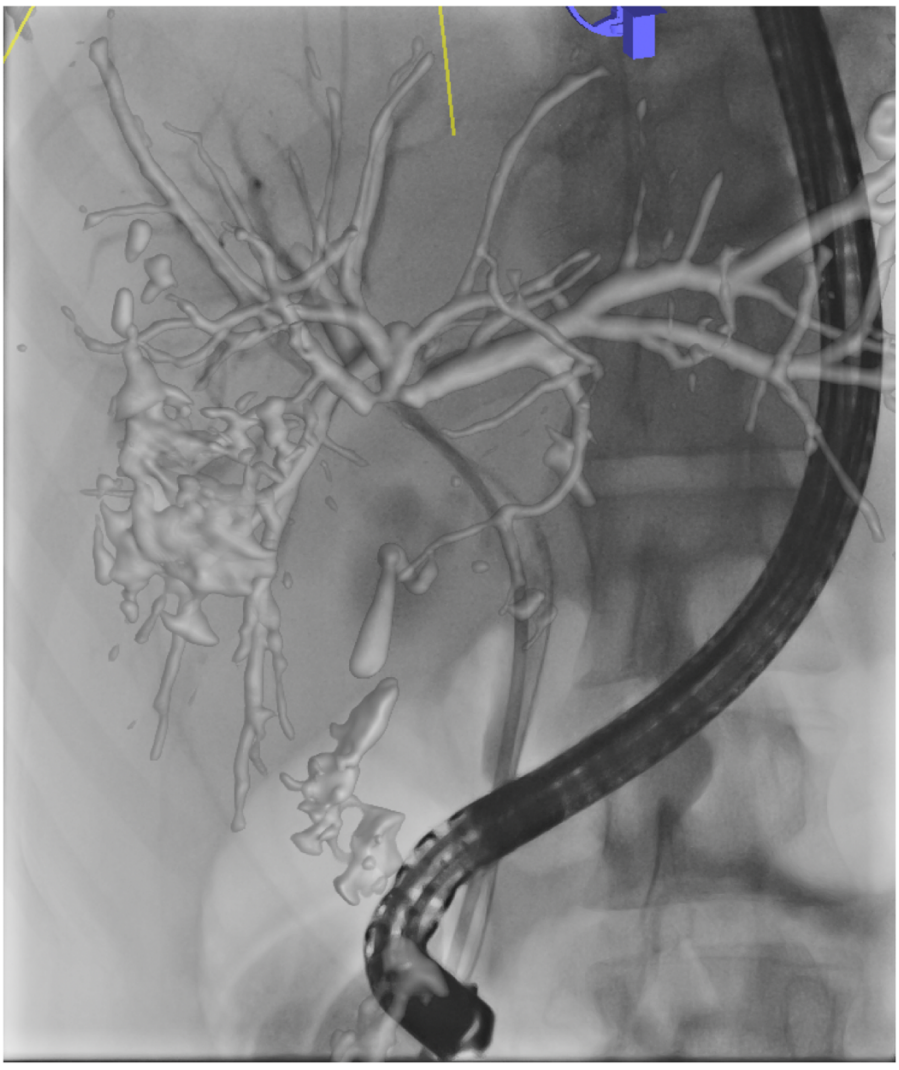


Figure 5 An example of a preprocedural T2-weighted MRCP fused with the conventional fluoroscopic image during ERCP.

3 RESEARCH AIMS

The general aim of this thesis was to explore and contribute to the understanding of emerging technologies used as an adjunct to ERCP.

Our specific aims were:

- To assess the diagnostic and therapeutic yield of single operator peroral cholangiopancreatoscopy in the diagnosis and treatment of biliopancreatic disease.
- To investigate patient-related risk factors for post procedural pancreatitis following single-operator peroral pancreatoscopy.
- To determine the feasibility and potential clinical yield of bimodal ERCP.
- To assess radiation dose in cone beam ERCP.

4 MATERIALS AND METHODS

4.1 ETHICAL CONSIDERATIONS

All studies were approved by regional ethics committee of Stockholm County; Paper I – dnr 2014/55-31/4; Paper II - dnr 2021-03989 and dnr 2014/55-31/4; Paper III and IV - dnr 2019-02109 and dnr 2017/2294-31/1.

4.2 PAPER I

4.2.1 Study population and design

From 2007 to 2014, all patients undergoing SOPCP at the Karolinska University Hospital with the SpyGlass® Direct Visualization System were included in this retrospective review. Unless complicated cholelithiasis was the indication for the procedure, all patients were discussed at a multidisciplinary team conference where an individualized management plan was decided on. The diagnostic yield and therapeutic value of each procedure were evaluated retrospectively using a predefined graded scale. A single independent reviewer applied the scale to each case, and the final decision on the grade was made by determining the impact the procedure had on the final multidisciplinary team conference outcome.

4.2.2 Main outcome and definitions

Main outcome of the study was clinical yield of SOPCP and adverse events related to the procedure. 'Difficult' to remove common bile duct stones (stone removal not achieved by conventional techniques) or intrahepatic stones were defined as complex cholelithiasis. American Society of Anesthesiologists (ASA) classification system of baseline physical status was used with: 1 – a normal healthy patient, 2 – mild systemic disease, 3 – severe systemic disease and 4 – systemic disease that is a constant threat to life. Indeterminate stricture of the bile duct was defined as "when basic work-up, including transabdominal imaging and endoscopic retrograde cholangiopancreatography with routine cytologic brushing, are non-diagnostic" as described by Khashab et al. (88). Main outcome of the study was clinical yield of SOPCP and adverse events related to the procedure.

4.2.3 Grading of clinical yield

The predefined graded scale utilized to assess the diagnostic yield and therapeutic value of each procedure: 1 - no diagnostic or therapeutic value, 2 - information gained did not impact clinical decision-making and in case of a therapeutic intervention, did not alter the clinical course of the patient, 3 - information gained had an impact on clinical decision-making and in case of a therapeutic intervention, assisted subsequent disease management, and finally, 4 -

information gained was essential and critical for clinical decision-making and in case of a therapeutic intervention, solved the clinical problem requiring no further diagnostic or therapeutic actions.

4.2.4 SOPCP Procedure

Prior to the procedure, all patients received antibiotic prophylaxis consisting of either intravenous piperacillin+tazobactam or oral sulfonamid+trimethoprim. All procedures were carried out with the fiberoptic SpyGlass® Direct Visualization System (Boston Scientific, USA) passed through a standard duodenoscope. The first generation legacy Spyglass® System consists of three components; first, a reusable SpyGlass fiber optic probe (allowing direct visual guidance and examination of the respective duct systems), second, a disposable access and delivery catheter system, SpyScope (capable of accommodating both optical and accessory devices used in the biliary system), and finally a single use mini-biopsy forceps (used to capture tissue specimens for histomorphologic diagnosis). The fiber optic probe has an outer diameter of 0.9 mm, image transmission of of 6000 pixels, a 0° direct view, and a field view of 70°. The light source is a Xenon light connected to the fiber optic probe. Electrohydraulic lithotripsy was performed using either a 1.9 Fr coaxial electrode probe (Olympus Lithotron EL-25, 1000 mJ; Olympus Inc., Stockholm, Sweden) or Nortech AUTOLITH® generator with bipolar biliary electrohydraulic lithotripsy (EHL) probe (Northgate Technologies Inc. Elgin, IL, USA). A ductogram was obtained after successful cannulation of the papilla and insertion of the guide wire into the desired duct to be visually inspected, i.e. biliary ducts or pancreatic duct. The instrument was then carefully advanced over the guide wire and into the appropriate duct. Ductal debris hindering proper visualization was cleared with saline irrigation. SOPCP was used for visually targeted biopsies in patients with indeterminate strictures or other pathology such as intraductal papillary and nodular features or irregular mucosal surfaces.

4.2.5 Adverse events

The severity grading system of the American Society for Gastrointestinal Endoscopy (ASGE) by Cotton et al. (44) was used to grade intra- and postprocedural adverse events.

4.2.6 Statistics

Descriptive statistics were used, including frequencies, median values, and ranges. Uni- and multivariate analyses were completed to address risk factors for the occurrence of postprocedural adverse events. All analyses were carried out using STATA 13.1 (StataCorp LP, College Station, Texas, USA).

4.3 PAPER II

4.3.1 Study design and cohort

In this retrospective, single-center study, we identified all patients (n=194) who underwent pancreatoscopy with the Spyglass® DS Direct Visualization system at Karolinska University Hospital between April 2015 and Nov 2020. The following exclusion criteria were applied: 1) Perioperative pancreatoscopy (use of pancreatoscopy during pancreatic resection) (n=53); 2) Transgastric or transduodenal pancreatoscopy (n=2); 3) If the indication for SOPP was acute pancreatitis and/or disconnected main pancreatic duct (n=2). 4) Altered anatomy after pancreatic surgery (n=1). 5) Preprocedural imaging of pancreas done more than six months before SOPP (n=24). Only the first examination during the study period was considered. The patient selection and final study cohort are illustrated in Figure 6.

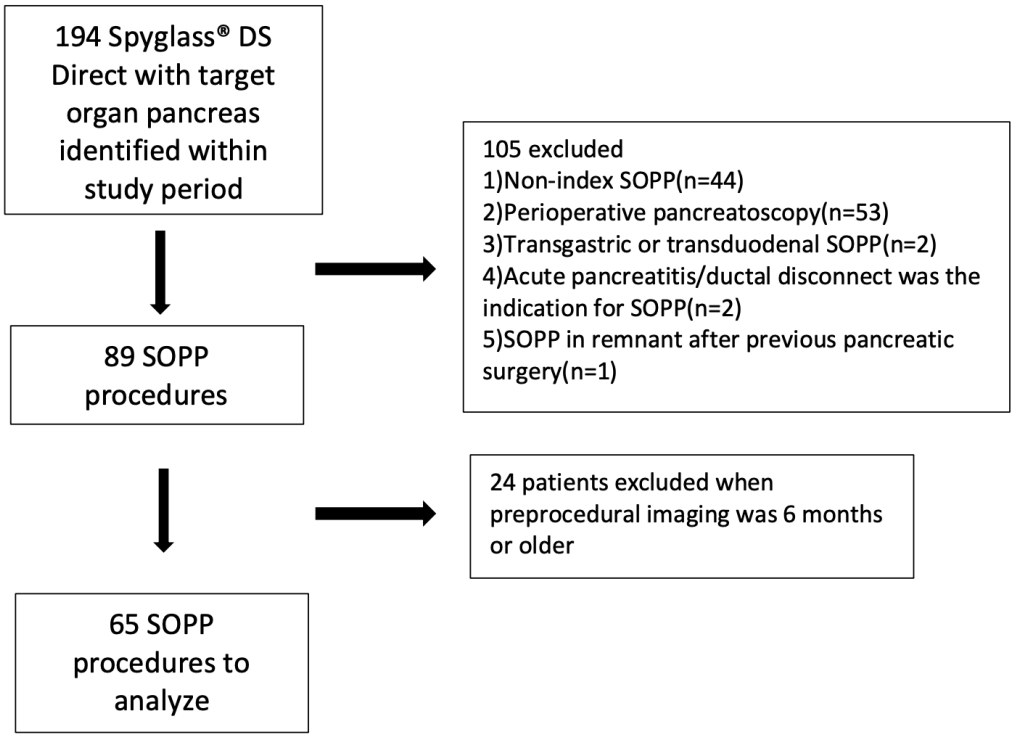


Figure 6 Characteristics of single operator peroral pancreatoscopy procedures included in the analysis.

4.3.2 Data collection and definitions

Patient and procedure related data were retrieved from the electronic medical record system and from the Swedish national registry for ERCP (Gallriks). The Gallriks registry is a prospective registry validated regularly by an independent audit group and the data match between the registry and the medical journal system is >90%. The Gallriks registry includes a

30-day follow up where postprocedural adverse events are registered(158). Classification of the severity grade of adverse events was made in accordance with “A lexicon for endoscopic adverse events: reports of an ASGE workshop” by Cotton et al. (44).

Main indication for SOPP was defined according to preprocedural multidisciplinary team (MDT) conference. In two cases, the indication for SOPP was retrieval of migrated stent from the main pancreatic duct (MPD). In seven cases, with the indication therapeutic intent in chronic pancreatitis, the patients were not discussed at a formal MDT conference and the decision to perform SOPP was made by a senior endoscopist.

Preprocedural chronic pancreatitis (CP) was defined as either a diagnosis according to national guidelines for CP (159) or radiological findings consistent with CP according to a preprocedural MDT conference. Any sphincterotomy was defined as a new or re-do endoscopic sphincterotomy of the biliary or pancreatic sphincter, including sphincterotomy of the minor papilla. A native papilla was defined as a papilla with no previous biliary or pancreatic sphincterotomy or previous balloon dilatation of sphincter. A post-procedural stent was defined as a pancreatic endoprothesis, with or without internal flares, deployed at the end of procedure, with therapeutic intention or with the intention of preventing PPP. A difficult cannulation was defined according to the 5-5-2 definition developed by Halttunen et al. (160, 161)

4.3.3 SOPP procedure

All SOPP procedures were carried out under general anaesthesia and with the patient in a supine position. A new or re-do pancreatic sphincterotomy was performed at the discretion of the endoscopist making use of a conventional ERCP sphincterotome. The Spyglass® DS Direct endoscope was advanced through the working channel of a standard duodenoscope into the main pancreatic duct freehand or via a 0.035" guidewire. To improve visualization inside the MPD, low pressure irrigation with saline was used intermittently. Depending on the clinical situation, a variety of adjunct endoscopic techniques (including balloon dilatation of the MPD, biopsies with miniaturized forceps, and electrohydraulic lithotripsy) was used at the discretion of the endoscopist. All patients included in the study had an intraprocedural pancreatogram obtained with conventional ERCP technique during the SOPP procedure.

4.3.4 Preprocedural imaging and assessment of pancreatic morphology

For the evaluation of imaging variables, we made use of available cross-sectional imaging (i.e. either CT or MRI with MRCP sequences) performed within 6 months prior to the date of SOPP. All images were evaluated on a picture archiving and communication system (Sectra

Workstation, IDS7 version 23.1, Sectra AB) by two senior radiologists. In patients who underwent CT, we used axial images after intravenous administration of iodine-based contrast agents if these were available (slice thickness 2.5-5 mm). In patients who underwent MRI with MRCP, we used axial T1-weighted fat saturated images after intravenous administration of gadolinium-based contrast agents, if these were available (slice thickness 2.5-4 mm). Images in these patients included axial T2-weighted images (slice thickness 4-7 mm), coronal thin-slice 3D MRCP (slice thickness 1-2.5 mm), and coronal thick-slab 2D MRCP (slice thickness 4-7 cm). For all patients, imaging parameters were evaluated in the following three portions of the pancreas: head (border: neck), body (border: at the level of splenic vein's dorsal course) and tail.

4.3.4.1 Pancreatic gland parameters:

Maximum lateral gland diameter at the head was measured in mm, excluding the uncinate process. The measurement was performed from the superior mesenteric vein (SMV) groove (i.e., the most medial part of the gland adjacent to the right border of the SMV) to the most lateral border of the head within the duodenal loop. Maximum anteroposterior gland diameter at the head (in mm) was measured perpendicular to the aforementioned maximum lateral gland diameter at the head. Maximum gland diameter at the body and tail was measured perpendicular to the longitudinal axis (in mm). The presence of normal parenchymal enhancement was also recorded.

4.3.4.2 MPD parameters:

Maximum MPD diameter (in mm) perpendicular to its axis, wherever in the gland it was observed (i.e., head, body or tail). In addition, the presence of stones was indicated (yes or no).

4.3.4.3 Pancreatic gland thickness and MPD diameter ratio in head and body of pancreas

Maximum MPD diameter was measured in the same projections as gland diameter in the head and body of pancreas. The pancreatic gland thickness and MPD diameter ratio was calculated by dividing gland diameter (in mm) with MPD diameter (in mm). Measurements of gland thickness and MPD diameter are described in Figure 7.

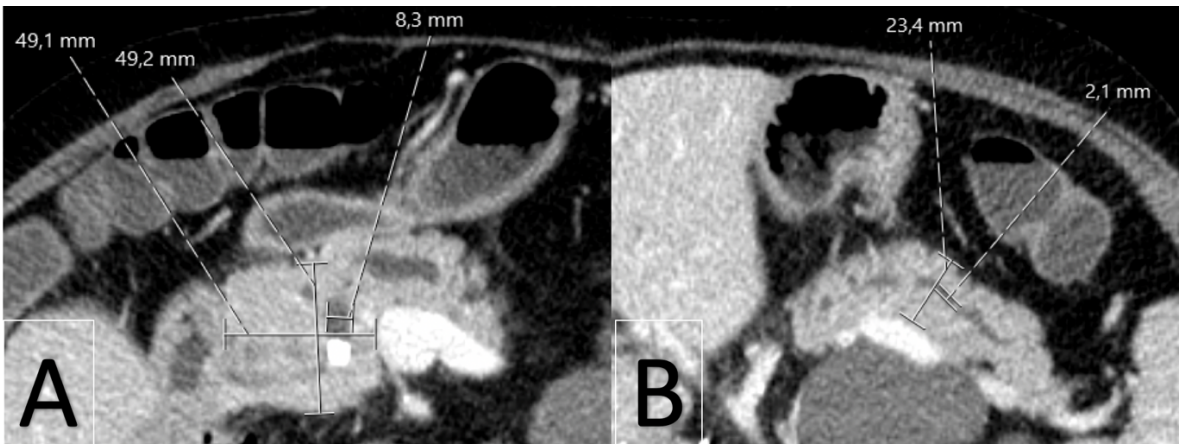


Figure 7 Examples of preprocedural CT imaging with measurements of gland thickness and MPD in A) Head of pancreas and B) Tail of pancreas

4.3.5 Statistical analysis

Categorical variables were summarized as frequencies and percentages, while numerical variables were summarized as the mean (SD) or median (IQR) depending on the distribution of data. Univariate logistic regression models were initially performed, then followed by multivariable logistic regression models to estimate the associations between the outcomes and the exposure variables. This yielded adjusted odds ratio (ORs) and their corresponding 95% CIs while controlling for preselected confounders. Missing data were handled by performing complete case analyses. Within the logistic regression analyses, we checked for the presence of influential values by assessing the standardized residual error. We additionally assessed whether there was multicollinearity among the covariates in the logistic regression models and tested for goodness of fit using the Hosmer-Lemeshow statistic. All the logistic regression assessments were satisfactory. All *P* values were two-sided and $P < 0{\cdot}05$ was considered statistically significant. Statistical analyses were performed in R Statistical software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

4.4 PAPER III

4.4.1 Study population, design and statistical analysis

Study III was a retrospective observational report of individuals undergoing bimodal ERCP at a single tertiary referral center. During the research period, patients who had a previously scheduled conventional ERCP at our single tertiary referral center were considered for inclusion. Patients were only eligible for inclusion if they had a previously obtained T2-weighted isotropic 3D MRI dataset. We selected cases from eligible individuals that represented a diversity of clinical problems. All statistical analyses were carried out using STATA 13.1 (StataCorp LP, College Station, Texas, United States).

4.4.2 Definitions and data collection

The co-registered MRI-derived cholangiopancreatogram represents the “co-MRCP”. When the images of the biliopancreatic ductal system from both the co-MRCP and the conventional fluoroscopic images of contrast-filled ducts were clearly visible in bimodal image mode, bimodal image quality was regarded as "good." If the co-MRCP revealed the lesion of interest in bimodal image mode with the conventional fluoroscopic image being native (i.e. not contrast medium enhanced) then bimodal ERCP was considered "an aid in visualizing the lesion of interest." If the co-MRCP provided information on ductal trajectory in the anteroposterior, mediolateral, or longitudinal axis not comprehensible with the conventional fluoroscopic image, bimodal ERCP was classified as "an aid in understanding 3D ductal anatomy." In bimodal image mode the absence of overlay misalignment was defined as: “The guidewire trajectory in a native fluoroscopic image and/or contrast filled ducts visible in conventional unimodal fluoroscopic mode matches the ducts from the co-MRCP perfectly regardless of angle of the c-arm unit”.

4.4.3 Co-registration of images derived from MRI and conventional fluoroscopy

4.4.3.1 Technical aspects of MRI imaging

All MRIs were performed using a 1.5 T system with a phased-array body and spine matrix coil (Magnetom Avanto or Magnetom Aera, Siemens Healthcare, Erlangen, Germany). The MRI examination was imported into the 3D-workstation (Siemens Healthcare, Erlangen, Germany) in the intervention suite on the day of the ERCP procedure and reconstructed in 3D volume-rendering formats using the Picture and Archiving Communication System (PACS) from Sectra AB, Linköping, Sweden. Technical parameters of the preprocedural MRI are summarized in Table 1.

Table 1 Technical parameters of the MRI examinations

Sequence	Plane	Slice thickness/gap	Te (ms)	Tr (ms)	Breathing technique	Scan time
T2w-HASTE	axial	4 mm/0	76,0	1000	Multi-BH[1]/PACE[2]	2-5 min
T2w-HASTE	coronal	4 mm/0	76,0	1000	PACE	2-5 min
T1w 3D GRE Dixon	axial	4 mm/0	2,4-4,8	6.93	BH	15-22 s
T2w 3D-SPACE MRCP	coronal	1 mm	900,0	2000	PACE	3-6 min
DWI[4]	axial	5 mm/0	77,0	5000	FB[3]	3-5 min
T1w 3D-GRE VIBE FS before contrast	axial	2,5 mm	1,9	4,29	BH	15-22 s
T1w 3D-GRE VIBE FS after contrast[5]	axial	2,5 mm	1,9	4,29	BH	5 min

[1]BH, breath-hold; [2]PACE, prospective acquisition correction navigator-triggered; [3]FB, free-breathing

[4]DWI was acquired with the following b-values: 50 and 800 s/mm²

[5]The following dynamic phases were acquired: late arterial phase by means of the Combined Applications to Reduce Exposure (CARE) bolus technique; portal venous phase, acquired with a delay of 50 s from the start of the arterial phase; delayed phases at 3 and 5 min respectively.

4.4.3.2 Co-registration of images and generation of bimodal ERCP

A frontal and lateral fluoroscopic image of the upper abdomen was obtained in our interventional suite utilizing a roof mounted c-arm system (Artis Q, Siemens Healthcare, Erlangen, Germany) as previously described in detail by Schwein et al. (155). All patients underwent general anesthesia with added breath-hold during image acquisition. T1-weighted 3D-GRE VIBE fat-sat sequences were usually selected in the initial steps of image co-registration due to better spatial resolution and were thereafter replaced with 3D T2-weighted MRCP images, rendering a more visible biliopancreatic ductal system. The liver dome and the spine, which are visible in both modalities, were used as landmarks to co-register the MRI and fluoroscopic images. These landmarks were electronically marked with dedicated software (syngo iGuide toolbox; Siemens Healthcare, Erlangen, Germany) and co-registered with dedicated software (syngo Inspace 3D-2D; Siemens Healthcare, Erlangen, Germany). This process was followed by manual alignment of landmarks visible in both image modalities. During bimodal ERCP, the co-registered MRI-derived cholangiopancreatogram (co-MRCP) was projected in real time onto the live conventional fluoroscopic image on the endoscopist monitor. The amount of opacity for each image, namely co-MRCP vs. conventional fluoroscopic, was manually chosen by the endoscopist. In addition, a change in table position and/or x-ray source ("C-arm") angulation resulted in automatic adjustment of the co-MRCP on the endoscopist monitor to correspond with the new fluoroscopic view. The workflow of co-registrating the fluoroscopic image with the preprocedural MRI is illustrated in Figure 8.

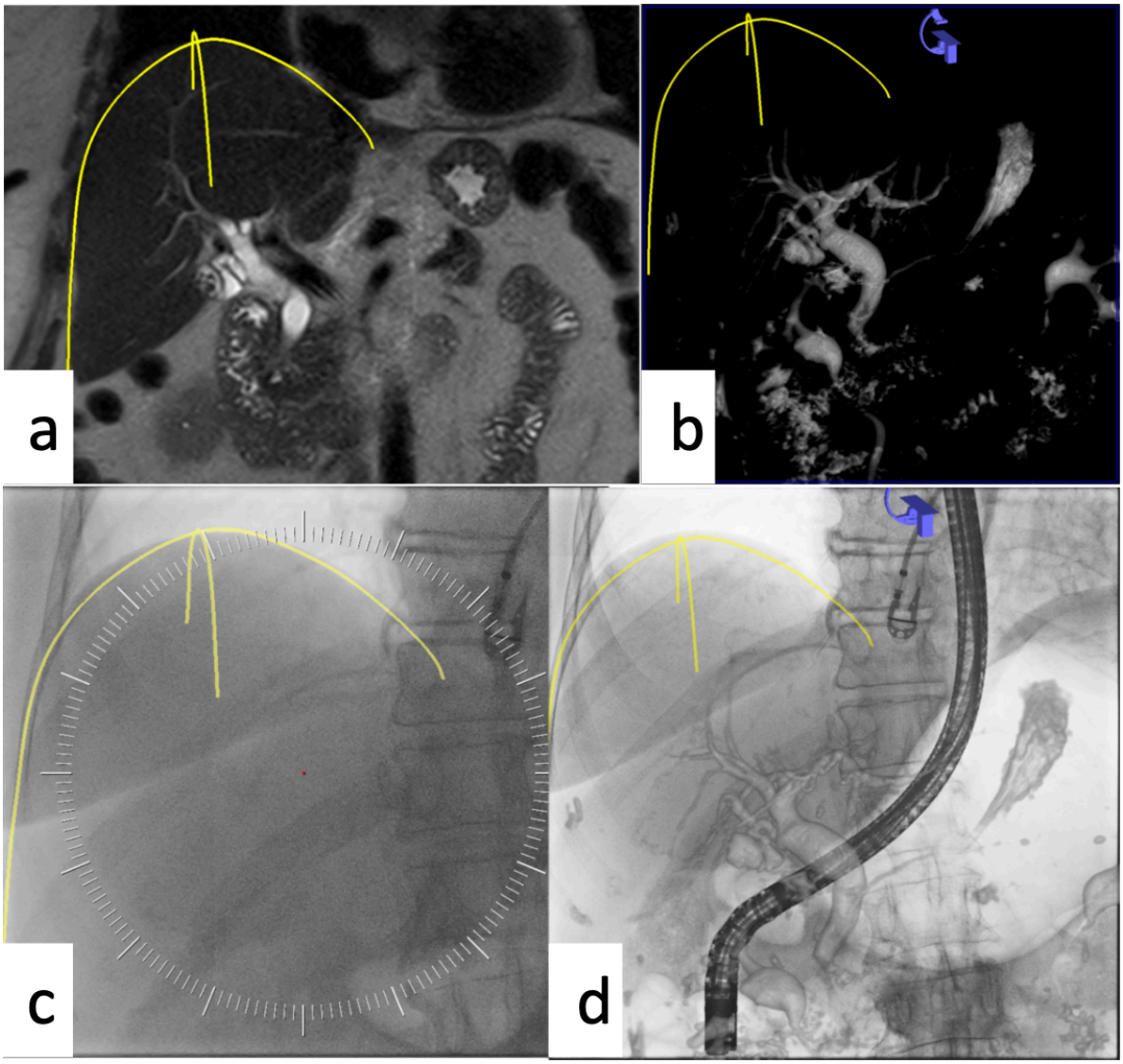


Figure 8 Workflow illustrates magnetic resonance imaging (MRI)–conventional fluoroscopy image coregistration and fusion to bimodal ERCP. Preprocedural planning involves marking of landmarks visible in both image modalities in coronar and lateral projections (only coronar projections shown here). a The liver contour is marked in T1-weighted 3D-GRE VIBE fat-sat MRI sequence where soft tissues are visible. b The initial MRI sequence is replaced by 3 D T2-weighted MRCP images where the biliopancreatic ductal system is better visualized. c The liver contour in a standard fluoroscopic image is marked. d After manual alignment of landmarks visible in both image modalities, the coregistered and fused bimodal image is projected in real time to the endoscopists monitor for intraprocedural guidance.

4.5 PAPER IV

4.5.1 Study design, data collection and statistical analysis

Study IV was a retrospective analysis of radiation exposure data from conventional ERCP procedures and cone beam computed tomography-ERCP (CB-ERCP) procedures performed between February 2016 and June 2017 at a tertiary high volume endoscopy unit. At the end of each procedure, data on radiation exposure from fluoroscopy protocols, CB-ERCP

protocols and single digital acquisitions protocols was automatically sent from an Artis Q interventional x-ray unit (Siemens Healthineers, Erlangen, Germany) to a dose monitoring server in the form of a Radiation Dose Structured Report DICOM object. All CB-ERCP procedures were identified and categorized according to protocol. Basic statistics (frequencies with percentages, means with SD, or median with IQR) was performed. To compare radiation doses between groups, the Mann-Whitney U test was utilized. SPSS version 24.0.0.0 was used for all statistical analyses.

4.5.2 Radiation dose protocols

Two different CB-ERCP exposure protocols were used: the standard default protocol 5sDR Body (DR) and 5sDR Body Care (DR care). The latter protocol was developed in collaboration between an application specialist and clinicians at Karolinska University Hospital. Both protocols are regarded as low-dose protocols. Furthermore, three different fluoroscopy programs were utilized, and two different protocols was used for single image digital acquisition. Technical aspects of the two CB-ERCP protocols, as well as fluoroscopy protocols and single image digital acquisition protocols, are presented in Table 2.

Table 2 Technical aspects of the imaging protocols used in the study.

a. CBCT programs

Protocol	Tube voltage (kV)	Detector dose per frame (µGy)	Copper filter (mm)	Rotation angle	Step per frame	Pixel resolution (binning)	Pixel pitch (µm)
DR	90	0.360	0.0	200°	1.5°	Medium (2 x 2)	154 x 2
DR care	90	0.100	0.1	200°	1.5°	Medium (2 x 2)	154 x 2

b. Fluoroscopy programs

Protocol	Target tube voltage (kV)	Detector dose per pulse (µGy)	Copper filter (mm)	Default pulse rate	% of fluoroscopy program use
Fluoro low	73	0.040	0.6 to 0.9	4 p/s	89 %
Fluoro medium	73	0.055	0.6 to 0.9	4 p/s	9 %
Fluoro high	73	0.080	0.1 to 0.3	4 p/s	2 %

c. Single image digital acquisition programs

Protocol	Target tube voltage (kV)	Detector dose (µGy)	Copper filter (mm)	% of single exposures performed
Single low	70	0.810	0.1 to 0.3	98 %
Single normal	70	1.200	0.1 to 0.3	2 %

5 RESULTS

5.1 PAPER I

365 SOPCP procedures were done in 311 patients over the seven-year study period. The vast majority of patients (88%) required one procedure. SOPCP lasted 99 minutes on average (range 50–275), with concurrent procedures such as endoscopic ultrasonography (EUS) conducted at the discretion of the endoscopist. Figure 9 lists the specific indications for SOPCP, and Table 3 summarizes patient demographics. The most common indication for the procedure was indeterminate bile duct strictures in non-PSC patients (33%), while in 16% of cases, complex cholelithiasis was the indication for the procedure. The bile duct was the primary target in 71% of our patients, followed by the pancreatic duct in 24%, while both ducts were targeted in 5%.

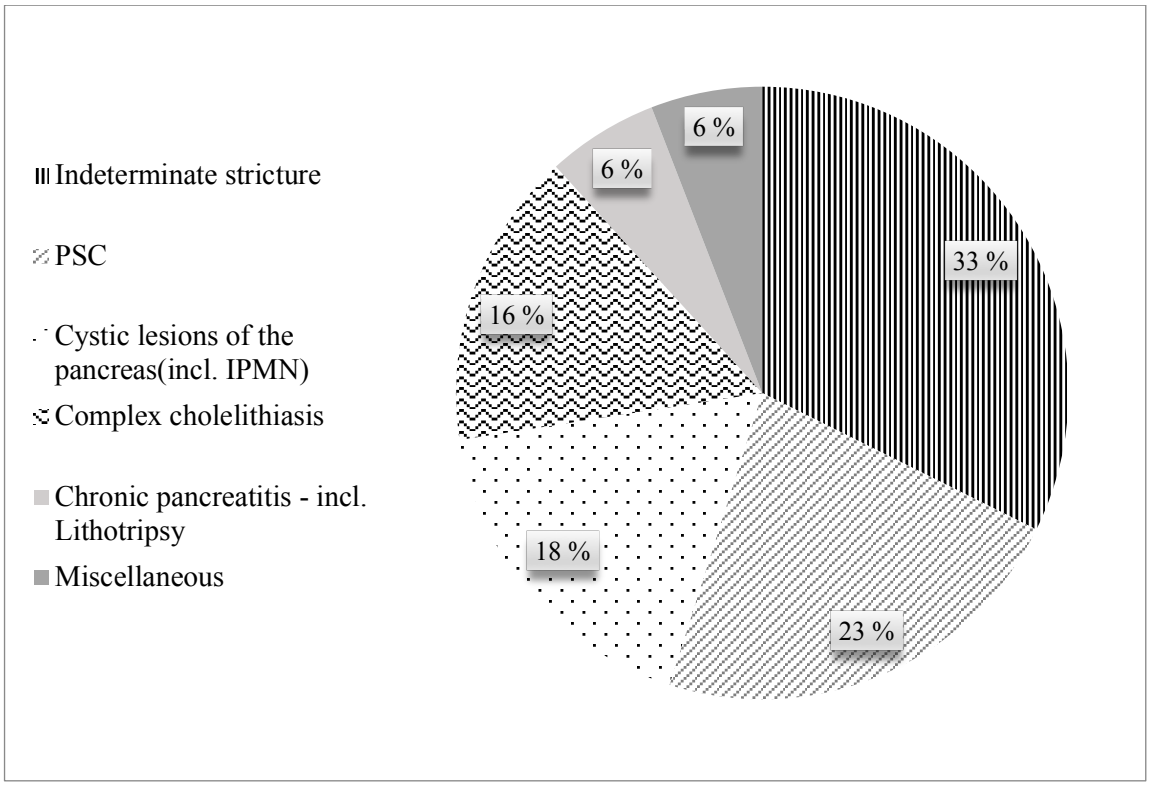


Figure 9 Indications for SOPCP

Table 3 Patient demographics for patients undergoing SOPCP

Patient characteristic	n(%), median (range)
ASA 1	58(16)
ASA 2	186(51)
ASA 3	121(33)
ASA 4	0(0)
Female sex	137(44)

Duration of procedure (minutes)	99(50-275)
Referrals from outside Stockholm	103(33)
Patients undergoing multiple procedures	38(12)
Patients undergoing a single procedure	273(88)

ASA, American Society of Anesthesiologists

5.1.1 Clinical yield of SOPCP

Figure 10 shows the relative distribution of diagnostic and therapeutic yield of SOPCP. In 19% of cases, SOPCP was assessed to be of pivotal clinical importance (grade 4) and of considerable clinical significance (grade 3) in 44% of cases. In 37% of cases, the procedure had no effect on clinical decision-making or did not alter clinical course (grade 1 and 2). The majority of grade 2 procedures (n = 54) were caused by an inability to definitively determine the relative contribution of the SOPCP's procedure in the face of several factors that ultimately influenced the clinical decision-making process.

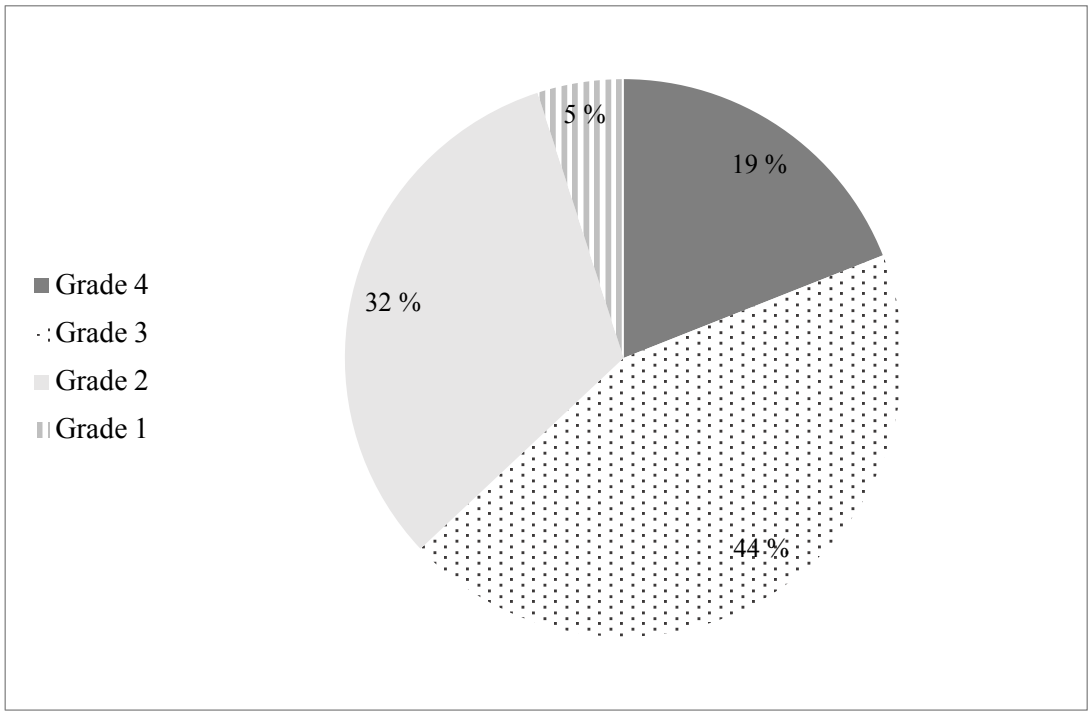


Figure 10 Relative distribution of diagnostic and therapeutic yield of SOPCP as graded to the predefined 4 grade scale

Figure 11 illustrates the assigned grades (grouped as grade 1–2, or grade 3–4) according to the specific SOPCP indications. Therapeutic value was evaluated as grades 3–4 in 79% of procedures performed for the treatment of difficult bile duct stones. In 66%of procedures performed as part of the work-up for cystic pancreatic lesions, cases were evaluated as grades 3–4. In non-PSC and PSC patients, the diagnostic yield for indeterminate biliary strictures was graded 3–4 in 57 % and 56 % of cases, respectively. In 55 % of patients with chronic pancreatitis the clinical value of SOPCP was graded as 1–2.

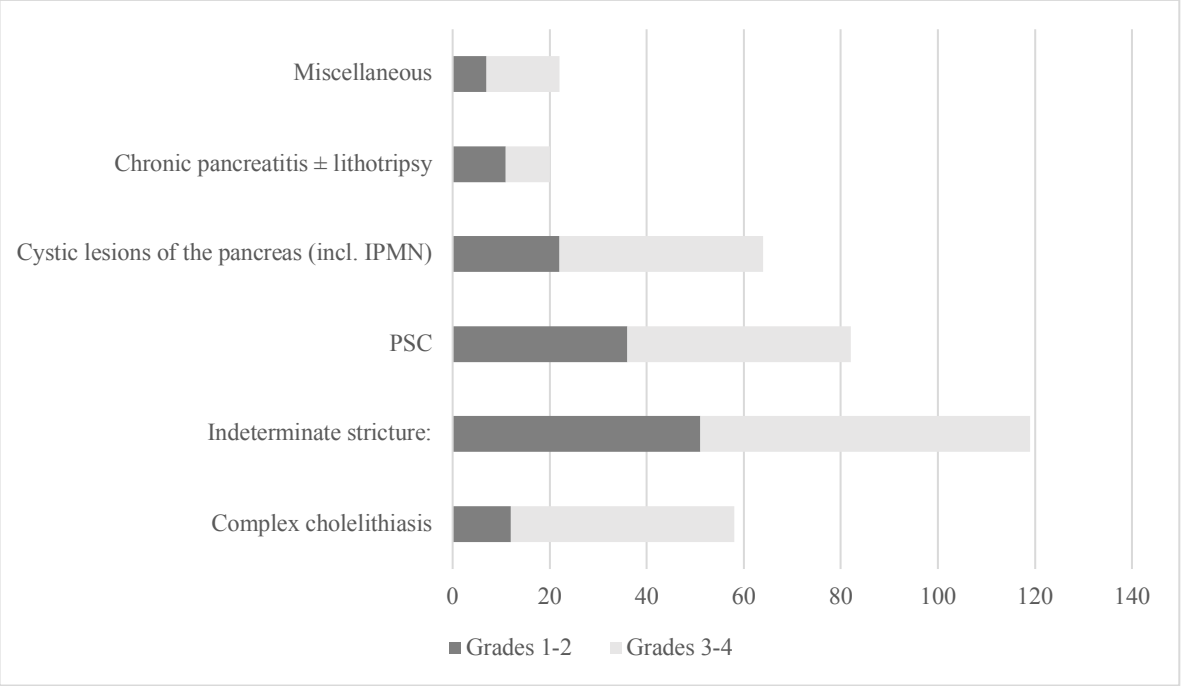


Figure 11 Distribution of assigned grades grouped as grade 1-2 and 3-4 according to indication for SOPCP

5.1.2 Adverse events

We observed a 16 % overall adverse event rate (AER), the majority of which were classified as mild or moderate. Pancreatitis was the most common adverse event, occurring in 8% of cases, with mild and moderate pancreatitis being equally distributed. When analyzing specific risk factors for the occurrence of postprocedural adverse events we observed that pancreatoscopy was associated with an AER of 20%, whereas cholangioscopy had an AER of 10%. We also observed a nondilated main pancreatic duct in 9 of the 17 pancreatitis cases in the pancreatoscopy group (53 %). We were unable to establish a change in the risk of this complication over time. Cholangitis was observed in 16 patients (4%), with no cases of severe cholangitis. We experienced one fatal adverse event as a result of acute severe pancreatitis. In this patient the SOPCP was combined with an endoscopic ultrasound-guided puncture of a cystic pancreatic lesion. A gastrointestinal perforation was suspected at first, but imaging could not confirm it. The clinical course was complex, and on day 101, the patient died of multi-organ failure.

5.2 PAPER II

5.2.1 Patient characteristics, preprocedural pancreatic gland morphology and pancreatic duct diameter

A total of 150 individuals underwent SOPP during the study period, and after exclusion criteria was applied, 89 remained in the study cohort (Figure 6 in section 4.3.1). In 24 of these, preprocedural imaging was older than 6 months resulting in 65 individuals being eligible for analysis. The median age of patients was 66 years and 37 (57%) were men. 48 (74%) of the patients had their physical status classified as mild systemic disease (ASA 2) and 15 (23%) as severe systemic disease (ASA 3). The most common indication for SOPP was suspicion of main duct IPMN in 44 patients (68%), followed by therapeutic intent in patients with chronic pancreatitis in 19 patients (29%). 45 patients (69%) fulfilled criteria for chronic pancreatitis or had suspicion of chronic pancreatitis raised at the preprocedural MDT conference. The modality used for preprocedural imaging consisted of MRI in 45 patients (69%) and CT scans in 20 (31%). The median of the maximum diameter of the MPD was 7 mm, with values ranging from 3-29 mm. Stones were present in the MPD at the time of preprocedural imaging in 25 patients (38%). We calculated the ratio between MPD diameter and gland thickness in the head of pancreas to be a median of 7.5 (range 2-34). In the body of pancreas this ratio was found to be a median of 7 (range 1-24). Patient characteristics, preprocedural pancreatic gland morphology and pancreatic duct diameter are summarised in Table 4.

Table 4 Clinical characteristics and results of preprocedural imaging of 65 patients included in study

Age, years (median, range)	66 (23-86)
Sex, n (%) Female Male	 28 (43%) 37 (57%)
BMI (kg/m^2) (median, range)	24(19-33)
ASA classification, n (%) ASA 1 ASA 2 ASA 3	 2 (3%) 48 (74%) 15 (23%)
Main indication for SOPP, n (%) Suspicion of main duct IPMN Chronic pancreatitis with therapeutic intent Other	 44 (68%) 19 (29%) 2 (3%)
Chronic pancreatitis, n (%) Yes No	 45 (69%) 20 (31%)
Maximum diameter of MPD, mm (median, range)	7 (3-29)
Stones in MPD, n (%) Yes No	 25 (38%) 40 (62%)

Head of pancreas ratio* (median, range)	7.5 (2-34)
Body of pancreas ratio** (median, range)	7 (1-24)

*ASA – American society of anesthesiologists; ERCP-endoscopic retrograde cholangiopancreatography; MRI – Magnetic resonance imaging; MRCP – Magnetic Resonance cholangiopancreatography; SOPP – single operator peroral pancreatoscopy; MPD – main pancreatic duct; *Ratio between gland thickness and diameter of MPD in head of pancreas; ** Ratio between gland thickness and diameter of MPD in body of pancreas.*

5.2.2 Procedure characteristics

The median time for performance of procedures (ERCP including SOPP) was 88 minutes (range 29-155) and 16 patients (25%) received preprocedural rectal administration of 100 mg diclofenac. A native papilla was encountered in 24 patients (39%) and pancreatic sphincterotomy was performed during the SOPP procedure in 32 (51%). In addition to the SOPP procedure, cholangioscopy was performed in 34 patients (52%) and EHL was used in the treatment of pancreatic stones in 16 (25%). Following the SOPP, a pancreatic stent was inserted in the MPD in 37 individuals (57%). Table 5 shows the procedure characteristics.

Table 5 Procedure characteristics in 65 patients undergoing SOPP

Preprocedural NSAID, n (%)	16 (25%)
Procedural time, min (median, range)	88 (29-155)
Native papilla, n (%)	24 (39%)
Difficult cannulation, n (%)	5 (10%)
Pancreatic sphincterotomy, n (%)	32 (51%)
Any sphincterotomy, n (%)	38 (58%)
Post-procedural stent, n (%)	37 (57%)
Cholangioscopy in addition to SOPP n (%)	34 (52%)
EHL, n (%)	16 (25%)

EHL - electrohydraulic lithotripsy

5.2.3 Adverse events

Postprocedural pancreatitis occurred in 15 patients (23%) during the 30-day follow up. It was mild in 5 (7.7%), moderate in 6 (9.2%), severe in 3 (4.6%) and fatal in 1 (1.5%). The single mortality occurred after 87 days in hospital with multiple organ system failure due to PPP. Cholangitis occurred in 3 patients (4.6%), with two of these cases having undergone a cholangioscopy procedure in the same session as SOPP. One of the patients with cholangitis had postprocedural pancreatitis as well. Perforation of the MPD occurred in 2 cases (3.1%), one case of guidewire perforation and one case where the pancreatoscope induced partial disruption of MPD. The former patient had a moderate postprocedural pancreatitis as well, the latter had an uneventful postprocedural period and was discharged after observation postprocedural day 2. Two patients experienced postprocedural bleeding of which one received transfusion and one went through a repeat endoscopy. Adverse events with grading of severity are presented in Table 6.

Table 6 Grading of postprocedural adverse events

Adverse event	Mild	Moderate	Severe	Fatal
Postprocedural pancreatitis(n=15)	5	6	3	1
Cholangitis[a]	1	2		
MPD perforation[b]	1	1		
Postprocedural bleeding[c]		2		

*Grading according to Cotton et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc, 2010. **71**(3): p. 446-54) a) Two of the patients with postprocedural cholangitis had a cholangioscopy procedure in same session as SOPP. One of the patients with cholangitis had postprocedural pancreatitis as well. b) One patient with guidewire perforation and one patient with pancreatoscope induced partial disruption of MPD. The former patient had a moderate postprocedural pancreatitis as well, the latter had an uneventful postprocedural period and was discharged after observation postprocedural day 2. c) One patient received transfusion, one patient had a repeat endoscopy.*

5.2.4 Risk factors for PPP identified by univariate analysis

Patient- and procedure-related risk- or protective-factors and their association with PPP were initially investigated in a univariate analysis. The patient related factors namely sex, indication, and presence of stones in the MPD, were not associated with PPP. However, preprocedural chronic pancreatitis was associated with a lower risk for PPP (OR 0.28 95% CI 0.08-0.92). Among the procedure-related factors, insertion of a postprocedural endoprothesis was associated with a lower risk (OR 0.28; 95% CI 0.08-0.95). In univariate analysis of preprocedural morphological characteristics and their association with PPP we found that an increased ratio between gland thickness and MPD diameter in the body of pancreas was associated with increased PPP risk (OR 1.14; 95% CI 1.03-1.28) whereas the head of pancreas ratio and maximum diameter of MPD were not. Risk factors for PPP identified by univariate analysis are presented in Tables 7 and 8.

Table 7 Patient- and procedure-related factors and their association with PPP

Factors	PPP yes	OR (95% CI)	p-value
Female sex	9 (32%)	2.44 (0.75-7.97)	0.14
Chronic pancreatitis	7 (16%)	0.28 (0.08-0.92)	0.036
Indication *IPMN* *Chronic pancreatitis* *Stent retrieval*	 12 (27%) 3 (15%) 0 (0%)	 Ref 0.5 (0.12-2.02) NA	 0.332

Stones in MPD	3 (12%)	0.32 (0.80-1.27)	0.11
Difficult cannulation (n=51)	1 (20%)	0.80(0.08-7.88)	0.84
Pancreatic sphincterotomy (n=63)	10 (31%)	2.36 (0.70-7.96)	0.17
Any sphincterotomy (n=65)	10 (26%)	1.57 (0.47-5.27)	0.464
Native papilla	7 (29%)	1.76 (0.53-5.88)	0.355
Post-procedural stent	5 (14%)	0.28 (0.08-0.95)	0.041
Endoscopic balloon dilatation MPD (n=65)	2 (10%)	0.27 (0.06-1.35)	0.11

MPD – Main pancreatic duct; IPMN - intraductal papillary mucinous neoplasm

Table 8 Morphological characteristics in preprocedural imaging and their association with PPP

Characteristic	OR(95% CI)	p-value
Body of pancreas ratio*	1.14(1.03-1-28)	0.012
Head of pancreas ratio**	0.98(0.87-1.08)	0.69
Maximum diameter of MPD	0.88 (0.67-1.06)	0.35

** Ratio between gland thickness and diameter of MPD in body of pancreas; **Ratio between gland thickness and diameter of MPD in head of pancreas*

5.2.5 Predictors for PPP in multivariate regression models

We further evaluated measurements of pancreatic morphology and MPD diameter as risk factors for PPP in three separate multivariate regression models. Individuals with incomplete data were excluded from the multivariate analysis. First, we investigated the body of pancreas ratio (n=59) and found that the association with PPP remained (OR 1.26; 95% CI 1.06-1.57) after adjustments for confounders. In our second and third multivariate models we investigated the head of pancreas ratio (n=55) and maximal diameter of MPD (n=55), respectively as main predictors for PPP with adjustments for the same confounders as in the first model. No statistically significant associations were found in multivariate models 2 and 3. In Table 9, 10 and 11 we present odds ratio for body of pancreas ratio, head of pancreas

ratio and maximum diameter of the MPD with adjustments for their independent association with PPP.

Table 9 Adjusted logistic regression model - postprocedural pancreatitis as binary outcome and body of pancreas ratio as main predictor

Characteristic	OR(95% CI)	p-value
Body of pancreas ratio	1.26 (1.06-1.57)	0.018
Age	1.08 (0.98-1.23	0.2
Chronic pancreatitis	1.73(0.30-12.1)	0.6
Preprocedural NSAID	1.88(0.3-11.9)	0.5
Native papilla	15.2 (1.13-456)	0.070
Any sphincterotomy	0.09(0.00-1.38)	0.12
Postprocedural stent	0.28(0.04-1.42)	0.14

Table 10 Adjusted logistic regression model - Postprocedural pancreatitis as binary outcome and head of pancreas ratio as main predictor

Characteristic	OR(95% CI)	p-value
Head of pancreas ratio	0.98(0.81-1.11)	0.8
Age	1.03(0.96-1.13)	0.5
Chronic pancreatitis	0.62(0.13-3.05)	0.5
Preprocedural NSAID	1.55(0.30-7.35)	0.6
Native papilla	1.84(0.28-16.8)	0.5
Any sphincterotomy	0.57(0.05-5.48)	0.6
Postprocedural stent	0.24(0.04-1.08)	0.073

Table 11 Adjusted logistic regression model - Postprocedural pancreatitis as binary outcome and maximal diameter of main pancreatic duct (MPD) as main predictor

Characteristic	OR(95% CI)	p-value
Maximal diameter of MPD	0.95(0.67-1.17)	0.7
Age	1.04(0.97-1.14)	0.4
Chronic pancreatitis	0.63(0.13-3.17)	0.6
Preprocedural NSAID	1.61(0.32-7.51)	0.5
Native papilla	1.83(0.28-16.5)	0.5
Any sphincterotomy	0.69(0.07-5.24)	0.7
Postprocedural stent	0.24(0.05-1.01)	0.062

5.3 PAPER III

5.3.1 Patient characteristics and indication

13 patients, ranging in age from 22 to 80, underwent bimodal ERCP at our tertiary endoscopy unit between March 15, 2017 and May 21, 2017. Ten of the patients were male and three were female, with five being classified as ASA 2 and eight being classified as ASA 3. Leakage from the biliary ducts was the indication for bimodal ERCP in two patients, and leakage from pancreatic ducts was the indication in a further two patients. In eight of the patients, bile duct stricture was the indication for bimodal ERCP. The clinical setting of biliary strictures included indeterminate stricture in non-PSC patients (n = 4), indeterminate stricture in PSC patients (n = 2), and stricture following liver transplantation (n = 2). In one patient, complex cholelithiasis was the indication for bimodal ERCP.

5.3.2 Feasibility, procedure characteristics and yield

In all 13 cases, MRI co-registration and fusion with fluoroscopic images were technichally feasible, and image quality was rated "good" in 11 and "poor" in two. In eight patients, bimodal ERCP aided in understanding the 3D anatomy of the biliopancreatic ductal system. In ten patients, bimodal ERCP aided to visualize the lesion of interest including one patient with PSC and a dominant stricture not identified with conventional fluoroscopy. Bimodal ERCP assisted in finding a favorable position for the c-arm for the subsequent procedure in

five patients without the use of conventional fluoroscopy. Table 14 summarizes patient characteristics, indication for bimodal ERCP, procedure characteristics and clinical yield of the procedures.

5.3.3 Radiation dose and procedure time in bimodal ERCP

As shown in Table 12, the total radiation dose for the entire bimodal ERCP procedure was a mean of 22.7 Gy cm^2 (range 1.5–62.6), and the co-registration radiation dose was 1.12 Gy cm^2 (range 0.17–3.53). The total procedure time was 75.7 minutes on average (range 22.4–147.6), with the image co-registration process taking 11.9 minutes on average (range 5.7–24.7). In one patient, the time for image co-registration included a software failure and a system reboot. The image co-registration radiation dose in two cases (patients 8 and 11) was much higher than the others. Long fluoroscopy times and/or the utilization of single image digital acquisitions during the lateral projections were characteristics of these two patients' image co-registration process.

Table 12 Radiation time and procedure time in bimodal ERCP

Patient	Total radiation dose ($gycm^2$)	Image registration radiation dose ($gycm^2$)	Fraction of radiation dose from registration (%)	Total fluoro time (min)	Total procedure time (min)	Time image registration process (min)	Total amount contrast medium(ml)
1	6,2	0,32	5%	6,4	35,3	8,1	35,0
2	21,7	0,82	4%	26,4	147,6	14,8	65,0
3	5,6	0,85	15%	8,1	103,1	24,7	20,0
4	11,3	0,36	3%	21,7	95,2	20,1	54,0
5	1,5	0,31	21%	5,7	34,6	10,2	25,0
6	23,3	<2,59*	11%	22,7	50,1	10,5	7,0
7	57,5	0,89	2%	35,1	90,2	15,1	62,0
8	21,0	2,95	14%	16,7	25,5	9,8	70,0
9	10,4	0,17	2%	32,6	56,3	7,1	50,0
10	41,7	0,33	1%	37,4	145,1	12,4	130,0
11	14,4	3,53	24%	6,9	22,4	6,8	6,0
12	18,5	0,51	3%	26,3	59,7	5,7	55,0
13	62,6	0,91	1%	49,3	118,7	10,0	140,0
MEAN	22,7	1,12	8%	22,7	75,7	11,9	55,3
MAX	62,6	3,53	24%	49,3	147,6	24,7	140,0
MIN	1,5	0,17	1%	5,7	22,4	5,7	6,0

*Radiation dose in the form of dose area product. *The exact period of the fusion process could not be identified in the exposure log. The real image registration dose was less than the listed "worst case".*

5.3.4 Image misalignment in bimodal ERCP

The dynamic live images generated during continuous fluoroscopy and the static co-MRCP images showed consistent overlay mismatch due to breathing artefacts. In extrahepatic structures, the overlay misalignment between the co-MRCP and the conventional fluoroscopic image was major in 11 cases, moderate in a single case and non-applicable in another patient. A Roux-en Y hepaticojejunostomy was used to reach the intrahepatic bile ducts in the non-applicable case. In the two cases where pancreas was the target organ, overlay misalignment between the co-MRCP image and conventional fluoroscopic images of the pancreatic ducts was major. Regarding misalignment when targeting the intrahepatic ducts, there was no misalignment in five patient, minor misalignment in two, moderate misalignment in three and major misalignment in one patient. In the one case with major misalignment between the co-MRCP and conventional fluoroscopy in the intrahepatic ducts, an endoprothesis which was removed during initiation of bimodal ERCP was present during the preprocedural MRI. Characteristics of overlay misalignment in bimodal ERCP is shown in Table 13 and images in Figure 12 illustrates extrahepatic misalignment.

Table 13 Characteristics of overlay misalignment in bimodal ERCP

Patient	Indication	Intrahepatic overlay misalignment? (none, +, ++, +++)	Extrahepatic overlay misalignment? (none, +, ++, +++)
1	Complex cholelithiasis	none	+++
2	Indeterminate biliary stricture(non-PSC)	+++	+++
3	Indeterminate biliary stricture(non-PSC)	none	+++
4	Indeterminate biliary stricture(non-PSC)	none	+++
5	Biliary duct leakage	++	+++
6	Postoperative pancreatic duct leakage	n/a	+++
7	Indeterminate biliary stricture(PSC)	++	+++
8	Indeterminate biliary stricture(non-PSC)	++	+++
9	Biliary duct leakage with disconnected duct	+	++
10	Bile duct strictures after liver transplantation	none	n/a

11	Pancreatic duct leakage	n/a	+++
12	Indeterminate biliary stricture(PSC)	+	+++
13	Bile duct strictures after liver transplantation	none	+++

Overlay misalignment in bimodal image mode evaluated using a custom developed qualitative assessment scale: none, minor(+), moderate (++) and major(+++).

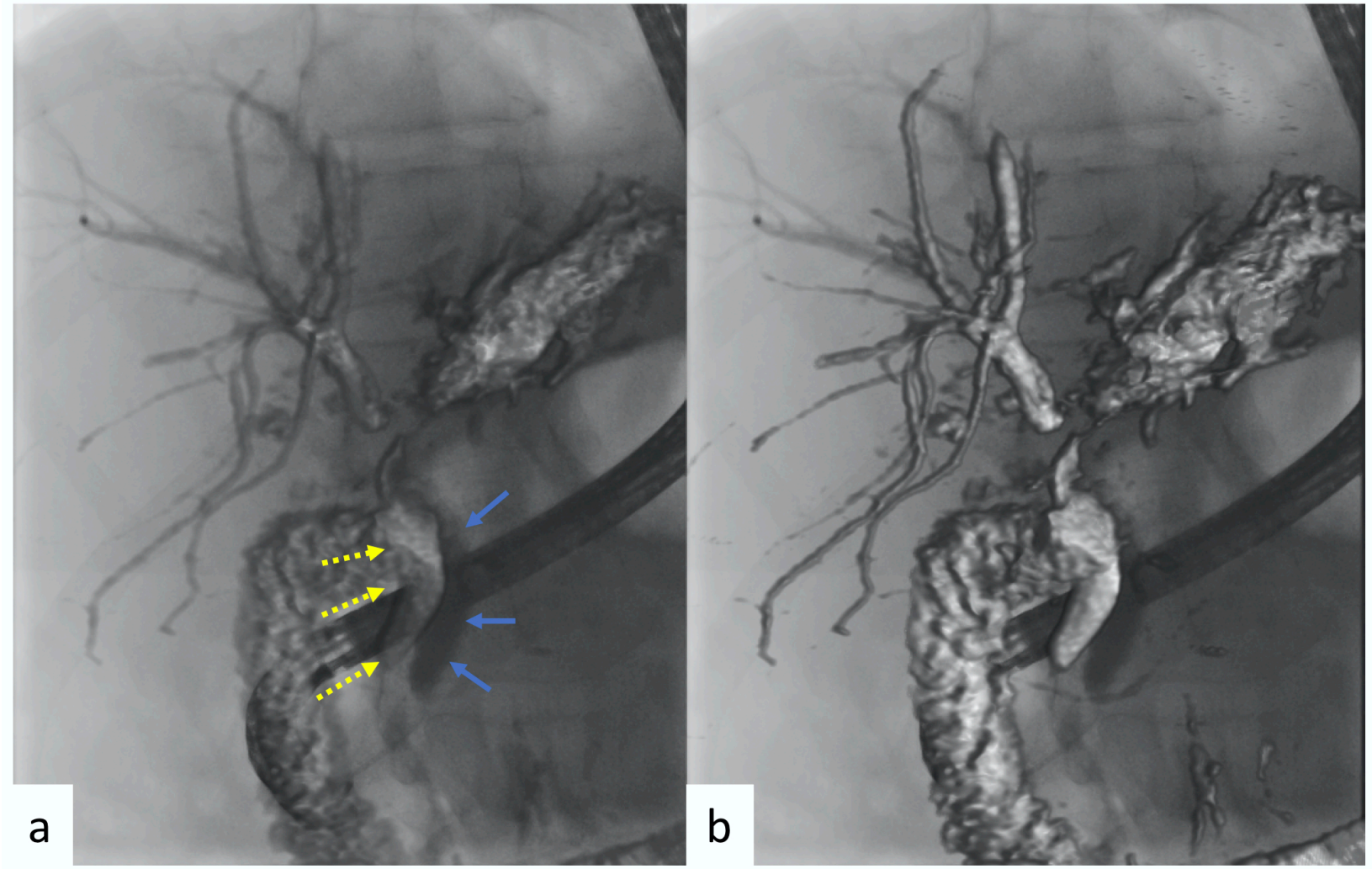


Figure 12 Examples of extrahepatic misalignment in bimodal ERCP. a) Bimodal ERCP in a patient with a hilar stricture. The image of the extrahepatic bile duct obtained from preprocedural MRCP (dotted arrows) is clearly misaligned with the image of the contrast filled extrahepatic duct obtained from conventional fluoroscopy (non-dotted arrows). In the intrahepatic ducts, there is only minor misalignment. b) Same patient as in a, but with increased overlay of an aligned and fused co-MRCP.

Table 14 patient characteristics, indication for bimodal ERCP, procedure characteristics and clinical yield of the procedures.

Patient	Age, years	ASA	Sex	Indication	Bimodal ercp image quality	Aid in visualize lesion of interest?	Aid in understanding 3D ductal anatomy?	Aid in finding c-arm position?
1	77	2	F	Complex cholelithiasis	good	yes	no	no
2	73	3	M	Indeterminate biliary stricture(non-PSC)	good	no	yes	yes
3	79	3	M	Indeterminate biliary stricture(non-PSC)	good	yes	no	no
4	80	3	F	Indeterminate biliary stricture(non-PSC)	good	yes	yes	no
5	22	2	F	Biliary duct leakage	good	yes	no	yes
6	74	3	M	Postoperative pancreatic duct leakage	poor	no	no	no
7	48	3	M	Indeterminate biliary stricture(PSC)	good	yes	yes	no
8	47	2	M	Indeterminate biliary stricture(non-PSC)	good	no	no	no
9	25	2	M	Biliary duct leakage with disconnected duct	good	yes	yes	no
10	37	3	M	Bile duct strictures after liver transplantation	poor	yes	yes	yes
11	51	3	M	Pancreatic duct leakage	good	yes	yes	no
12	27	2	M	Indeterminate biliary stricture(PSC)	good	yes	yes	yes
13	60	3	M	Bile duct strictures after liver transplantation	good	yes	yes	yes
Mean	54							

MR -, Magnetic resonance imaging; ASA - American Society of Anesthesiologists; PSC - Primary sclerosing cholangitis

5.4 PAPER IV

5.4.1 Radiation dose in conventional ERCP and Cone beam ERCP

Between February 2016 and June 2017 a total of 728 conventional ERCP procedures were performed, and 42 cases utilized CB-ERCP. In 17 (40%) of the CB-ERCP cases the protocol "DR" was used and in 25 (60%) the protocol "DR Care" was utilized. In the CB-ERCP group 37 cases (88%) had a single cone beam acquisition and five cases (12%) had two acquisitions. The cone beam acquisition in CB-ERCP using "DR" protocol accounted for almost half of the total dose area product (DAP) while the cone beam acquisition in CB-ERCP using "DR Care" protocol accounted for 26% of total DAP. As presented in Table 15, one cone beam acquisition during CB-ERCP using "DR" protocol contributed to a median DAP of 24.4 $Gycm^2$ and one cone beam acquisition during CB-ERCP using "DR Care" protocol resulted in a median DAP of 5.1 $Gycm^2$.

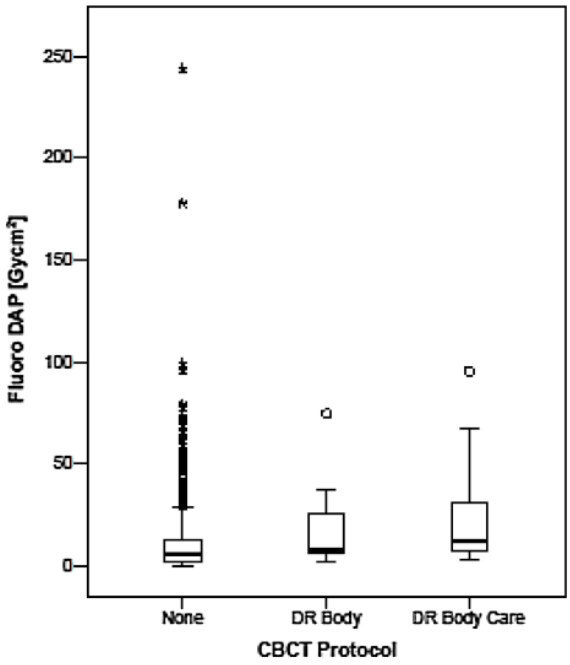
Tabell 15 Radiation dose grouped on exposure protocol used in the study

Exposure protocol	Total DAP [$Gycm^2$]	Fluoro DAP [$Gycm^2$]	Fluoro Time [min]	DAP for one Cone beam acquisition [$Gycm^2$]
Conventional ERCP	6.52 (2.63, 15.2)	5.52 (2.02, 13.1)	11.6 (5.43, 22.7)	n/a
CB-ERCP "DR"	48.9 (35.0, 58.4)	8.19 (6.40, 26.1)	12.0 (6.17, 28.0)	24.4 (17.4, 30.2)
CB-ERCP "DR care"	19.7 (12.4, 48.2)	12.7 (7.02, 31.5)	25.1 (16.3, 38.3)	5.07 (2.89, 6.88)

DAP – Dose area product

Values presented as: median (first quartile, third quartile).

Conventional ERCP generated a significantly reduced total DAP compared to both CB-ERCP using "DR" protocol ($U=908$, $p < 0.001$) and CB-ERCP using the "DR care" protocol ($U=3823$, $p < 0.001$). When comparing DAP from CB-ERCP using "DR" protocol with CB-ERCP using "DR Care" we observed that the total DAP for CB-ERCP using "DR" protocol resulted in significantly higher radiation doses than procedures utilizing "DR Care" protocol ($U = 123$, $p = 0.022$). For CB-ERCP with "DR" protocol the total DAP was median 48.9 $Gycm^2$, for CB-ERCP with "DR Care" 19.7 $Gycm^2$ and for conventional ERCP 6.52 $Gycm^2$. As illustratred in Figure 16, when we compared the DAP values that continuous fluoroscopic imaging added during the different exposure protocols we observed that fluoroscopy contribution to DAP during CB-ERCP was higher (Conventional ERCP fluoroscopy median DAP 5.52 $Gycm^2$, CB ERCP using "DR" protocol fluoroscopy median DAP 8.19 $Gycm^2$ and CB ERCP using "DR care" protocol median DAP 12.7 $Gycm^2$) than when conventional ERCP was utilized.



Figur 16 Fluoroscopy radiation doses categorized by exposure protocol

As seen in Figure 17, most conventional ERCP procedures resulted in a relatively low total DAP compared to CB-ERCP, but there were also several outliers with considerably higher DAP when conventional ERCP was utilized.

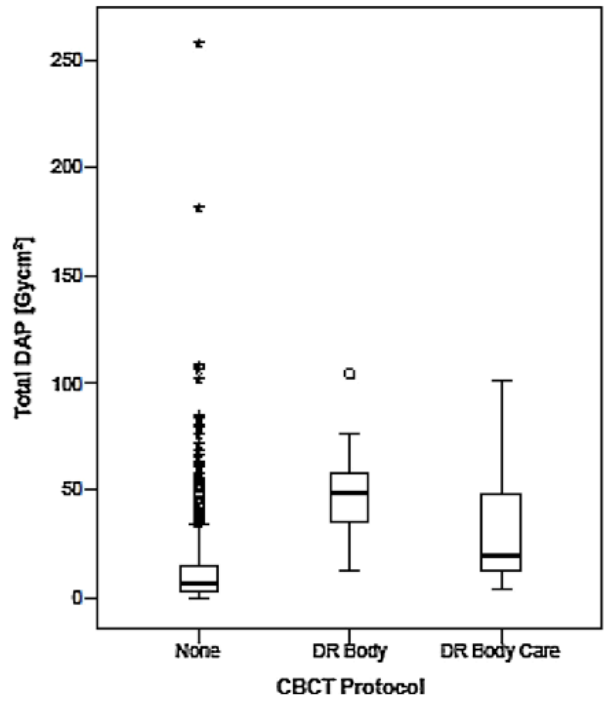


Figure 17 Total DAP for one procedure grouped by which exposure protocol utilized

DAP – Dose areas product

6 DISCUSSION

6.1 LIMITATIONS AND METHODOLOGICAL ASPECTS

New does not equal better, and advancements in technology will not always result in improved patient management. There are several examples throughout medical history of hastily introduced new technology that provided little benefit to patients, or even had a negative impact on overall patient outcome (162). Previous research in the field of this thesis is scarce and rarely provides robust evidence that can guide clinicians on how these new technologies should be applied in clinical practice. Possible explanations for the lack of high-quality studies scrutinizing emerging technology in the field of this thesis include the fast-paced evolution where older generations are rendered obsolete as soon as an upgraded version is developed, as well as built-in incentives in certain health systems where compensation is based on number of procedures instead of benefit to the patient. Prior to implementation of new technology in everyday clinical practice, it should be assessed within the framework of prospective studies and carefully compared to best current practice. However, in the very early phases of evaluation and exploration of new technology, it is justified to utilize study designs which can determine feasibility, generate hypotheses for subsequent prospective studies, and form the basis for future power calculations. The retrospective design of the studies included in this thesis is a general limitation which entails several sources of potential systematic errors:

Selection bias

Selection bias occurs when the study population differ from the population of interest in a systematic way (163). Study populations in this thesis were recruited from consecutive individuals in a tertiary care setting who were chosen for intervention based on a wide spectrum of prevailing clinical variables . For instance, in paper I and II the prior MDT recommendation that the patient undergo either SOPCP or SOPP instead of surgery could have been based on the patient's unfitness for surgery or preference among MDT attendees for one procedure over another. In paper III, cases representing a variety of different clinical scenarios were selected among eligible individuals to assess feasibility of bimodal ERCP. This decreases generalizability of the results to a wider population, and increases the risk of both under- and overestimating the results of the study. In paper IV the CB-ERCP technique was chosen in individuals where the endoscopist expected a clinical benefit, and differences

in radiation dose between the CB-ERCP group and the conventional ERCP group may represent selection bias.

Information bias

Information bias is derived from erroneous measurements of exposure and/or outcome, and can arise in several ways (163). In paper I and II the investigator had access to all clinical information when data regarding outcome after exposure was collected. There is a substantial risk of observer bias (an example of information bias) as a result of this, and especially in paper I the clinical and therapeutic yield of SOPCP may have been overestimated as a consequence. In contrast, in paper II we used prospective data from the Gallriks registry, where data on outcomes were entered by an independent assessor, which in turn decreases the risk of information bias. The grading system used in paper I to evaluate the impact of SOPCP on patient management was created anew due to a lack of similar instruments in the literature. The reliability and validity of this instrument remains to be determined in future studies and until then, this instrument should be used with awareness of the risks of information bias.

Confounding

When a researcher tries to link an exposure to an outcome, but instead assesses the effect of a third factor, this is known as confounding (163). In papers I and II SOPCP and SOPP was on occasion performed together with an additional intervention (for instance sphincterotomy, EUS, or confocal laser endomicroscopy), introducing the possibility that measured/reported outcomes might have been wrongly attributed to the SOPCP and SOPP procedure. In paper II we attempted to address plausible confounders with a multivariate analysis, but even this attempt at controlling for confounders cannot completely rule out all possibility of confounder interference.

6.2 DIAGNOSTIC AND THERAPEUTIC YIELD OF SOPCP

Chen et al. (77) explored and conducted the first clinical trials of the fiberoptic Spyglass® system in 2006. Since then, numerous groups have reported on their initial experiences with this technique, but most previous studies have focused mainly on aspects of procedural and technical success (87, 92, 107, 164-166). While this is important and note-worthy, it contributes little to our understanding of the final impact of SOPCP on patient management. In paper I, with the largest SOPCP study population to date, we attempted to assess the diagnostic and therapeutic yield of this procedure by evaluating how each procedure ultimately affected patient management and the final MDT decision. Even though the study

design and the novel assessment scale used entails methodological limitations and introduces several sources of bias we believe this approach, when validated in future studies, may contribute to the understanding of SOPCPs future role in patient management.

The treatment of 'difficult' bile duct stones, when biliary ducts cannot be cleared with conventional methods, is an increasingly used therapeutic indication for SOPCP. A meta-analysis of the overall performance of several different peroral cholangioscope platforms found that bile duct stones were cleared in 88% of the cases(100). In paper I, the indication of 'difficult' bile duct stones constituted 16% of all cases and SOPCP's therapeutic value was assessed as high (grade 3–4) in 79% of these. The findings that SOPCP is a valuable complementary tool in the management of 'difficult' bile duct stones is consistent with previous studies (14, 30).

Despite recent contradictory results regarding the usefulness of SOPCP in the work-up of indeterminate strictures (84), SOPCP is increasingly used as a complementary tool when conventional methods are unable to establish a diagnosis. SOPCP's sensitivity in diagnosing indeterminate strictures with visual impression alone have been reported to be 85%-90% in two meta-analyses, and the specificity of miniaturized forceps biopsies used with SOPCP have been reported to be up to 98%(167, 168). Investigation of indeterminate strictures in non-PSC patients and PSC patients was the most common indication for SOPCP in paper I. In 56% of patients with indeterminate strictures in cases with PSC and in 57% of patients with indeterminate strictures without PSC the diagnostic value of SOPCP was assessed as high (grade 3-4). The diagnostic yield of SOPCP in indeterminate strictures in paper I was somewhat less than expected. This might in part be attributed to the fact that in truly benign strictures the outcome of SOPCP (with or without histology) is not considered conclusive in clinical practice, and further surveillance or additional investigations are often deemed necessary. In chronic pancreatitis, which was the indication for undergoing SOPCP in 20 patients in paper I, the therapeutic value of SOPCP was assessed as poor (grade 1-2) in 55% of cases. Although several previous studies reported on the high level of technical success regarding stone clearance in chronic pancreatitis (108, 169) the comparably low clinical yield in our study may be reflect a general inattentiveness to the symptoms and follow up of patients in this group. In cases where SOPCP was used as a complementary instrument to determine further management of patients with suspected IPMNs, the clinical yield of SOPCP was assessed as grade 3 and 4 in 66%. Similar observations regarding the beneficial role of SOPCP in the work-up of IPMN has been reported in several (102, 170) studies. The high rate of adverse events (20%) in our pancreatoscopy group, however, cautions against

indiscriminate use of this new technology in the pancreatic duct, and mandates further investigation. The SOPCP system used in paper I is now considered historical and has since then been replaced by newer SOPCP generations with incremental improved visualization and operator control. Future studies may clarify if these technological advancements result in improved patient management and outcomes.

6.3 SOPCP, SOPP AND ADVERSE EVENTS

Previous studies on the use of SOPCP have focused primarily on technical success, with adverse events merely concurrently reported on as incidentally observed. The risk factors for post-ERCP pancreatitis are well studied (47, 161), but this knowledge is not directly transferable to SOPCP as major differences exist in both indication and technique between the procedures. Although individual risk factors such as high intraluminal pressure of irrigation fluid and small calibre MPD has been suggested from earlier anecdotal reports, our current understanding about specific risk factors for PPP after SOPP is insufficient. In paper I, where SOPP emerged as an individual risk factor for PPP, a considerable proportion of the PPP cases had a non-dilated main pancreatic duct. In paper II, which to our knowledge is the first study to investigate patient-related risk factors identified in preprocedural imaging for PPP following SOPP, we suggest that findings in preprocedural imaging may be useful to risk stratify patients before undergoing SOPP. In paper II we furthermore present a higher total incidence (23%) of PPP compared to previously conducted studies. A strength of paper II is that we used prospectively collected data on adverse events from a large validated national quality register, which reduces the risk of underdiagnosing adverse events, including PPP. Most of the PPP reported in paper II are classified as mild or moderate (17%) according to Cotton et al. (44), but 3 (4.6%) severe and one fatal outcome emphasizes the importance of improving our knowledge of the risk factors for PPP. The main finding of our paper II is that we identified a high ratio between pancreatic gland thickness and MPD in the body of pancreas as an important risk factor for PPP and that this association maintains after we adjusted for plausible confounders including chronic pancreatitis in a multivariate analysis. Furthermore, a gland/MPD ratio in the body of pancreas above 6 carries a 3-fold increase in risk (30% vs 10%) for PPP compared to a ratio below 6.

Chronic pancreatitis has been suggested as a protective factor against PEP in several studies investigating adverse events after ERCP (47, 171, 172). A plausible mechanism behind this decreased risk is the morphological and physiological alterations that occurs over time. A pancreatic gland with a wider MPD and atrophic parenchyma may be less susceptible to the trauma of ERCP and SOPP. MPD dilatation and atrophy of the pancreatic parenchyma are

also common findings in other diseases affecting the pancreatic gland and these conditions are notoriously difficult to distinguish both clinically and radiologically. These morphological changes can also be seen in clinical scenarios such as older age, a fatty pancreas or premalignant conditions (including MD-IPMN). In addition, ductal and parenchymal changes may be discrete in patients with early chronic pancreatitis. In our multivariate analysis, the association between the gland/MPD ratio in the body of pancreas and PPP remained after adjustement for CP as a confounding variable. The mechanism behind PPP after SOPP is most likely multifactorial and includes patient- and procedure-related factors, most of which are yet unknown. A large gland/MPD ratio, i.e. a voluminous pancreatic gland with a small diameter MPD, probably represents a gland most responsive to the tissue trauma introduced by SOPP, and thus highly capable of initiating an inflammation cascade which ultimately leads to PPP. We suggest that the gland/MPD ratio, which in our opinion is simple to measure and easily reproduced, can be used as a clinical tool in risk stratification for the development of PPP after SOPP, regardless of the patient's medical history.

Paper II has several limitations, of which a relatively small study population eligible for analysis is one of the most important. In an attempt to reduce the risk of bias, we excluded all non-index procedures and all procedures where preprocedural imaging was older than 6 months. This latter time limit was based on the assumption that a prolonged interval allowed for disease progression which could affect the morphology of the pancreatic gland and MPD at the time of intervention. One solution to this methodological problem may be to perform relevant measurements based on intraprocedural images, i.e. the fluoroscopy images. However, in such a setting the possibility of measuring gland thickness is lost and other sources of systematic errors would be introduced (such as image magnification effects and issues related to lack of standardized projections in fluoroscopic imaging). In our study, we chose to characterize pancreatic gland and MPD morphology based on the consensus interpretations of preprocedural cross-sectional imaging by two senior radiologists.

The case mix regarding indication for SOPP in our paper II study population introduces confounding issues which we attempted to address in our multivariate analysis model. The indication ‘IPMN’ constituted 68% of cases, and the indication ‘therapeutic intent in CP’ constituted 29% of cases. This case mix resembles, in our opinion, real clinical scenarios and likely increases the generalizability of our results.

6.4 NEW IMAGING TECHNIQUES AND ERCP

Emerging imaging techniques, such as cone beam computerized tomography and image fusion techniques, have recently seen widespread adoption in other image-guided disciplines where they are increasingly viewed as valuable tools (173, 174). However, as technical adjuncts to ERCP these imaging techniques are largely unexplored. The reason for this latency in image-guided interventions in the biliopancreatic ductal system is not obvious. It might be attributed to the fact that advanced endoscopic procedures such as ERCP are mainly performed by non-radiologist clinicians, where aspects of the imaging component of the procedure would not be emphasized or included in training.

Paper III represents the first report on bimodal ERCP, and here we described the feasibility and potential clinical yield of preprocedural 3D MRI datasets fused with the live 2D fluoroscopic imaging used in conventional ERCP. In this study, the bimodal ERCP technique was technically feasible in all 13 patients and good bimodal images were acquired in 85%. Additionally, in 77% of the cases bimodal ERCP assisted in visualization of the lesion of interest, and in 62% of the cases it aided in understanding 3D ductal anatomy, indicating potential clinical value. The image co-registration process added little additional radiation (mean 1.12Gycm2) to total procedure radiation dose (mean 22.7Gycm2) and no injection of contrast media was utilized during this initial phase of bimodal ERCP. Although our results are not sufficient to support the hypothesis that this bimodal technique can reduce total radiation dose, total procedure time or total contrast volume in ERCP, there are an increasing number of observations regarding other image guided procedures that the utilization of this bimodal 3D road map facilitates procedures with increasing complexity while keeping the radiation dose, procedure time and contrast usage unchanged or even reduced (140, 155, 175, 176).

In patients with biliopancreatic ductal disconnect, contrast extravasation from ductal leak can make it impossible to fill the duct upstream of the lesion. The ability of bimodal ERCP to visualize non-contrast filled ducts may in this clinical setting aid in traversing the lesion with a guidewire, for subsequent placement of a therapeutic endoprothesis. This concept was demonstrated in paper III, where the bimodal technique aided in understanding 3D ductal anatomy in a patient with biliary ductal disconnect. Furthermore, during evaluation and treatment of biliary strictures, the 3D roadmap provided by bimodal ERCP has the potential, independent of contrast opacification, to visualize both the lateral and anteroposterior orientation of a duct proximal to a stricture, and additionally give information about periductal soft tissue lesions that are not visible or accessible with conventional ERCP.

Whether these technical advantages increase the clinical yield of ERCP in the management of indeterminate biliary strictures remains to be better defined, but in paper III we observed that the bimodal technique aided in understanding 3D anatomy in 75% of patients undergoing the procedure for stricture evaluation or therapy. These initial promising results warrants further study in future larger patient populations.

A technical limitation with the bimodal imaging technique presented in paper III relates to misalignment issues, i.e. overlay mismatch between the static co-registered MRI derived image and the conventional fluoroscopic image which represent dynamic tissue prone to displacement by insufflated air and the traction from the duodenoscope. When targeting the intrahepatic ducts, alignment of co-MRCP and ERCP images in the frontal, sagittal, and transverse planes was correct in 77% of cases, whereas less fixed extrahepatic biliary ducts were commonly misaligned during bimodal ERCP. In the two patients where the main pancreatic duct was the target, overlay misalignment also proved a major challenge. Future updates of the software utilized in the co-registration process may alleviate these issues of misalignment. Until then we consider bimodal ERCP as a promising adjunct tool when targeting the intrahepatic biliary ducts.

CB-ERCP utilizes a rotating c-arm to generate 3D images of the biliopancreatic ducts, and has previously been described by Weigt et al. (141) in a case series of six patients. Other than this publication it is essentially unexplored as an adjunct to ERCP. Regarding aspects of radiation safety, Weight and colleagues concluded that radiation doses in CB-ERCP procedures were similar to other advanced biliary interventional procedures and suggested that future use of this novel technology may result in lower total radiation doses. This hypothesis is based on the idea that the necessity for continuous conventional intraprocedural imaging is reduced when CB-ERCP is applied.

In paper IV, we compared radiation dose in 42 CB-ERCP procedures, using two different exposure protocols, with 728 conventional ERCP procedures. We observed that conventional ERCP resulted in lower total median radiation dose (6.5 Gycm2) regardless of which CB-ERCP exposure protocol was used (DR 48.9 Gycm2 and DR care 19.7 Gycm2). Fluoroscopy contribution to total DAP was also higher when CB-ERCP was utilized, which might reflect an increased clinical complexity among CB-ERCP cases included in this retrospective study. During the course of the study we observed a learning curve regarding utilization of the two different CB-ERCP exposure protocols. The low dose CB-ERCP exposure protocol(DR care) was developed anew in cooperation with an application specialist and we discovered, early in the study period, that this protocol was sufficient for intraprocedural guidance. Subsequently

the higher dose standard vendor protocol (DR) was disused. The median DAP for the acquisition of a cone beam volume in paper IV using 'DR care' was 5.1 Gycm2. In the context of reported total radiation doses for conventional ERCP, ranging between 8-333 Gycm2 as reported by ESGE, a dose of 5.1 Gycm2 may be considered low (177). As an adjunct technique to percutaneous transhepatic cholangiography and endovascular interventional procedures, several studies report on the capabilities of cone beam assistance to provide enhanced intraprocedural guidance and immediate post-procedural evaluation of performed therapy (141, 143, 178-180). Future studies may clarify whether this also applies to cone beam as an adjunct to ERCP.

7 CONCLUSIONS

The following conclusions are supported by the results in this thesis:

- SOPCP has a high impact on management of patients with complex cholelithiasis, indeterminate biliary strictures and pancreatic cystic lesions in a tertiary care setting, but the procedure contributes to a considerable risk of adverse events.

- There is an association between the pancreatic gland thickness and MPD diameter in the pancreatic body with the risk of developing PPP after SOPP.

- Bimodal ERCP is feasible and can aid in understanding biliary anatomy and visualizing the lesion of interest. Its future area of use may lie in the assessment and treatment of complex intrahepatic biliary disease.

- Cone beam asssisted ERCP procedures are associated with higher total radiation doses than conventional ERCP procedures, but it is possible to decrease radiation doses to acceptable levels with adjustments of exposure protocols. These adjustments do not compromise the capabilities of cone beam ERCP to provide enhanced intraprocedural guidance.

8 FUTURE PERSPECTIVES

While working on these papers, we have gained an increasing awareness of the capabilities of new imaging techniques as an adjunct to ERCP. We imagine that these technologies will become important tools in future endoscopic management of patients with biliopancreatic disorders. Some of the potential future areas of use that needs to be assessed includes:

- Assesment of indeterminate strictures – will it be possible to further characterize biliary stricture morphology using CB-ERCP or bimodal ERCP which also gives information on periductal soft tissue? If intravenous contrast medium is used in combination with intraductal contrast medium during CB-ERCP, can periductal vascularisation patterns be visualized and aid in the determination of the stricture origin? Will it add value in the evaluation of strictures in PSC patients? Analogous to CT colonography, can you obtain images of the bile ducts with high diagnostic value with the CB-ERCP technique if you inflate the ducts with air/carbon dioxide?
- Bimodal ERCP allows for preprocedural planning in collaboration with a dedicated radiologist who can characterize and mark areas of interest in the bimodal image used for intraprocedural guidance. May this result in increased accuracy of tissue and cytological yield?
- Will the enhanced intraprocedural guidance that bimodal ERCP and CB-ERCP offers increase procedural success? Reduce the need for continuus fluoroscopic imaging and thus reduce total radiation dose? Can bimodal ERCP alleviate the need for radiation in pregnant women?
- CB-ERCP allows for detailed 3D characterization of biliary anatomy with higher spatial resolution than MRI – is there a role for CB-ERCP in the preoperative planning phase of liver surgery?
- In the endoscopic treatment of malignant biliary strictures with radiofrequency ablation - will CB-ERCP capability to immediately characterize the post-treatment effect in periductal tissue increase therapeutic yield?

Regarding miniendoscopes, SOPCP is increasingly used and regarded as valuable tools in the treatment of complex cholelithiasis and in the management of indeterminate biliary strictures, but its role in the management of pancreatic disorders has not yet been established. Uncertainties regarding safety aspects might be one explanation for this, and future studies

are needed to establish patient- and procedure-related risk factors to better clarify which patients benefit from this procedure.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Det kan ofta vara utmanande att undersöka och behandla sjukdomstillstånd i leverns och bukspottskörtelns gångsystem. Dessa gångsystem är otillgängligt belägna djupt inne i kroppen och kan inte enkelt nås för närmare utredning eller behandling. Sjukdomstillstånden i dessa gångsystem inbegriper allt från ofarliga förändringar som inte ger några besvär till mycket aggressiva och svårbehandlade tumörformer. Dessa olika tillstånd kan vara svåra att särskilja från varandra, framför allt under tidiga delar av sjukdomsförloppet. ERCP (endoskopisk retrograd kolangiopankreatografi) är en bildstyrd minimalinvasiv procedur som används både vid utredning men framförallt vid behandling av sjukdomstillstånd i leverns och bukspottskörtelns gångsystem. Vid ERCP för man in ett slangliknande instrument (endoskop) genom munnen ned till gångsystemens mynningar som är belägna i tolvfingertarmen. ERCP-instrumentet har en sidoblickande kamera och en arbetskanal som används för att föra tunnare instrument in i gångsystemen för vidare utredning eller behandling. Figur 1 på sida 3 visar en schematisk framställning av ERCP-tekniken. För att åskådliggöra gångsystemen och få vägledning under proceduren, ingjuter man kontrastvätska i gångarna och framställer bilder av dessa med hjälp av röntgenstrålar.

ERCP har visat sig vara en mycket värdefull teknik vid handläggning av flera sjukdomstillstånd i leverns och bukspottskörtelns gångsystem, men den är också förenad med flera begränsningar: 1) När ERCP används för att utreda misstänkta tumörtillstånd har tekniken en begränsad förmåga både att upptäcka tumörförändringar och att bidra med tillförlitliga vävnadsprover för att avgöra om dessa misstänkta tumörförändringar är godartade eller elakartade. 2) De röntgenbilder som används för vägledning vid ERCP visar inte insidan av gångsystemen eller den vävnad som finns utanför. Bilderna återspeglar inte heller gångsystemens tredimensionella natur. 3) ERCP medför flera risker för patienten varav den mest fruktade komplikationen är bukspottskörtelinflammation orsakat av själva ingreppet. Även risker för både patient och personal som är relaterade till de röntgenstrålar som används vid bildframställning behöver beaktas när ingreppet utförs.

De senaste decennierna har det skett en snabb teknikutveckling som teoretiskt skulle kunna bidra till att övervinna några av dessa begränsningar. Bland annat har tunna miniendoskop utvecklats, som ger möjlighet till att under ögats kontroll inspektera insidan av gångsystemen, ta riktade vävnadsprover från tumörsuspekta förändringar och utföra behandling. En schematisk framställning av ett miniendoskop, som förts in i bukspottskörtelns gångsystem

via ERCP-instrumentets arbetskanal kan ses i Figur 2 på sida 8. Vidare har den röntgenutrustning som används för att framställa vägledande bilder utvecklats. Dessa nya röntgentekniker har visat lovvärda resultat när de används vid bildstyrd utredning och behandling av tillstånd i andra organsystem, men i samband med ERCP är de i princip outforskade. Vid bimodal ERCP länkas och sammanfogas informationsrika tredimensionella bilder med den konventionella röntgenbild som normalt används för vägledning vid ERCP. Tredimensionella bilder av leverns och bukspottskörtelns gångsystem med hög detaljrikedom kan också framställas med hjälp av en röntgenutrustning som roterar kring patienten under ERCP proceduren. För att se videoexempel på tredimensionella bilder vid ERCP som framställts med roterande röntgenutrustning följ qr länkarna i Figur 4 på sida 14.

Ovanstående tekniker utforskas i avhandlingens 4 delarbeten.

I delarbete I studerades 365 fall där miniendoskop använts tillsammans med ERCP vid Karolinska Universitetssjukhuset. Syftet med studien var att undersöka vilken betydelse miniendoskopitekniken hade vid handläggningen av ett flertal olika sjukdomstillstånd i leverns och bukspottskörtelns gångsystem. I de fall tekniken använts som led i en utredning av misstänkt tumörsjukdom, fastställdes värdet genom att gradera den påverkan ingreppet hade på det beslut angående vidare handläggning som fattades vid ett formellt möte, så kallad behandlingskonferens, där flera olika läkare deltog. I de fall tekniken använts för behandling, fastställdes värdet av tekniken genom att gradera den betydelse ingreppet hade i att lösa patientens problem. Det viktigaste resultatet av studien var att tekniken bedömdes ha ett stort värde vid behandling av besvärliga och svåråtkomliga stenar i de djupa gallvägarna, vid utredning av oklara förträngningar i gallvägarna och vid utredning där slembildande tumörer i bukspottskörteln misstänktes.

I delarbete II undersökte vi riskaspekter vid användandet av miniendoskop i bukspottskörtelns gångsystem. Det är känt att denna metod medför en risk för bukspottskörtelinflammation men vi vet mycket lite om varför vissa men inte andra drabbas. Syftet med denna studie, som innefattade 65 patienter, var att identifiera riskfaktorer för att utveckla bukspottskörtelinflammation efter proceduren. Tillsammans med 2 röntgenläkare granskade vi alla röntgenbilder av bukspottskörteln som tagits före ingreppet och letade efter gemensamma drag bland de patienter som drabbats av bukspottskörtelinflammation. Resultaten visade att en stor bukspottskörtel i kombination med en liten bukspottskörtelgång var förenad med en större risk att drabbas av bukspottskörtelinflammation. Denna information kan bidra till att vi i framtiden bättre kan väga förväntad nytta mot förväntad risk för varje enskild patient och undersökning.

I delarbete III undersökte vi en ny teknik som tidigare är outforskad i samband med ERCP. 13 patienter undersöktes med en bildfusioneringsteknik, där tidigare framtagna tredimensionella magnetkamerabilder länkades och sammanfogades med de röntgenbilder som normalt vägleder ERCPisten. Vi fann att denna teknik var möjlig att utföra hos alla patienter vi undersökte och att tekniken hjälpte till att bättre åskådliggöra gångsystemen och förändringar i dessa hos flertalet av patienterna. Tekniken förefaller vara mest lämpad för de organsystem som är fast fixerade i omgivande vävnad och största värdet med tekniken finns sannolikt då man undersöker eller behandlar de gångsystem som är belägna inuti levern.

I delarbete IV jämförde vi den mängd röntgenstrålning som alstrades vid ERCP där konventionell röntgenteknik användes med den som alstrades vid användandet av en roterande röntgenutrustning. Resultatet visade att användandet av en roterande röntgenutrustning medförde högre mängd röntgenstrålning, men att skillnaden minskade allteftersom som studien pågick i takt med att vi lärde oss hantera denna nya teknik på ett effektivare sätt.

De studier som presenteras i denna avhandling har sammanfattningsvis bidragit till en ökad kunskap och förståelse för vissa aspekter av flera av dessa nya tekniker som används i samband med ERCP.

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