From Department of Medicine, Huddinge - MedH
Karolinska Institutet, Stockholm, Sweden

ADVANCED TECHNIQUES IN ERCP

Alexander Waldthaler

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Advanced techniques in ERCP

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Alexander Waldthaler

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Principal Supervisor:
Professor Annika Bergquist
Karolinska Institutet
Department of Medicine
Division of Gastroenterology

Co-supervisor(s):
Professor Urban Arnelo
Department of Diagnostics and Intervention (DDI), Surgery, Umeå Universitet

Professor Johannes-Matthias Löhr
Karolinska Institutet
Department of Clinical Science, Intervention and Technology (CLINTEC)
Division of Surgery

MD Phd Martin Delle
Karolinska Institutet
Department of Clinical Science, Intervention and Technology (CLINTEC)
Division for Interventional Radiology

Opponent:
Professor Mark Ellrichmann
Christian-Albrechts-University zu Kiel
Department of Internal Medicine
Division of Gastroenterology

Examination Board:
Docent Gabriele Wurm Johansson
Lund University
Department of Gastroenterology, Malmö

Professor Peter Thelin Schmidt
Uppsala Universitet
Department of Clinical Sciences
Division of Gastroenterology/Hepatology

Docent Jacob Freedman
Karolinska Institutet
Department Clinical Sciences
Division of Surgery and Urology KI DS

“I left the catheter
inserted in the papilla and the scope on the side of the patient and
I run to the other side to make the x-ray picture.” – Nib Soehendra describing his first ERCP in 1970. Alone with the patient, after everyone had gone home.

Abstract

Endoscopic Retrograde Cholangiopancreatography (ERCP), first described over 50 years ago, has fundamentally remained unchanged. Despite the potential for technical and clinical innovations in the x-ray field, their implementation has progressed at a slow pace. ERCP is a common procedure that is both cost- and resource-intensive but there is a notable absence of tools to assist with scheduling, and the topic of ERCP duration remains largely unexplored. The technique of implanting multiple plastic stents side by side in the pancreatic duct has been well known for nearly 20 years, yet its role remains ambiguously defined. The 4 projects described in this thesis investigated clinically relevant yet scientifically insufficiently explored topics in ERCP with the goal of advancing the technique and improving clinical care.

In Studies I and II, we aimed to adapt the use of advanced imaging techniques for ERCP. Study I assessed radiation doses during ERCP with cone beam computed tomography (CBCT) and discussed lessons learned from early clinical experiences with this technique. We showed that, although CBCT requires more radiation, doses were moderate, and highlighted the importance of appropriate case selection. Study II is the first-ever description of image fusion technique used during ERCP which proved feasible and helpful in most cases.

In Study III, we created and validated the first specific tool for estimating ERCP duration using large datasets from a national database. A simple addition score achieved estimation of the expected ERCP duration with a mean absolute error of 17 min.

Study IV focused on treating pain in chronic pancreatitis with multiple plastic stents in the pancreatic duct. We demonstrated that ERCP with multiple plastic stents is safe and effective for pain relief in patients with co-morbidities in which the risk of standard treatment with surgical resection of the pancreatic head is high. However, our results also highlighted that pain relapse is common in the long-term.

Our studies demonstrate that an open-minded approach to established techniques might lead to new knowledge and could help paving the way for broader clinical use of advanced ERCP techniques in the future.

List of scientific papers

I. **Radiation dose in cone beam CT guided ERCP**

Alexander Waldthaler, Marcus Reuterwall Hansson, Urban Arnelo, Nils Kadesjö

European Journal of Radiology 2020; 123.108789

II. **Bimodal ERCP, a new way of seeing things**

Marcus Reuterwall Hansson, Alexander Waldthaler, Jeanne Lubbe, Nils Kadesjö, Raffaella Pozzi Mucelli, Marco Del Chiaro, Johannes-Matthias Löhr, Urban Arnelo

Endoscopy International Open 2020; 8: E368-E376

III. **Predicting ERCP procedure time - the SWedish Estimation of ERCP Time (SWEET) tool**

Alexander Waldthaler, Anna Warnqvist, Josefine Waldthaler Miroslav Vujasinovic, Poya Ghorbani, Erik von Seth, Urban Arnelo, Johannes-Matthias Löhr, Annika Bergquist

Endoscopy 2025; 57: 31-40

IV. **Multiple plastic stents for treatment of obstructive chronic pancreatitis**

Alexander Waldthaler, Ebba Asplund, Paula Steiner, Laura Vossen Engblom, Erik von Seth, Miroslav Vujasinovic, Urban Arnelo, J.-Matthias Löhr, Annika Bergquist

Manuscript

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List of abbreviations

2D	2-dimensional
3D	3-dimensional
ASA	American Society of Anesthesiologists
ASGE	American Society for Gastrointestinal Endoscopy
BMI	Body mass index
CBCT	Cone beam computed tomography
CP	Chronic pancreatitis
CT	Computed tomography
DAP	Dose area product
ERCP	Endoscopic retrograde cholangio-pancreatography
ERP	Endoscopic retrograde pancreatography
ESGE	European Society for Gastrointestinal Endoscopy
ESWL	Extracorporeal shockwave lithotripsy
EUS	Endoscopic ultrasound
Fr	French / Charrière
$Gycm^2$	Gray-centimetres squared
IPMN	Intraductal papillary mucinous neoplasm
IQR	Interquartile range
KAP	Kerma area product
MAE	Mean absolute error
MRCP	Magnetic resonance cholangio-pancreatography
MRI	Magnetic resonance imaging
PEP	Post ERCP pancreatitis
PSC	Primary sclerosing cholangitis
RMSE	Root mean square error
SEMS	Self-expanding metal stents
SOC	Single operator cholangioscopy

SWEET	Swedish Estimation of ERCP Time
UEG	United European Gastroenterology

1 Introduction

Endoscopic retrograde cholangio-pancreatography (ERCP) was first described by William McCune in 1968, utilizing a working tract taped to a fiberoptic endoscope (Figure 1), a catheter, standard x-ray equipment, and contrast medium [1]. The first endoscopic cleavage of the sphincter of Oddi in 1974 opened not only the access to the bile duct, but to a new area of interventions [2]. First, the main therapeutic intervention was extraction of bile duct stones [3], and tissue acquisition was initially performed with brush cytology in 1975 [4, 5]. Despite significant advancements in various aspects of this interventional procedure, its core method has remained largely unchanged over the decades. The procedure still involves placing the patient on an x-ray table, intubating the duodenum with a side view endoscope, using a device to inject iodine-based contrast into the pancreatic or biliary duct, and capturing a 2-dimensional (2-D) x-ray image of the ductal filling, even if image quality has improved dramatically (Figure 2).

Over time, numerous alternative imaging methods, such as computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI), have become routine in clinical practice, largely replacing traditional 2-D x-ray imaging. As these alternative imaging methods provide precise information, it is no longer necessary to contrast-fill or even access the pancreatic duct for diagnostic purposes. For instance, the "double duct sign" in ERCP - a classic pathognomonic diagnostic criterion for pancreatic cancer characterized by significant dilation of both the pancreatic and biliary ducts – is nowadays rarely observable as the pancreatic duct is no longer routinely filled with contrast to avoid complications [6].

These changes have led to a new paradigm, transforming ERCP from a primarily diagnostic procedure to its current role as a therapeutic intervention with a limited indication spectrum and a considerable risk of adverse events [6]. Around the turn of the millennium, ERCP lost most of its diagnostic purposes due to the rise of magnetic resonance cholangio-pancreatography (MRCP). However, it simultaneously gained interventional capabilities, leading to a continuous increase in the number of ERCPs performed [7, 8].

ERCP has become a collaborative intersection of gastroenterology, surgery, and radiology. Many consider it the highest-ranked endoscopic procedure due to its associated risks and the extensive knowledge and skills required in radiology, anatomy, and the use of various tools and alternative or rescue procedures. In

recent years, advances in 3-dimensional (3D) radiology, intraductal endoscopy, and endoscopic ultrasound (EUS) have expanded the possibilities of combining different imaging and therapeutic modalities in this field. These developments have led to changes in peri-interventional risks, the need for anaesthetic techniques, and extended procedure times [6, 9].

This project evaluates the implementation of advanced techniques in the field of ERCP. The research questions addressed are common, and most individuals working with ERCP, even at a non-academic level, should find them relatable. However, there is a notable lack of evidence based on high-quality data for all investigated topics. This PhD study aimed to expand the knowledge in these areas.

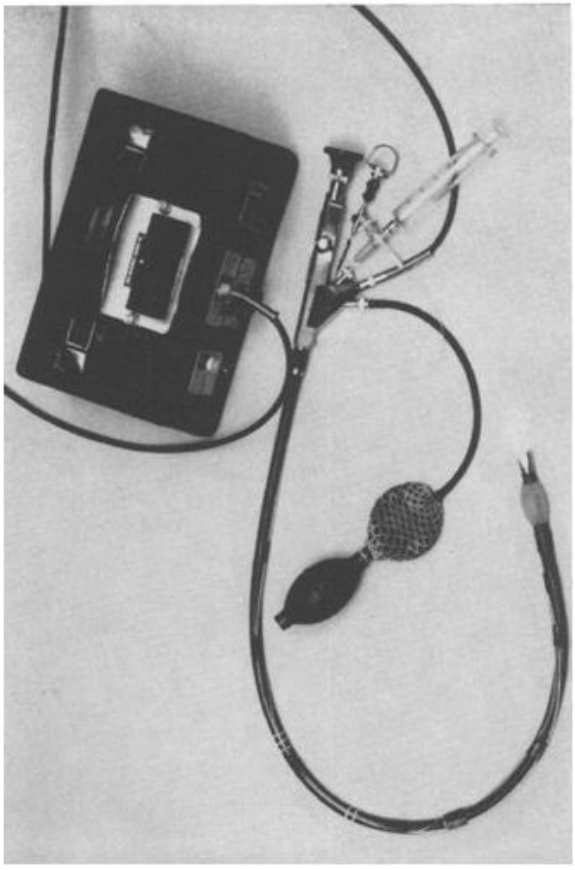

Figure 1. The Eder fiberduodenoscope used for the first ever ERCP. It was fitted with a balloon to bring the mucosa into focus and a channel for passage of a cannula.
Printed with permission [1]

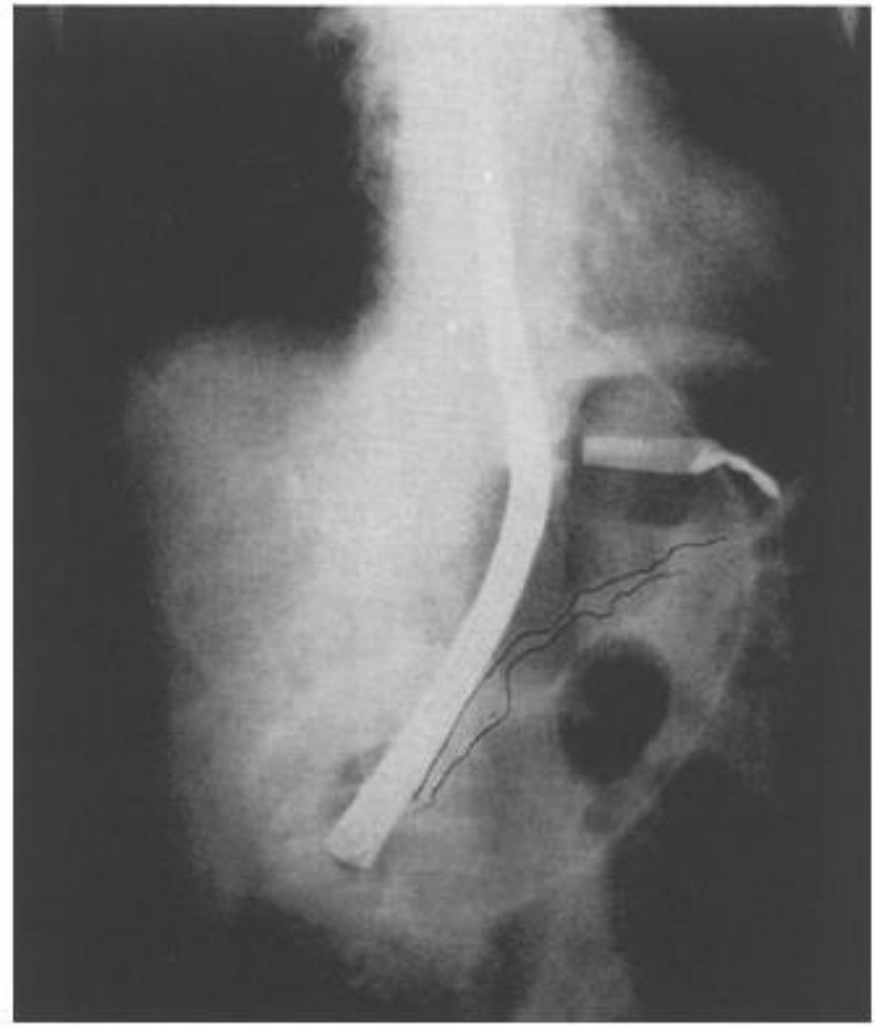

Figure 2. A picture from the original publication describing ERCP [1]. Since the pancreatic duct is barely visible, the authors chose to outline the contour. The authors already were conscious about the risk of causing pancreatitis, and therefore used at first only a 25% solution of Hypaque, as in this picture, later augmenting to 40% and even 50%.

Printed with permission [1]

1.1 Common indications for ERCP

Today, the most common indication for ERCP in Sweden is suspected or confirmed choledocholithiasis, followed by unclear jaundice and malignant diseases [10]. In other words, most ERCPs are performed because of some kind of obstruction in the bile duct. Already in the early days of ERCP, the workup of patients with jaundice was the main indication - with the sole purpose to obtain a cholangiogram/pancreatogram. The previously mentioned advent of advanced interventional techniques in ERCP led to changes in the types of ERCP performed, while the overall number of ERCP procedures as well as scientific publications on ERCP continuously increased [11, 12].

The 2025 ESGE guideline for workup of indeterminate bile duct strictures does still include ERCP, but its role has diminished from the primary method for imaging and later, tissue acquisition to a drainage intervention in selected cases [13]. Before ERCP is considered, imaging with MRI/MRCP, transabdominal ultrasound and laboratory workup including tumour markers are recommended. Only if drainage is needed, ERCP is performed as a therapeutic procedure, under which also brush cytology sampling in addition to EUS tissue acquisition, can be performed [13, 14]. Only if these measures are inconclusive, ERCP with single operator cholangioscopy (SOC) workup is warranted.

The indications for endoscopic retrograde pancreatography (i.e. ERP, which because of the established acronym ERCP will be called pancreatic ERCP in this thesis) have narrowed down to treatment of ductal obstructions in chronic pancreatitis (CP) and leakage problems after surgery or trauma, while other indications such as diagnostics, resection and ablation of neoplastic ductal or papillary lesions represent rare exceptions [15-17].

1.2 Chronic pancreatitis

The most common indication for pancreatic ERCP in Sweden is CP [10]. Due to its crucial role for paper IV, we especially emphasize it in this literature review. CP is an inflammatory condition of the pancreas, primarily caused by alcohol and smoking, that leads to a loss of function of the organ and pain [18]. Many patients with CP develop ductal obstructions due to calcifications, stones, or strictures of the pancreatic duct [19] Pain in CP varies in intensity and character over time [20] and most commonly is thought to be of obstructive type, i.e. due to an outflow obstruction of the pancreatic juice by a ductal stone or stricture [21]. The classic "burn out hypothesis" suggesting a slow spontaneous improvement of pain with

progressing disease is considered outdated due to contradictory studies and lack of supportive controlled trials [19, 22, 23]. Today, the initial approach to pain management in CP is analgetic medication [18]. However, timely intervention is recommended, particularly for younger patients and those in the initial stages, to achieve the best long-term outcomes for pain relief [24]. Interventions aimed at pancreatic drainage are most effective when performed early [18, 24-26].

1.2.1 Interventional treatment of chronic pancreatitis with ERCP

Pain is the main indication for treating pancreatic flow obstructions and there is no evidence that drainage procedures preserve pancreatic function [27]. Symptoms usually improve after obstruction removal, but some patients suffer from neuropathic pain unaffected by ductal disobstruction [26, 28, 29]. Primary stone extraction of pancreatic ductal stones in CP with ERCP has a low success rate (9-14%) and carries risks, most importantly, acute pancreatitis, but also bleeding and perforation as described in 1.3 Complications of ERCP [30-32]. An established concept for treatment of ductal obstructions with good technical success and clinical short-term effect is to place a plastic stent in the pancreatic duct [18, 27, 30]. Therefore, it is reasonable to consider endoscopic flow disobstruction via insertion of a single stent in the main pancreatic duct, followed by re-evaluation of symptoms [18]. In patients that feel an improvement of symptoms after stenting, a persistent favourable effect can be assumed if the ductal disobstruction is maintained in the long term [33].

A limitation of endoscopic treatment of CP is its long-term efficacy. A large retrospective multicentre study on over 1000 patients by Rösch and colleagues showed that about a quarter of patients eventually require surgery after endoscopic treatment. In an intention-to-treat analysis, endoscopic treatment was successful in only 65% of patients in the long term [27]. Other similar studies affirm these results, with good short term success rates for endoscopic treatment of painful CP, but relapses of symptoms during follow up after endoscopic treatment [21, 34, 35]. Of note, these studies describe treatment with a single plastic stent.

Extracorporeal shock wave lithotripsy (ESWL) as an adjunction or alternative to ERCP is described under 1.8 Alternatives to ERCP. Pancreatoscopy with direct lithotripsy is a newer technique for treating pancreatic stones. It involves passing a single-use endoscope through the duodenoscope into the pancreatic duct, where stones are fragmented using shock wave or laser technology [36-40]. This

method can address stones that are not visible on x-ray images or cannot be extracted endoscopically without prior fragmentation. A 2024 meta-analysis reported high ductal stone clearance (88%) and clinical success (90%), with a moderate adverse event rate (12%) [36] for this approach, but relapse of stones and/or symptoms are common problems during follow-up [39].

1.2.2 ERCP with multiple plastic stents in the pancreatic duct in chronic pancreatitis

Plastic stents are the stents of choice for the pancreatic duct [30]. The diameter of plastic stents is limited by the size of the endoscopes working channel. Stents with diameters of up to 12 Charrière (fr) are available; however, the maximum stent diameter commonly used is 10 fr [41, 42]. To overcome this limitation, multiple plastic stents (MPS) can be placed side by side, which, in contrast to biliary indications, in the pancreatic duct is preferred over self-expanding metal stents (SEMS) [30, 43]. While the benefits of SEMS for treatment of ductal obstructions in CP are comparable to MPS, complications in form of frequent stent dislocations and de novo ductal strictures caused by the stent have been reported [43-46].

Although the concept of MPS placement in the pancreatic duct in CP is mentioned in a multitude of guidelines there is usually no clear recommendation for it, but it is rather described as an additional or escalation method [16, 18, 30, 47, 48]. For example, the ESGE suggests "consideration of surgery or MPS side-by-side for symptomatic pancreatic duct strictures persisting beyond 1 year after the initial single plastic stenting, following multidisciplinary discussion" [30]. The first study reporting MPS placement in the pancreatic duct in 2006 described a single relatively large (6-10 mm) ballon dilatation using off label pneumatic pressure followed by insertion of multiple plastic stents [49]. All later publications on MPS in CP describe hydraulic dilatation [50-53]. Even the figures in a follow up publication to the very first study [49] show contrasted agent in the balloons and therefore indicate that pneumatic dilatation was abandoned also by this group [54], even if not stated explicitly. In the limited existing literature, placement of MPS in the pancreatic duct leads to pain improvement in75-84% [49, 50, 52] and stricture resolution in 89.6% of cases [54]. Relapse of pain, stricture or both after stent extraction is common and described to occur in 10.5% [49], 22% [52], 25.6% [54] and (37%)[50] of patients, respectively. Differences in the results might be attributable to variations in methodology and follow-up time. For example, the main conclusion of the study by Papalavrentios and colleagues [50] is that pancreatic ERCP with a single stent is associated with better clinical outcome

compared to treatment with exclusively 2 stents during the stenting period. This study compares the pain response of 3 patient groups: A.) Single stent only B.) Single and double stent C.) Double stent only. Patients in group C had the most distinct CP features and received the most aggressive treatment in this retrospective study, thus indicating potential bias as no information on group allocation procedures was given. Studies comparing pancreatic MPS to surgery are reviewed separately in section 1.8.4.

1.3 Complications of ERCP

ERCP is associated with risk for several complications, among which post ERCP pancreatitis (PEP) is the most common serious complication occurring in approximately 3-10% of cases [55]. Risk factors for PEP include difficult cannulation, sphincter of Oddi dysfunction, a history of pancreatitis and primary sclerosing cholangitis (PSC) [6, 56]. In most procedures, where the aim is to cannulate the bile duct, the initial cannulation crucially determinates the risk for PEP. The 5-5-2 rule is a common threshold used during biliary cannulation of the papilla Vateri. It suggests that if it takes longer than 5 minutes to achieve biliary cannulation, if more than 5 attempts are made, or if more than 2 guidewire passages of the pancreatic duct occur, the risk of complications increases significantly [57]. The PEP risk varies also among morphological variants of the papilla, with small and protruding or pendulous papillae presenting the largest risk for post ERCP pancreatitis [58, 59]. Rectal administration of diclofenac or indomethacin is widely recommended for all patients immediately before ERCP to reduce the risk for PEP [6, 60, 61].

Other complications of ERCP include infections such as cholangitis and cholecystitis. The ESGE suggests antibiotic prophylaxis in cases of anticipated incomplete biliary drainage, severely immunocompromised patients, and when performing cholangioscopy for risk reduction [6]. Bleeding is another potential complication occurring in 0.3- 2 % of all ERCPs, often in relation to sphincterotomy. The risk of bleeding can be minimized by careful patient selection [62-64]. Perforation is a serious but less common complication with an incidence of about 0.1-0.6% [6, 63, 64].

1.4 Duration of ERCP

A basic ERCP is typically a short procedure performed with the patient in a prone or lateral position under sedation, requiring only the endoscopy staff [65, 66]. However, more complex interventions may take longer and necessitate intubation

and an anaesthesia team. While various scores and tools exist to predict ERCP difficulty [67, 68], probability to develop complications according to the course of the procedure [57, 69] and papilla morphology [58, 59], factors impacting the duration of ERCP have been only superficially explored. Mehta et al. reported a mean duration of 45.6 ± 30.1 minutes for 291 ERCPs performed between 2006-2008 [70]. Von Seth's study using Gallriks data found longer durations for PSC patients (51 ± 34 minutes) compared to non-PSC patients (35 ± 22 minutes) [56].

1.5 Radiation exposure in ERCP

Radiation exposure during ERCP is a critical issue due to its association with cancer development and the risk of acute skin damage, ranging from erythema to hair loss and tissue necrosis [71, 72]. Both occupational and patient radiation doses have gained importance, with progress seen in both areas [73]. Table 1 displays patient ERCP radiation doses with descending publication year. Besides large variation a decreasing trend over time is visible. In Japan, the diagnostic national reference level of dose area products (DAP) for ERCP is 26 Gray-centimetres squared ($Gycm^2$) for diagnostic and 36 $Gycm^2$ for therapeutic ERCPs, based on national data collected in 2015 [74]. Updated data from 2019/2020 shows an average ERCP DAP of 16 $Gycm^2$ [75].

A 2024 multicentre study revealed a concerning difference of radiation doses between study centres with an up to 50-fold increase in a single centre, which was attributed to potential disparities in dose optimization, radiation safety practices and x-ray equipment [76]. Compared to the other centres participating in the study, this centre had up to 5-fold longer fluoroscopy time, 35 times higher reference kerma area product (KAP) and 20 times the number of exposures. A difference in radiation dose was described according to ERCP complexity grading with both the H.O.U.S.E. and American Society for Gastrointestinal Endoscopy (ASGE) grading systems for ERCP complexity as well as procedure duration [67, 68, 76, 77]. Recently, a basic predictive score for high radiation exposure during ERCP has been published [78]. The wide variation in the way x-ray technique is applied in endoscopy is reflected in the ESGE guideline on radiation protection that quantifies common DAP during ERCP to 3-115 Gycm2 for diagnostic and 8-333 Gycm2 for therapeutic ERCP. Doses exceeding 300 $Gycm^2$ per procedure are considered high by the ESGE [79].

Table 1. Radiation doses in ERCP with descending publication year. [1]median [2] mean

First author	publication year	Type	DAP/KAP [Gycm²]
Kaasalainen [76]	2024	not specified	0.9 to 64.4 [1]
Varma [80]	2022	not specified	1.6-2.3 [1]
Hayashi [75]	2022	not specified	16 [1]
Del Olmo Martinez [81]	2021	not specified	2,06 [2]
Hayashi [82]	2018	therapeutic	18,1 [1]
Barakat [83]	2018	therapeutic intent	5,7-13,9 [1]
Saukko [84]	2018	mainly therapeutic	2,33 [2]
Hadjiconstanti [85]	2017	therapeutic	2,03 [2]
Tsapaki [86]	2016	therapeutic	16 [2]
Kruit [87]	2015	not specified	19,07 [1]
Liao [88]	2015	97% therapeutic	9,56 [1]
Olgar [89]	2009	therapeutic	69,8 [2]
Brambilla [90]	2004	not specified	28 [2]
Tsalafoutas [91]	2003	therapeutic	41,8 [2]
Buls [92]	2002	therapeutic	49.9 [2]; 39,0 [1]
Larkin [93]	2001	therapeutic	66,8 [2]

1.6 Radiation reduction in ERCP

The radiation dose differences between different centres in the earlier mentioned multicentre study [76] underscore the responsibility that lies with the personnel operating and working around the x-ray equipment. This includes monitoring doses, regularly comparing your centre's doses and practices to those of other centres, using x-rays judiciously, and understanding your machine settings to optimize radiation safety practice [16, 75, 94]. Radiation dose during ERCP can be reduced by simple measures, reflecting the relatively liberal and naïve use of radiation in ERCP. For example, a pilot study found that using a flashing light during active fluoroscopy reduced the radiation dose by about 15% [95]. A study using data obtained in Californian hospitals was able to cause a persisting reduction of total DAP in high (35%) and low (48%) volume ERCPists by showing them a 20-

minute-long educational video [83]. Still, it is likely that this reflects that in many parts of the world no special education is required for doctors to operate an x-ray system and the effect may not be as high among personnel highly trained in x-ray safety [96]. With increasing experience, interventionalists become more selective in determining which steps of ERCP require x-ray supervision, quicker at interpreting fluoroscopy images, and more efficient in reducing procedural fluoroscopy time [88, 97, 98]. Both lifetime experience as well as ERCP volume during the previous year influence an interventionalists x-ray use [83, 98]. Also radiopaque resistance affects x-ray dose and depends on non-modifiable factors (indication, patient's sex, size, and mass) and modifiable factors (patient or c-arm position) [76, 78, 80, 99].

1.7 Radiation-free ERCP

A major driver of radiation reduction and even radiation-free ERCP is pregnancy [79]. Physiological changes during pregnancy can contribute to the development or exacerbation of bile stone disease, and the clinical symptoms often require immediate attention, rather than being postponed until after pregnancy [100]. In part, the need for radiation can be replaced by direct visualization of the structure of interest with a camera via SOC [101]. This is of interest for treatment of biliary stones, where SOC can be used to visualize and potentially fragment intraductal stones [102]. Furthermore, aiding of orientation using percutaneous or endoscopic ultrasound have been described, but are not used as a standard approach today [103, 104].

1.8 Alternatives to ERCP

1.8.1 Magnetic resonance cholangio-pancreatography as alternative to ERCP

A major factor that influenced the development of ERCP towards an interventional procedure, as opposed to a diagnostic one, was the advent of magnetic resonance imaging (MRI). It became evident that a heavily T2-weighted MRI could produce images of the biliary and pancreatic ducts in a quality sufficient for most clinical needs [105]. With continuous improvements in image quality and considering that ERCP is an invasive procedure with notable peri-interventional risks, MRCP began to replace ERCP for diagnostic purposes regarding the biliary and pancreatic ductal systems [106].

As with most new procedures that emerge as alternatives to established options, the usefulness of MRCP was initially described in cases where ERCP, as the gold

standard, had failed [107, 108]. During the second half of the 1990s, numerous publications focused on the technical possibilities and requirements of MRCP [105, 107, 109, 110]. Around the millennial shift, the increasing availability and quality of MRCP began to significantly impact clinical practice and number of diagnostic ERCPs rapidly decreased as they were replaced by MRCP [12].

MRCP proved valuable in diagnosing conditions such as choledocholithiasis, pancreatic cancer, cholangiocarcinoma, CP, PSC, and many more [7, 106, 107, 111-113]. The evolving roles of MRCP and ERCP and their evaluation fuelled scientific research from 2000 to 2010, with only selected studies covered in this literature review [8, 111, 113, 114]. Endoscopic ultrasound (EUS) and MRCP are similarly effective in predicting choledocholithiasis and can be used complementary, according to local resources and expertise [115]. MRCP is not only less invasive and risky than ERCP, but also cost-effective [113, 116].

Multimodal approaches, including 3D diagnostic cholangiograms from MRCP, can enhance therapeutic ERCP planning by providing a better understanding of individual anatomy [7, 117]. In cases where ducts are completely obstructed and cannot be filled retrogradely, MRCP can provide additional information over a cholangiogram obtained via ERCP [118]. Imaging ducts in their natural filling state, rather than being pressure-filled retrogradely with an external medium, can result in certain differences in the ductal image [8]. The addition of negative oral contrast agents and secretin stimulation for assessing pancreatic flow dynamics and duodenal filling further expanded the capabilities of MRI [119, 120]. Gadolinium-based contrast agents allowed for better vascular imaging and differentiation of anatomical structures [121].

1.8.2 Endoscopic ultrasound as alternative to ERCP

EUS was invented already in the 1980s [122] and is not directly related to this thesis. Still, its gain in popularity and availability around the millennial shift might in part have caused x-ray techniques not to receive the same kind of attention in the field of interventional endoscopy as they did in other disciplines, even though technical advancements were ready to use [123]. During this golden age of hepatobiliary imaging development, numerous studies examined whether EUS or MRCP would replace ERCP and their cost-effectiveness in various settings [114, 116, 124-128], with equal or favourable results for the competitors of ERCP. Besides the diagnostic use of EUS, there has emerged also a therapeutic aspect. Extra-anatomical ductal drainage can be accomplished with EUS, if ductal access via

ERCP is not favourable or failed. In the field of biliary drainage in malignant diseases, this role is well established, especially since 3 randomized prospective trials showed non inferiority to ERCP in 2018 [129–131]. This led to broad recognition of the procedure and in 2022 a dedicated ESGE guideline for therapeutic EUS was published [132]. EUS can be seen as an equally effective and risky alternative to ERCP in malignant indications in experienced hands [129, 132, 133]. EUS guided biliary drainage is usually relatively quick and there is a very low risk for postinterventional acute pancreatitis, but especially in EUS guided choledocho-duodenostomy in combination with duodenal strictures, the longtime patency is limited [134]. For the pancreatic duct, this role is less well established and usually, EUS guided pancreatic duct drainage is considered if ERCP is not successful or possible [132, 135, 136]

1.8.3 Extracorporeal shockwave lithotripsy (ESWL)

ESWL fragments stones non-invasively and is often used for kidney stones but can also be applied to radiopaque pancreatic stones [31]. For a long time, based on the dogma that if stones are fragmented the fragments could cause a downstream impaction with worsening of ductal obstructions, ESWL in combination with ERCP was suggested. A 2016 meta-analysis reported 70% complete and 22% partial stone clearance after ESWL, with quality-of-life improvements in 88.2% of patients [137]. A Japanese survey found ESWL alone had a higher risk of early postoperative complications compared with ERCP (8% vs. 4.5%) [32]. Both ESGE and UEG in their latest guidelines recommend ESWL as a first-line interventional approach to ductal obstruction due to pancreatic stones, with ERCP reserved for radiolucent or smaller stones <5 mm [18, 30]. Studies comparing ESWL to direct intraductal stone fragmentation via pancreatoscopy show that direct lithotripsy requires fewer sessions to achieve stone clearance, but has a higher complication rate than ESWL, while stone recurrence rates are similar between the 2 approaches [37, 138].

1.8.4 Endoscopic vs. surgical treatment of chronic pancreatitis

Whether patients with painful CP should be treated endoscopically or surgically has been a hot topic for discussion during the last 20 years. Three randomized controlled trials comparing the effect of surgery and endoscopy in this patient group show superiority of surgery in terms of long-term symptom relief [51, 53, 139–142]. The discussion was kept alive probably in part due to the invasive nature

of pancreatic surgery, but also because the 2 earlier studies had severe limitations. The study by Petr Dite included 140 patients, of which only 72 consented to randomization [139]. Consequently, the results of the randomized arm were reported separately, but baseline characteristics and other outcomes, such as complications, were reported for the whole group. Patients in this study were treated with a single stent only and were not treated with ESWL. The second study was a prospective randomized trial in 39 patients comparing surgery and endoscopic treatment [51, 142]. The endoscopic treatment arm had a rather complex design, involving pancreatic stenting with single or multiple stents, depending on the number of previous ERCPs and impression of success on radiological appearance, which was also applied as criterion for termination of the endoscopic treatment. The study reported a better Izbicki pain score [28] and fewer interventions needed in the surgery group. The correspondence part of the following issue of the New England Journal of Medicine contained letters from the most famous protagonists from both the surgical and endoscopic side, commenting on the publication and the accompanying editorial [143]. In the editorial Grace Elta had discussed the question *"Is there a role for the endoscopic treatment of pain from chronic pancreatitis?"* and stated that endoscopic treatment "remains a reasonable treatment option, depending on patient preferences."[144], which was criticized as a backdoor to offer endoscopy as a first line treatment against the current evidence [143].

The main criticism towards the study by Cahen and colleagues was that patients were not treated with appropriate pancreatic stents, but biliary stents without side holes, only 9 patients were treated with MPS, the maximum number of simultaneously implanted stents was limited to 3, the stenting period was too short, balloon dilatation was performed only optional, resolution of strictures on radiologic studies was applied as the criteria for termination of endoscopic therapy, and only 16 out of 19 patients were treated with ESWL [143].

Despite all these criticisms, the body of evidence supporting that surgery is superior to ERCP treatment for long term outcomes has become accepted, at latest after publication of the ESCAPE trial, that faced less criticism [53]. In this randomized prospective study comparing ERCP and surgery, again the surgery group had better mid-term and long-term outcomes concerning Izbicki pain score with fewer interventions needed (1 vs 3 in the ERCP group). In an 8-year follow-up study, outcomes for surgery were still superior and patients who were converted to surgical therapy after unsuccessful endoscopic therapy had inferior

outcomes compared to patients that got surgery in first place [140]. In summary, surgery is more effective for pain relief, needs less reinterventions and is more cost effective and should therefore be preferred over ERCP in painful CP [51, 53, 139-142].

1.9 Cone beam computed tomography

Cone beam computed tomography (CBCT) is an x-ray method, in which a diverging, cone shaped x-ray beam rotates partially around the object of interest to generate a dataset that can be transformed computationally into a 3-D image with characteristics very similar to a regular computed tomography (CT) [145], in which a multidetector-row rotates completely around the patient [146]. CBCT has first become commercially available in the 1990s. This technique produces decent quality pictures, especially in high contrast settings such as the visualisation of bony structures or contrast medium. CBCT is frequently used in orthodontics, since devices are relatively small and affordable and perform well in the field of dental imaging [145, 146].

1.9.1 Cone beam computed tomography in interventional radiology

In cholangiography, the transition from 2 dimensional (2D) to 3D imaging involved rotational cinematography with dynamic 2D sequences from a rotating C-arm, allowing experienced interventionalists to mentally reconstruct 3D information [147]. Initial CBCT publications focused on the technical aspects of 3D image computation from multiple 2D cone beam images [148, 149]. Subsequent studies described the implementation of CBCT in interventional clinics [150, 151], enabling 3D reconstructions of cholangiograms and angiograms to be displayed on-screen, rather than relying solely on the interventionalist's perception [152]. There are dedicated machines for CBCT, but in recent years, most manufacturers have equipped their motor driven C-arms (Figure 3) with the ability to perform CBCT during angiography and ERCP. Early innovations in imaging techniques often came from radiologists, who are likely more accustomed to technical advancements. It took 15 years to adapt CBCT from imaging of contrast medium injected via percutaneous transhepatic cholangiography [152] to the first publication of imaging of the same contrast medium injected retrogradely via ERCP [153] and the vast majority of publication on interventional use of CBCT remains for angiographic purposes.

1.9.2 Cone beam computed tomography in ERCP

In 2015, Weigt and colleagues reported the first use of CBCT in a case series of 6 patients undergoing ERCP to create a 3-D cholangiogram for intraprocedural use [153]. In a later publication, the use of CBCT was described by the same group in addition to cholangioscopy on a single patient [154]. We are not aware of further publications about CBCT use in ERCP, besides the publication included in this PhD project focusing on radiation doses of CBCT in ERCP [155].

1.9.3 Radiation dose in CBCT

Data exists in abundance on the radiation doses for CBCT for other applications than ERCP [145, 156-167]. CBCT during interventions can be used for guidance in angiographic interventions and radiologically guided biopsies and certain structures of interest can be visualized adequately with the use of low radiations doses [145, 161, 163, 167]. Since there is no software available for specific use in ERCP, our centre partially adapted our x-ray parameters according to our needs and allow to perform CBCT in sufficient quality with a relatively low dose [155]. This might partially be because the contrast injected in the biliary system in high concentration is diluted only by the small intraductal bile volume circulating only at a very low speed. Still it is important to notice that radiation doses are not only dependent on settings, contrast density and distribution, but to a relevant extent also on patient-related factors, mainly body mass [145].

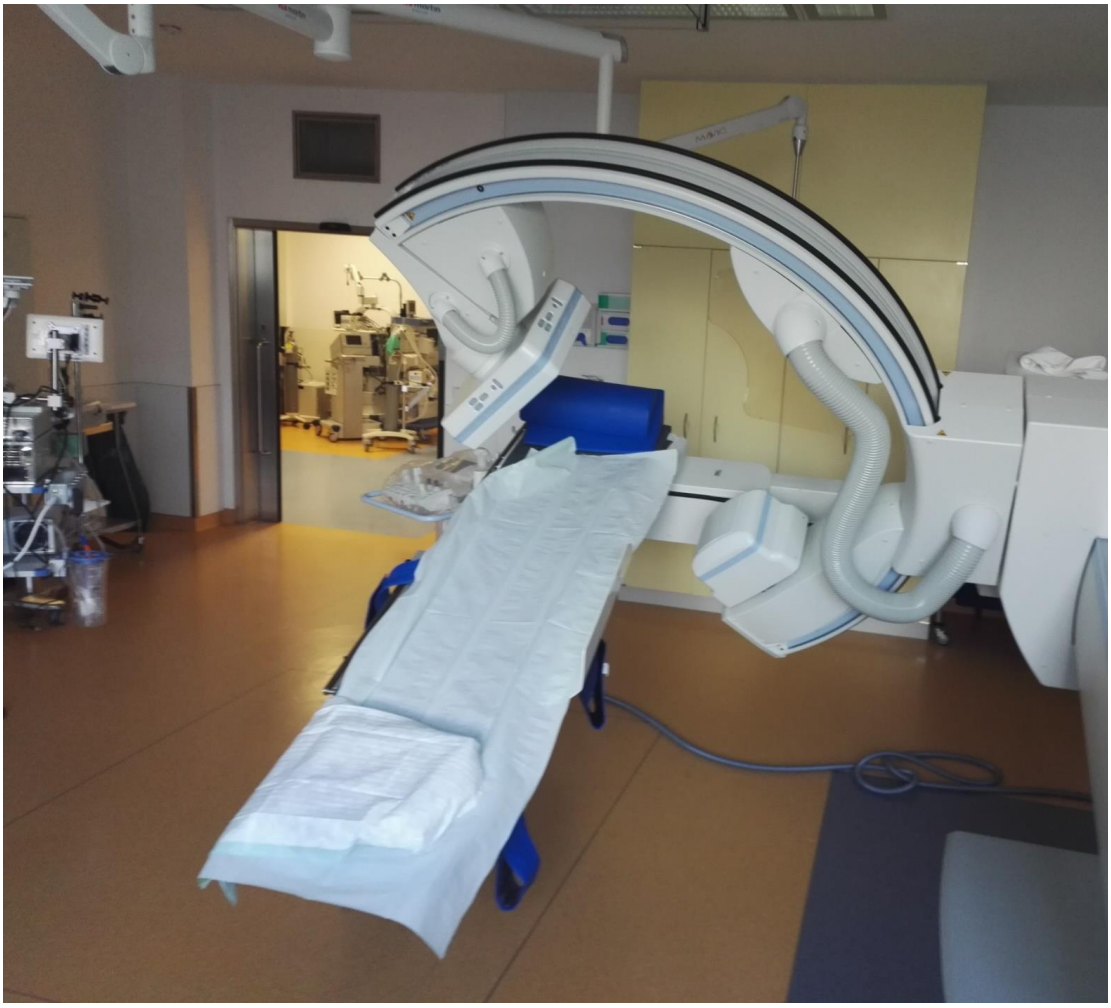

Figure 3. Modern wall mounted C-arm with possibility of cone beam computed tomography (CBCT) implementation (Siemens Artis Q™).

1.10 Image fusion in ERCP

The second technique for 3-D intraprocedural orientation besides CBCT discussed in this thesis is the use of pre-existing image data with image fusion. Like the use of CBCT in ERCP, the technique is not totally new. A multitude of publications exist on its use during different imaging procedures for both diagnostic as well as interventional-therapeutic measures on similar technical equipment and software as used for ERCP, just in different medical fields [168-171]. Existing literature on similar imaging requirements from radiological disciplines showed that using 3-D image fusion of pre-existing datasets can improve angiographic interventions by increasing technical success and reducing

procedure length, contrast media volume, and radiation dose for both the patient and the personnel [172-175]. To our knowledge, the publication included in this thesis was the first describing the use of image fusion procedures during ERCP so far [176]. Since then, Zhang et al. in 2023 published a study on 18 patients using 2D/3D registration of a CT image from which a 3D cholangiogram was isolated that was both 3D printed as well as used for co-registration on fluoroscopy [177]. A next step that we see developing in several surgical disciplines is co-registration of images to create an augmented reality view. For the use in ERCP on the videoendoscopic picture, to this point only the use in cadaveric and phantom scenarios are described [178].

1.11 The Gallriks register

The Swedish register for gallstone surgery and ERCP, Gallriks, accounts for most cholecystectomies and ERCP procedures performed in Sweden. Multiple studies on ERCP using data from the Gallriks register were conducted, on topics such as outcomes and safety measures [179-181], characteristics of PSC patients [56, 182], cholangioscopy [101, 183], risk reduction by rendezvous cannulation [184, 185], precut techniques [186], prophylactic pancreatic stenting [187], and antibiotic treatment [182, 183, 188].

2 Research aims

The general aim of this thesis was to explore under-studied yet clinically relevant areas within the field of ERCP with focus on technical and methodical innovations.

Paper I:

To assess the radiation doses in CBCT guided ERCP, compare it with conventional fluoroscopy guided ERCP and describe practical considerations when performing CBCT guided ERCP.

Paper II:

To explore feasibility of image fusion of 3D MRCP data and fluoroscopy for guidance during ERCP and investigate its potential clinical yield.

Paper III:

To identify patient- and procedure-related features of ERCP that influence its duration focusing on variables available prior to the procedure and create an estimation tool to predict the ERCP time based on these findings.

Paper IV:

To describe the efficacy of ERCP with MPS placed side-by-side for pain relief in highly selected patients with painful CP and ductal obstruction at a tertiary care centre.

3 Materials and methods

3.1 Ethical considerations

When we first gained access to x-ray equipment capable of CBCT, ethical approvals from the ethics committee Stockholm (2017/2294-31/1) and radiation safety board Karolinska University Hospital (K2017-5242) were obtained to perform a prospective randomized study comparing CBCT guided ERCP to conventional ERCP without limitation to certain clinical features. After exploring the technique deeper, we decided not to perform such a study because of ethical considerations. Instead, an amendment to the existing ethical approval (Dnr 2019-02109) was signed in and approved, in which data of patients we had deliberately exposed to a CBCT because of clinical necessity would be analysed retrospectively. To avoid exposing patients clinically not necessitating especially good x-ray quality to unnecessary high radiation doses, we accepted the introduction of potential selection bias to the groups. At the same time, the discussion about which patients could potentially profit both clinically and in overall radiation exposure from CBCT guided ERCP inspired the idea for paper III.

All studies were approved by the regional ethics committee of Stockholm County.

Paper I and II: Dnr 2017/2294-31/1, addition Dnr 2019-02109 and K2017-5242 radiation safety board Karolinska University Hospital;

Paper III: Dnr 2019–04786 and addition Dnr 2020-04480;

Paper IV: Dnr 2016/1571-31 and Dnr 2020-06525.

3.2 Paper I

3.2.1 Study population

The study population of this retrospective study consisted of patients who underwent classic fluoroscopy guided ERCP and CBCT-guided ERCP procedures at a tertiary care centre between February 2016 and June 2017. The study included automatically recorded DAP radiation doses from all patients that underwent ERCP during the study period. Data recorded included 728 conventional ERCPs and 42 CBCT-ERCPs.

3.2.2 Data collection and definitions

All procedures were conducted in a dedicated ERCP suite utilizing the Artis Q™ interventional x-ray system (Siemens Healthineers, Erlangen, Germany), equipped with a single-plane ceiling-mounted C-arm. The DAP is reported by the system. Before data recording, the accuracy of the DAP values was verified with measurements by dedicated radiation safety personnel using instruments calibrated to standards traceable to the Swedish secondary standard laboratory. In addition to the dose index, exposure and patient parameters were recorded for all examinations, such as exposure dose during the procedures, fluoroscopy duration, patient age, height and weight. Data was automatically transmitted as Radiation Dose Structured Reports (RDSR) DICOM objects to a dose monitoring server.

3.2.3 Statistics

Data were categorized on a per-examination basis as well as for each individual exposure or fluoroscopy series. Test examinations not involving patient exposures were excluded from the dataset, along with patient examinations that recorded zero radiation dose. All CBCT exposures were identified and grouped according to the exposure protocol. Corresponding patient examinations were also categorized based on the CBCT protocol used: 1. none, 2. "DR", 3. ""DR care"". Mann-Whitney U test was employed to assess the statistical significance of differences in radiation doses between the groups. A p-value of less than 0.05 was considered statistically significant. Descriptive statistics, including median, interquartile range (IQR), and range, were calculated for each group to summarize the distribution of radiation doses. Box plots were generated to visually represent the distribution and identify any potential outliers. Statistical analyses were performed using SPSS version 24.0.0.0 (International Business Machines Corporation, Armonk, New York).

3.3 Paper II

3.3.1 Study population and design

This retrospective observational study included data from 13 patients that underwent ERCP using 2D/3D image fusion at a single tertiary referral centre.

3.3.2 Data collection and definitions

Patient demographics included age, sex, American Society of Anesthesiologists' (ASA) functional classification, and the indication for ERCP. The time interval between the MRI used for 2D/3D fusion and the ERCP was obtained and whether ERCP with image fusion was technically feasible. Qualitative procedural parameters included image quality, aid in visualization, aid in understanding 3D ductal anatomy, aid in finding a favourable C-arm position, and both intra- and extrahepatic overlay misalignment. All recordings were made by 2 endoscopists, in case of discrepant results, the images were retrospectively reviewed by a 3rd senior endoscopist and evaluated again in consensus. Overlay misalignment in image fusion was evaluated using a custom-developed qualitative assessment scale. Radiation dose data including the DAP and fluoroscopy time were automatically archived as a Radiation Dose Structured Report DICOM object. Radiation dose used for the image fusion process was identified from the C-arm and table movements listed in the exposure log, combined with the total image co-registration time. Total procedure time, image co-registration time, and the total amount of contrast medium used were documented manually.

Image fusion was performed under general anaesthesia and breath-hold and is summarized in Figure 4. Fusion landmark lines typically using the spine and liver dome were manually drawn on 3D T1-weighted sequences using dedicated software (Syngo iGuide toolbox™; Siemens Healthcare, Erlangen, Germany). For ERCP, the landmarks were used in combination with the corresponding 3D T2-weighted MRCP images. The landmarks were overlayed with the corresponding anatomical structures in frontal and lateral fluoroscopic images and again, a dedicated software package (Syngo Inspace 3D-2D™; Siemens Healthcare, Erlangen, Germany). This results in the 3D MRI-derived cholangio-pancreatogram being assessable and available for overlay to the fluoroscopy view live from all angles during ERCP on the endoscopist's monitor. Any change in table position or C-arm angulation resulted in automatic adjustment of the co-MRCP to

correspond with the new fluoroscopic view, and virtually found optimal view angles could be translated into the C-arm position without the need of additional x-ray exposure. Fusion image quality was deemed "good" when both the co-MRCP and conventional fluoroscopic images of the biliopancreatic ductal system were clearly visible. If the co-registered MRCP revealed the lesion of interest with the conventional fluoroscopic image being native (i.e., not contrast-enhanced), bimodal ERCP was considered "an aid in visualizing the lesion of interest." Bimodal ERCP was classified as "an aid in understanding 3D ductal anatomy" if the co-MRCP provided information on ductal trajectory not comprehensible with conventional fluoroscopy. Absence of overlay misalignment was defined as the guidewire trajectory in a native fluoroscopic image and/or contrast-filled ducts matching the ducts from the co-MRCP, regardless of the C-arm unit angle.

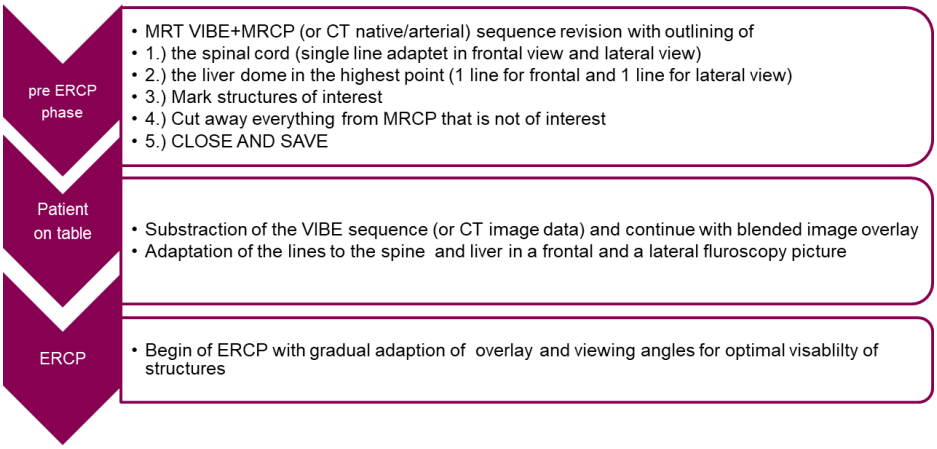

Figure 4. Illustration of the practical workflow of 2D/3D fusion during ERCP.

3.4 Paper III

3.4.1 Study population

The study included data from 74,248 ERCP procedures performed between January 1, 2010, and December 31, 2019. The Swedish Estimation of ERCP Time (SWEET) tool was externally validated using 9,472 ERCPs from 2020 to 2021. All data were extracted from the Gallriks Registry.

3.4.2 Data collection and definitions

Hypotheses were formulated based on clinical considerations about what variables may affect ERCP time and what information is known prior to most ERCPs, and variables were selected accordingly. Data were pseudonymized, allowing identification of repeated interventions in the same patients. Procedures with missing duration or an operation time of 0 minutes were excluded and procedures taking longer than 180 minutes were censored at 180 minutes. Training ERCPs and procedures on patients with altered anatomy were excluded. Indications that from an ERCP point were similar were grouped: "choledochal stone" and "cholangitis/sepsis" became "cholangitis/choledocholithiasis"; "planned follow-up/intervention after earlier ERCP" and "stent dysfunction" became "follow-up ERCP/stent dysfunction". Mother–baby endoscopy and single-operator intraductal endoscopy procedures were investigated separately and combined. Stricture locations were stratified into extrahepatic, hilar, and intrahepatic. For adjustment purposes, we created the dummy variable "stent length" by summating the length of all the stents. Therapeutic pancreatic stenting was defined as intended primary stenting of the pancreatic duct, in contrast to prophylactic pancreatic stenting to decrease the risk of PEP after unintended pancreatic cannulation.

3.4.3 Statistics

Statistical analysis was performed using Stata 15.0 (StataCorp, LLC, 2017) and R Statistical Software v4.1.0 (R Core Team 2021, R Foundation for Statistical Computing).

At first, single variable linear regression models were employed to assess the relationship between ERCP duration and each independent variable, either using the entire dataset or an appropriate subsample. This analysis aimed to provide a detailed examination of the data and to illustrate the impact of individual procedural steps on procedure duration, as well as their interaction with potential confounding factors. For each variable of interest, 2 models were estimated: an unadjusted model and an adjusted model. The adjusted model consistently accounted for the target duct. Additional adjustments included total stent length, intraductal endoscopy, dilation, and whether the underlying pathology was intrahepatic, hilar, or extrahepatic. These linear regression models allowed insight into the role of single factors, and the adjustment gave insight on how much these

single factors are interlaced with surrounding factors. Cluster-robust standard errors accounted for repeated ERCPs.

The SWEET tool development was performed using a linear regression model with internal validation after splitting the initial dataset 80%/20%. Later external validation was done with newly extracted data from the time that had passed since the first data extraction. The tool's estimates were compared to actual times using root mean square error (RMSE) and mean as the primary performance metric.

Using backwards elimination with tenfold validation, the fit improved with up to 8-10 variables; adding more variables did not enhance the loss function. A least absolute shrinkage and selection operator was used to select interaction terms, but they did not improve RMSE. Variable selection was guided by insights from the linear regression analyses and clinical expertise. Model refinement was conducted through collaboration between researchers, clinicians, and statisticians to ensure both statistical robustness and clinical relevance. This led us to the first model, that incorporated the following predictors: age, sex, ASA classification, target duct for cannulation, presence of a native papilla, planned minor papilla cannulation, gallstone disease, bile leakage, documented extrahepatic, intrahepatic, or hilar strictures, therapeutic pancreatic stenting, papillectomy, intraductal endoscopy, and lithotripsy (Model 1). From this model, a simplified linear regression model was derived by retaining only predictors associated with a time change exceeding 3 minutes (Model 2). Multicollinearity was assessed using the Variance Inflation Factor, which remained below 5 for all included variables. To enhance practical applicability, coefficients were rounded to 5 for integration into the SWEET tool and subsequently recalibrated.

3.5 Paper VI

3.5.1 Study population

Patient identification was conducted using a local database of individuals with CP treated at the pancreatology outpatient clinic of Karolinska University Hospital, Huddinge, Stockholm, Sweden. Inclusion criteria consisted of patients who underwent ERCP with the placement MPS in the pancreatic duct due to painful CP between 2007 and 2021. Exclusion criteria were I) Diagnosed or suspected malignant disease mimicking CP at any point during follow-up. II)Therapeutic ERCP

performed for pancreatic duct treatment other than initial single stent placement or final stent removal occurring outside Karolinska University Hospital. III.) Age <18 years at the time of the first ERCP with MPS.

3.5.2 Data collection and definitions

Data were retrospectively extracted from medical records, including information on pain improvement, pain relapse, technical procedural details, CP aetiology, date of CP diagnosis, body mass index (BMI) at baseline and during follow-up, history of pancreatic surgery, and any documented suspicion of intraductal papillary mucinous neoplasm (IPMN) discussed in multidisciplinary conferences. Recorded complications included post-procedural abdominal pain, acute pancreatitis, bleeding, and bowel perforation. Data were collected from all ERCP procedures performed during the follow-up period. CP aetiology was classified according to the M-ANNHEIM system [189]**.** The primary clinical outcome was pain improvement**,** assessed through medical records 6–8 weeks post-ERCP and categorized as (I) no improvement, (II) partial improvement, (III) complete improvement. For patients who subsequently underwent surgical treatment, pain response was evaluated using the same classification system. Pain relapse was defined as the recurrence of pain after a period of improvement following ERCP. Each pancreatic plastic stent was recorded by length (cm), diameter (fr), and ERCP session**.** The maximum number and total diameter of all simultaneously placed stents were calculated. The first multistenting period was defined as the initial series of ERCP sessions with continuous stenting, that included use of MPS but extended also to ERCPs with single plastic stent placement if the stent treatment was not interrupted. The first multistenting period ended when all stents were intentionally removed without replacement or scheduled follow-up ERCP. In certain patients, SEMS were inserted at some point during ERCP treatment. However, SEMS were not included in calculations of cumulative stent number and diameter, although their placement was recorded as an intervention.

3.5.3 Statistics

Data processing and statistical analyses were performed using Stata 16.0 (StataCorp, College Station, TX, USA) and R Statistical Software v4.1.2 (R Core Team 2023, R Foundation for Statistical Computing). Descriptive statistics are reported as absolute numbers and percentages for categorical variables and medians with IQR for continuous variables. Data from all ERCPs, MPS ERCPs, and the first multistenting period are presented in a descriptive manner. Graphical

representations include only the first multistenting period to illustrate treatment progression. Kaplan-Meier analysis was used to evaluate relapse-free survival. Time to relapse was defined as the duration (in months) from the date of the first stent placement in the first multistenting period to either documented relapse, death, or last patient contact, whichever occurred first.

4 Results

4.1 Paper I

In 728 cases, no CBCT dataset was acquired, while a single CBCT was obtained in 37 cases, and 2 CBCTs were acquired in 5 cases. In 17 CBCTs (40%), the "DR" protocol was used and in 25 CBCTs (60%), the "DR care" protocol was selected. Figure 5 graphically presents the radiation doses for the different protocols and conventional procedures. BMI was consistent across the groups. Most conventional procedures resulted in a low radiation dose (median = 6.5 Gycm²), although there were outliers with significantly higher doses. Conventional ERCP resulted in significantly lower radiation doses compared to both "DR" ($U = 908$, $p < 0.001$) and "DR care" protocols ($U = 3823$, $p < 0.001$). Additionally, "DR care" resulted in significantly lower radiation doses than "DR" ($p = 0.022$). For "DR", the median dose was 48.9 Gycm², corresponding to the 95th percentile among conventional procedures. For "DR care", the median dose was 19.7 Gycm², corresponding to the 82nd percentile among conventional procedures. In "DR" procedures, approximately 50% of the total dose was attributed to CBCT acquisition, whereas for "DR care", this figure was 26%. When examining only the fluoroscopy component of the procedures (Table 2), CBCT-ERCP still resulted in significantly higher doses compared to conventional ERCP. There was no significant difference in fluoroscopy dose between "DR" and "DR care" ($U = 181$, $p = 0.42$), but a substantial difference in doses for single CBCT acquisition ($U = 0$, $p < 0.001$). The median dose from one CBCT using "DR" (24.4 Gycm²) was approximately five times higher than the median dose from one CBCT using "DR care" (5.07 Gycm²).

Table 2. Radiation doses for conventional ERCP and the CBCT protocols "DR" and "DR care". Values are presented as median, first/third quartile.

Exposure protocol	Total DAP [Gycm^2]	Fluoroscopy DAP [Gycm^2]	Fluoroscopy Time [min]	DAP for 1 CBCT [Gycm^2]
Conventional ERCP	6.52 (2.6, 15.2)	5.52 (2.0, 13.1)	11.6 (5.4, 22.7)	-
"DR"	48.9 (35.0, 58.4)	8.19 (6.4, 26.1)	12.0 (6.2, 28.0)	24.4 (17.4, 30.2)
"DR care"	19.7 (12.4, 48.2)	12.7 (7.0, 31.5)	25.1 (16.3, 38.3)	5.07 (2.9, 6.9)

DAP: dose area product; CBCT: Cone beam computed tomography

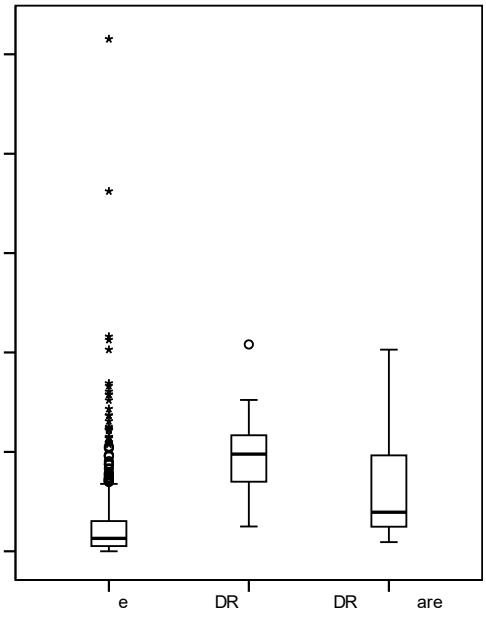

Figure 5. Tukey box plot of the total DAP for one procedure, grouped by the CBCT protocol.

DAP: dose area product; CBCT: Cone beam computed tomography

4.2 Paper II

Thirteen patients aged 22 to 80 underwent ERCP using 2D/3D fusion of MRCP cholangiogram and fluoroscopy at our tertiary endoscopy unit between March 15 and May 21, 2017. The cohort included 10 males and 3 females, with 5 classified as ASA 2 and 8 as ASA 3. The mean interval between MRI and ERCP was 91 days. Indications included biliary stricture (62%), ductal leakage (30%), and complex choledocholithiasis (8%). Primary 2D/3D fusion was technically feasible in all cases, with good image results in 85% of patients. We did not use breath movement compensation software and breathing artifacts caused consistent overlay mismatch to some degree. Still, the small dynamic misalignment did not hinder the usefulness of the image overlay. Image fusion was helpful in visualizing the area of interest in 77% of cases. Fusion ERCP aided in understanding 3D ductal anatomy in 62% of cases and finding favourable c-arm positions without additional radiation exposure in 38%. Major extrahepatic overlay misalignment occurred in 84% of patients. Intrahepatic misalignment was absent in 38%. In the 2 cases targeting the pancreas, overlay misalignment was major. Results of image fusion ERCP are displayed for all patients in Table 3.

Table 3. Results from 2D/3D image fusion. Image quality was good and contributed clinically to several aspects in most patients. Misalignment was greatest for extrahepatic structures.

Patient	Image Fusion Quality	Helped Visualizing Lesion of Interest	Helped Understanding 3D Ductal Anatomy	Helped Finding C-arm Position	Intrahepatic Overlay Misalignment	Extrahepatic Overlay Misalignment
1	Good	Yes	No	No	None	Major
2	Good	No	Yes	Yes	Major	Major
3	Good	Yes	No	No	None	Major
4	Good	Yes	Yes	No	None	Major
5	Good	Yes	No	Yes	Moderate	Major
6	Poor	No	No	No	N/A	Major
7	Good	Yes	Yes	No	Moderate	Major
8	Good	No	No	No	Moderate	Major
9	Good	Yes	Yes	No	Minor	Moderate
10	Poor	Yes	Yes	Yes	None	N/A
11	Good	Yes	Yes	No	N/A	Major
12	Good	Yes	Yes	Yes	Minor	Major
13	Good	Yes	Yes	Yes	None	Major

4.3 Paper III

Basic patient characteristics and frequency of indications for ERCP are displayed in Table 4. Before data cleaning, ERCP times ranged from 1 to 600 minutes (maximum duration in the web interface), with an IQR of 20 to 48 minutes. Adjusted and unadjusted results of univariate regressions are displayed in Table 5. The most common indication was "suspected/known gallstone" (36.2%) with a mean ERCP time of 36.8 minutes. Indications PSC (60.4 minutes) and CP (54.9 minutes) had the most influence on ERCP time. Procedures via a native papilla (36.1 minutes) were shorter than those with a cut papilla (39.9 minutes). ERCP times were 36.5 minutes on average for biliary duct cannulation, 52.2 minutes for pancreatic duct access, and 58.4 minutes for both ducts. Papillectomy procedures lasted 62.1 minutes. Hilar (57.0 minutes) and intrahepatic strictures (64.1 minutes) had a greater impact than extrahepatic strictures (41.1 minutes). ERCP with dilatation took longer (67.9 minutes) than without (35.2 minutes). Biliary stenting took 40.2 minutes, while pancreas stenting took 54.6 minutes. Unilateral intrahepatic stenting lasted 53.9 minutes, bilateral 70.1 minutes. Left-sided stenting (65.4 minutes) was more time-consuming than right-sided (61.2 minutes). Biliary (88.2 minutes) and pancreatic (84.0 minutes) intraductal endoscopy times increased with lithotripsy. Mother-baby procedures (79.8 minutes) were shorter than single-operator procedures (88.5 minutes).

Adjustments for associated factors often had strong impact on the results of single variables. More results from univariate regressions can be found in the original publication and its supplementary material.

The validation of the SWEET tool using 20% of the data showed comparable R^2, mean absolute error (MAE) and RMSE for Models 1 and 2. All results for both models are presented in Table 6. Model 2 was chosen for the prediction tool, with a range of 25 to 210 minutes. The MAE was 17.0 minutes, and RMSE was 23.5 minutes. The SWEET tool is displayed in Figure 6. External Validation using 9,453 ERCP procedures resulted in an MAE of 17.463 and RMSE of 24.871 (R2 = 0.171). ERCP time was predicted within 15 minutes in 61.9% of procedures and within 30 minutes in 86.5% of procedures. The SWEET tool tends to overestimate short procedures (30 minutes or less) by an average of 10.8 (7.7) minutes. For procedures lasting 30 to 60 minutes, it underestimates the duration by an average of -10.0 (13.2) minutes. Long procedures, especially those over 2 hours, are also underestimated, with high variability in precision. For example, ERCP

procedures lasting 61 to 120 minutes are underestimated by an average of -38.7 (24.2) minutes.

Table 4. Basic patient characteristics, duct intended to cannulate and indications for ERCP before data preparation for derivation and validation dataset.

Basic patient characteristics	**Derivation dataset**	**Validation dataset**
Mean age in years	66.5	65.0
Female sex (%)	43,548 (52.0%)	5,065 (50,4%)
Duct(s) intended to cannulate	Number of ERCPs (%)	
Bile duct	81,972 (97.9)	9794 (97.5)
Pancreatic duct	1,208 (1.4)	211 (2.1)
Both ducts	561 (0.7)	39 (0.4)
Main indication for ERCP	Number of ERCPs (%)	
Suspected or known gallstone	30,322 (36.2)	3647 (36.3)
Jaundice or cholestatic liver tests	12,386 (14.8)	1132 (11.3)
Malignancy	8,380 (10.0)	1258 (12.5)
Planned follow up ERCP	8,367 (10.0)	1117 (11.1)
Cholangitis/sepsis	6,912 (8.3)	1045 (10.4)
Stent dysfunction	3,467 (4.1)	401 (4.0)
Other	3,455 (4.1)	342 (3.4)
Postoperative gall leakage	2,261 (2.7)	223 (2.2)
Acute pancreatitis	2,196 (2.6)	176 (1.7)
Suspected or known PSC	2,099 (2.5)	313 (3.1)
Chronic pancreatitis	1,444 (1.7)	203 (2.0)
Prophylaxis of biliary pancreatitis	958 (1.1)	95 (0.9)
Perioperative anatomical orientation	362 (0.4)	69 (0.7)

PSC: primary sclerosing cholangitis.

Table 5. Results of univariate regressions with sample and adjustment. ERCP time at the top of a category is used as a reference. The β̂ values indicate the time difference to this ERCP time in minutes, across different patient group samples. Additional univariate linear regressions are shown in paper III and its supplementary part.

M i n indi i n	Sample, a justme t	Mea time (mi)	(SD)	$\hat{\beta}$	$\hat{\beta}$ a j.	p
h la gitis/ h le ch lithiasis	A	33.7	.6			
Primar scler si g ch la gitis	A, a	6 .4	3 .	6.7	7.	< .
hr ic pa creatitis	A, a	4.9	33.	.	.	< .
Malig a c	A, a	4 .8	7.8	9.	.	< .
Jau ice	A, a	38.9	3.6	.	.4	< .
n i f s	Sample, a justme t	Mea time	(SD)	$\hat{\beta}$	$\hat{\beta}$ a j.	P
ative papilla Vateri		36.	4.			
- ative papilla	, a	39.9	9.8	3.7	- .3	< .
u in ended nnu e						
Pa creatic uct a bile uct	A	8.4	33.4			
ile uct	A, a	36.	.	- .9	- 6.7	< .
Pa creatic uct	A, a	.	33.	-6.	-7.	< .
a ulati papilla mi r		47.	8.7			
a ulati papilla mi r es	, b	79.	4 .	3 .8	8.6	< .
i i s en si s in						
Extrahepatic ste sis	A	3 .	4.9			
Extrahepatic ste sis es	A, g	4 .	6.	.6	- .9	< .
Ste sis hilum	A	3 .7	4.3			
Ste sis hilum es	A, c	7.	3 .9	.	. 6	. 6
l trahepatic ste sis	A	3 .	3.8			
l trahepatic ste sis es	A, h	64.	36.3	8.6	7.6	< .
edu e s eps	Sample, a justme t	Mea time	(SD)	$\hat{\beta}$	$\hat{\beta}$ a j.	p
Papillect m	A	36.8	.3			
Papillect m es	A, a	6 .	8.	.4	8.8	< .
Dilatati	A	3 .	3.6			
Dilatati es	A, f	67.9	3 .3	3 .7	9.9	< .
S en ing						
iliar ste t i t rahepatic	A	3 .3	3.8			
U ilateral i t rahepatic ste t	A,	3.9	3 .	8.	.9	< .
ilateral i t rahepatic ste t	A,	7 .	36.	34.8	.9	< .
Therapeutic pa creas ste t	A	36.3	4.9			
Therapeutic pa creas ste t es	A, a	4.6	3 .4	8.4	9.	< .
In du end s p (IE)	Sample, a justme t	Mea time	(SD)	$\hat{\beta}$	$\hat{\beta}$ a j.	p
IE	A	3 .7	3.8			
IE es	A, e	88.	3 .8	.4	46.6	< .
iliar IE lith trips	E	84.6	34.			
iliar IE lith trips es	E, e	3.	39.	8.6	3 .	< .
Pa creatic IE lith trips	D	79.	38.			
Pa creatic IE lith trips es	D, e	.6	3 .	33.	6.8	< .

Sample		A justme t	
A	All (=74 48)	a	Dilatati , ste t le gth, uct i.t.c., IE
		b	Dilatati , uct i.t.c., ste t le gth, IE, i icati
	All where papilla status was available (= 3)	c	Dilatati , ste t le gth, uct i.t.c., IE, ste sis extrahepatic, ste sis i t rahepatic
			Dilatati , uct i.t.c., IE, ste sis extrahepatic, ste sis i trahepatic, ste sis hilum
		e	Dilatati , ste t le gth, uct i.t.c.
	Pa creatic uct ca ulati : eep (=9)	f	ste t le gth, uct i.t.c., IE
		g	Dilatati , ste t le gth, uct i.t.c, IE, ste sis i trahepatic, ste sis hilum
D	iliar uct ca ulati : t trie , pa creatic uct ca ulati : eep, IE = es (=)	h	Dilatati , ste t le gth, uct i.t.c, IE, ste sis extrahepatic, ste sis hilum

Table 6. Results of the multivariate linear regression models "Model 1" and "Model 2". Variables marked with * have been included in the SWEET tool.

Variable	M e l		M e l	
	Estimate	9 % l	Estimate	9 % l
l tercept*	3.3	9. - 7.4	7.3	3.3 - 3 .4
Age	- .	- . 4 - - .		
Sex	- .	- .7- .		
a ulati bile uct*	.	. - 9.	.	. - 9.6
a ulati pa c. uct*	4.4	. - 7.8	4.3	.9 - 7.7
a ulati papilla mi r*	.	3.4 - 3 .8	.4	3.7 - 3 .
Extrahepatic stricture*	3.9	3.4 - 4.	4.	3.7 - 4.7
l trahepatic stricture*	7.8	6. - 9.6	8.	6.4 - 9.8
Hilar stricture	.	8.9 - .6	.6	9.3 - .
l tra uctal ER P*	4 .	39.3 - 43.7	4 .	38.9 - 43.
Lith trips *	34.7	7.9 - 4 .4	34.8	8. - 4 .6
Papillect m *	.3	7.3 - 7.4	.	7. - 6.9
i le leakage	.	.8 - 3.4		
i le st es	.7	. - .		
Therapeutic pa c.ste t*	.	7.9 - 4.4	.	8. - 4.4
ASA classificati	.4	. - .8		
	F-statistic: 86.8 a 4 697 egrees f free m, p < .		F-statistic: 397. a 4 697 egrees f free m, p < .	

ASA: American Society of Anesthesiologists

SWEET tool			
Addition of procedure steps and baseline			25 min baseline
Intended cannulation	Bile duct [5 min] □ Pancreatic duct [15 min] □ Papilla minor [20 min] □	+	
Strictures intended to be addressed	Extrahepatic stricture [5 min] □ Hilar stricture [10 min] □ Intrahepatic stricture [20 min] □	+	
Planned interventions	Pancreas stenting [10 min] □ Papillectomy [25 min] □ Intraductal endoscopy [40 min] □ Direct lithotripsy [35 min] □	+	
Estimated ERCP duration in minutes		=	

Figure 6. The **SW**edish **E**stimation of **E**RCP **T**ime (SWEET) tool. Information about the planned ERCP, including ducts to be cannulated, strictures to be addressed, and further interventions, is collected in a scheme and added to the baseline duration of 25 minutes to give an estimate of the total ERCP time.

4.4 Paper IV

Patient Cohort and Characteristics: We identified 50 patients who met our inclusion and exclusion criteria. The cohort's clinical characteristics are detailed in Table 7. Most patients were male (58%), and the predominant aetiology of chronic pancreatitis (CP) was a combination of alcohol and nicotine (52%). Treatment strategies for most patients (89%) were discussed in one or more multidisciplinary conferences.

ERCP Treatments and Outcomes: Table 8 displays the treatments and outcomes of all ERCPs. A total of 273 ERCPs were performed, with up to 15 ERCPs per patient. Among these, 129 ERCPs involved MPS insertions, with 122 performed during the first multistenting period. ESWL was conducted in 8 out of 36 (22%) patients with ductal obstruction caused by a stone. Pancreatoscopy with direct lithotripsy was performed in 9 (25%) patients, with a single session in 8 patients and 4 sessions in 1 patient. Direct lithotripsy was combined with MPS insertion in 5 patients. The total number of stents used was 397, including 13 (3.3%) self-expanding metal stents (SEMS). SEMS were implanted in the pancreatic duct of 11 patients, with 2 patients receiving a SEMS twice. No cases of simultaneous side-by-side placement of plastic stents and SEMS were recorded. The first multistenting period typically consisted of 4 ERCPs in most patients (60%) and lasted for a median duration of 18 months (IQR: 13-24 months). Typically, 2 (50%) or 3 (40%) stents were implanted simultaneously. The largest summed diameter used per patient was 21 Fr (IQR: 16-23 Fr). In 43 (86%) patients, stents were extracted via ERCP at the end of the first multistenting period. Three (6%) patients had their stent extraction with a gastroscopy, while 6 (12%) patients had their stents removed during surgery.

Complications: Across all procedures, 82 complications (30%) were reported. The most common complication was peri-interventional abdominal pain (70 cases, 26%), followed by acute pancreatitis (12 cases, 4.4%). No cases of bleeding, perforation, or complications requiring surgical or interventional management were observed. Among the 129 ERCPs involving MPS placement, 33 complications (26%) occurred, including postprocedural abdominal pain in 28 cases (22%) and acute pancreatitis in 5 cases (3.9%). Among the 5 procedures that combined pancreatoscopy, direct lithotripsy, and MPS insertion, 1 case of acute pancreatitis (20%) and 1 case of postprocedural pain (20%) were documented.

Pain Improvement: Complete cessation of pain was observed in 27 (54%) patients at some point during their ERCP treatment. Eighteen (36%) patients experienced partial pain improvement, and 5 (10%) patients had no pain improvement from ERCP. Figure 7 shows the number of patients reporting full, partial, or no pain improvement over ERCP sessions. The largest number of patients reported full pain improvement within the first 3 to 4 sessions. From session 5 to 7, the proportion of patients reporting full pain improvement decreased. After the 7th ERCP, only partial pain improvement was reported. Conversion to surgery occurred in 7 (14%) patients, among whom 4 (57%) had experienced no pain improvement from ERCP treatment at any point. The other 3 had a relapse of pain after earlier partial (2 patients) or full improvement (1 patient) before surgery. IPMN discussed in the multidisciplinary discussion as a potential differential or additional diagnosis to CP was 43% among the 7 patients who converted to surgery and 12% among the 43 patients who did not convert to surgery. After surgery, 4 out of 7 patients (57%) had full pain improvement, and 3 out of 7 (43%) had no pain improvement. Figure 8 shows the combined stent diameter for full, partial, and no pain improvement. A clear increase in stent diameter was observed between the first and subsequent sessions, with a tendency to further increase over the first 5 sessions. The group of patients reporting full pain improvement had a higher median stent diameter in sessions 3, 4, and 5, but only to a small extent. Nineteen out of the 45 patients who experienced pain improvement from ERCP had a renewed worsening of pain symptoms later in the follow-up period. Figure 9 illustrates pain relapses after improvement form ERCP treatment.

Table 7. Characteristics of CP patients treated with ERCP and MPS

h e is i s	N=50*
Age at first ER P	6 (4 , 67)
Male	9 (8 %)
Multi iscipli ar i scussi	44 (88%)
Pa creas i visum	8 (6%)
Diabetes at iag sis f P	9 (7.3 %)
F l l w u p (m th s)	7 (47, 9)
Eti l g f P acc r i g t M-A H EIM classificati [ ]	
Alc h l a ic ti e	(%)
i c ti e	6 (3%)
Effere t u ct	6 (3%)
Here itar	6 (3%)
Alc h l	3 (6.3%)
Here itar a e ffere t uct	(. %)
Misc./ ther	(. %)
Sm ki g [ ]	
ev er	(%)
Ever	36 (7 %)
MI (kg/m^3)	
MI at iag s is f P	.9 (9.9, 4 .) [ ]
MI at f ll w up	. (9. , 4.) [ ]

* Median (Q1, Q3); n (%) [unknown]; BMI: Body mass index; CP: chronic pancreatitis; MPS: Multiple plastic stents

Table 8. ERCP characteristics, pain response and complications in 50 individuals with chronic pancreatitis and pain treated with MPS

Resu s pe p ien	**N=50**
Pa creatic sphi c ter t m	49 (98%)
Duct bstructe b st e	36 (7 %)
ESWL	8/36 (%)
Pa creat s c p + i rect lith trips	9/36 (%)
est pai resp s e per patie t after a ER P	
i mpr v eme t	(%)
Partial impr v eme t	8 (36%)
Full impr v eme t	7 (4 %)
Pai re curre ce	
Yes	7 (39%)
	7 (6 %)
U k w	6
v ersi t surger	7 (4%)
Effect f surger pai	
mp lete cessati f pai	4/7 (7 %)
i mpr v eme t	3/7 (43%)
Suspici f IPM	8 (6%)
Surger gr up	3/7 (43%)
surger gr up	/43 (%)
Resu s pe p ien fi s u is en ing pe i d	**N=50**
Durati (m ths) *	8 (3 , 4)
umb er f ER Ps *	4 (3, 6)
Ste ts use i t ta l	6 (4, 9)
Max. r. ste ts use s imulta e usl	
	(%)
3	(4 %)
4	4 (8%)
	(%)
Max. simulta e u s ste t iameter (fr) *	(6 , 3)
Resu s f ER s	**N= 73**
Pa creat s c p + i rect lith trips	(4.4%)
mp licati s i all ER Ps	8 (3 %)
Ab m i a l pai	7 (6 %)
Acute pa c reatitis i all ER P s	(4.4%)
Perf r ati	
lee i g	
Resu s f ER wi h M S	**N=1 9**
Pa creat s c p + i rect lith trips	(3.9%)
mp licati s i ER P s with MPS	33 (6 %)
Ab m i a l pai	8 (%)
Acute pa c reatitis i ER P s with MPS	(3.9%)

* Median (Q1, Q3); ESWL: Extracorporeal shockwave lithotripsy; IPMN: Intraductal papillary mucinous neoplasm; MPS: Multiple plastic stents

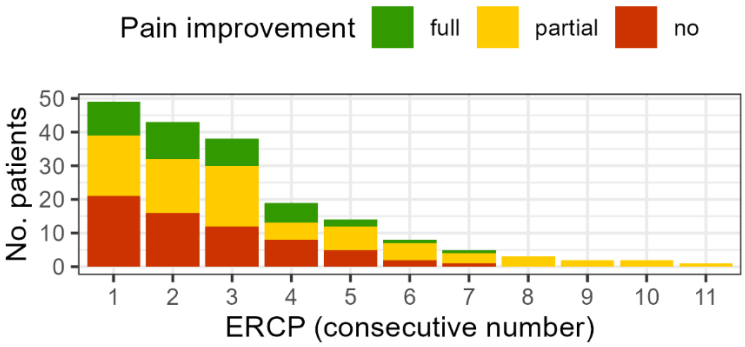

Figure 7. Stacked bar graph of the number of patients that reported full (green), partial (yellow) or no (red) pain improvement after treatment with ERCP and MPS. Only ERCPs with placement of new stents within the first multistenting period were considered. The same patient may occur as part of several boxes depending on the number of ERCPs the patient underwent.

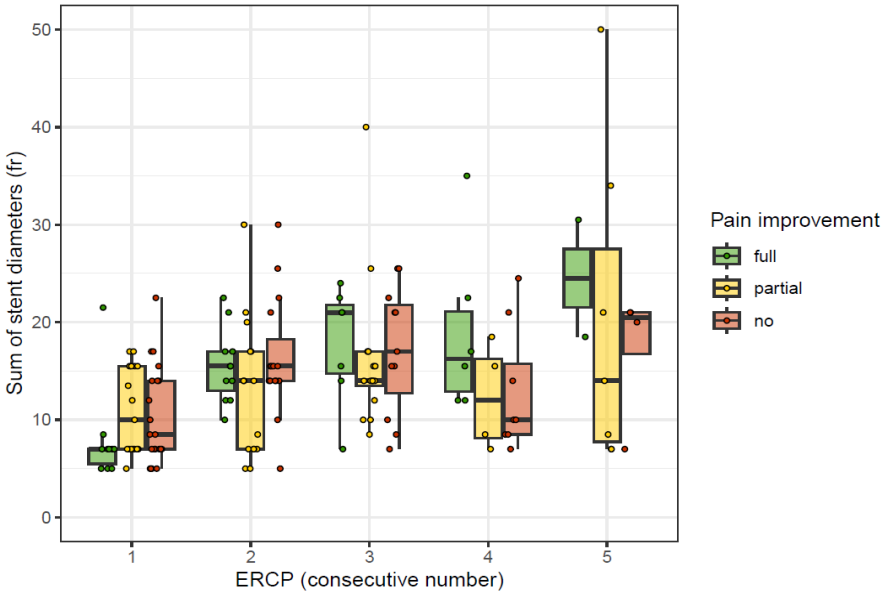

Figure 8. Cumulative stent diameter of stents placed simultaneously over the first 5 ERCPs of the first multistenting period. Data is divided according to pain improvement. The horizontal line inside of the boxes indicates the median stent diameter per ERCP. The whiskers extend to 1.5 times the interquartile range. Points represent individual data points. The same patient may occur as part of several box/ whisker boxes and as several data points, depending on the number of ERCPs the patient underwent.

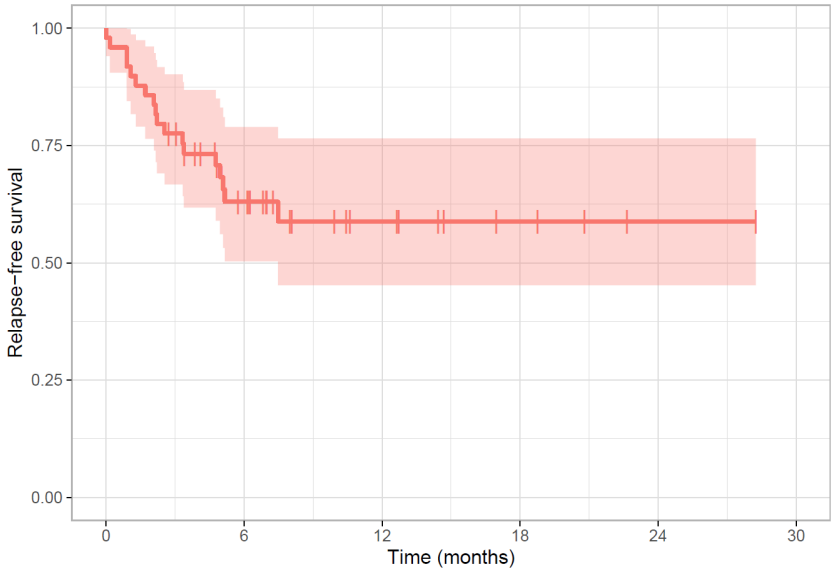

Figure 9. Time to relapse of pain in 44 patients with CP who experienced initial improvement of pain from ERCP and multistenting.

5 Discussion

5.1 General discussion

In this thesis, we explored under-studied areas within the field of ERCP. We showed that radiation doses in CBCT ERCP were higher than in traditional ERCP, although a strong selection bias can be assumed. The low dose protocol "DR care" generated about 80% less radiation than the "DR" protocol and still resulted in sufficient image quality for the purpose of ERCP. We reported the first use of manual 2D/3D image fusion for ERCP in a case series of 13 patients. The use of pre-interventional acquired 3D data during ERCP proved feasible and useful in most cases, even though it had some limitations. For instance, extrahepatic and pancreatic anatomy was dislocated, probably due to the pull of the duodenoscope. Also, in a few cases, the fused image quality was poor. Still, for the intrahepatic or hilar orientation, as well as for finding a favourable angle for assessment, the technique was helpful. We also generated the first score for pre-interventional estimation of ERCP time. The SWEET tool is easy to use, and its estimate has a MAE of 17 minutes from the actual ERCP time in the validation dataset. Furthermore, by using the large data pool from the Gallriks register, additional insights about the impact of several procedure steps and their relationships were granted. In a retrospective evaluation of selected cases of painful CP, in which MPS placement in the pancreatic duct was done, we showed that ERCP with MPS safe. Among the studied 50 individuals, complete cessation of pain at some point of treatment was observed in 54%, partial improvement in 36%. Pain relapse was, however, common during follow up. Conversion to surgery was done in 14%, often in cases with insufficient pain response and suspicion of IPMN.

Our work on radiation dose in CBCT includes a summary of our early experiences with using CBCT for ERCP from a practical perspective. CBCT was performed selectively, particularly in cases requiring detailed understanding of intrahepatic or hilar anatomy. With increasing experience, the use of rotational cinematography can increase the understanding of the 3rd dimension in many cases, but not for overlapping and crossing ducts, as for example in advanced cholangiocarcinoma involving the liver hilus. Therefore CBCT ERCP has clinical advantages over rotational cinematography that cannot be replaced by experience in those cases. The radiation doses in this study indicate a strong selection bias, as CBCT cases had higher radiation doses, yet only half ("DR" protocol) or a quarter ("DR care"

protocol) of the dose originated from CBCT. The radiation doses in CBCT in our study were lower in "DR care" and higher in "DR" than those previously published by Weigt and colleagues [153].

Despite the 3D cholangiograms, fluoroscopy usage was higher in these cases. Our results indicate that the "DR care" protocol, which uses significantly less radiation, is adequate for most situations, especially when the team is experienced in breath hold, patient/machine positioning, and ductal contrast filling during CBCT. The differences in fluoroscopy time between "DR" and "DR care" likely reflect our increased experience with optimal utilization of 3D cholangiograms since we rarely used the "DR" protocol after the very initial phase. Together with the manufacturer of our x-ray equipment, we were able to modify the settings of our x-ray suite to fit the exact purpose of ERCP. Our findings will be implemented into broader clinical use as a ERCP specific preset to be delivered in the manufacturer's presets of x-ray machines. Our experiences during this project also led to potential advancement in x-ray safety to be studied in the future. We originally recorded CBCTs with the physician standing next to the patient holding the duodenoscope while wearing both x-ray protection and x-ray dose monitoring equipment. During this project, we discovered that, even though no alarming doses of radiation were recorded on the monitoring equipment, it is inopportune to be exposed to a relative high dose of radiation with the source passing close to the head/eyes. This promoted discussions with the manufacturer about the development of a dedicated duodenoscope stand for allowing the physician to move away whilst reducing the risk for the equipment dislocating from its position.

While the use of preexisting imaging data for guidance in ERCP with 2D/3D fusion differs significantly from CBCT it faces similar challenges. It demands even more time and preparation than CBCT and is most effective for hilar and intrahepatic interventions. In most extrahepatic and pancreatic procedures, 3D imaging is rarely necessary. In our work with CBCT and image fusion for ERCP, even though innovative projects as such, we leveraged the insights from our radiology colleagues, who use the same equipment and face similar challenges. We applied their solutions, albeit with a decade's delay, in the field of ERCP.

The diverse use of ERCP outlined in the introduction illustrates that ERCP is an adjustable procedure resulting in highly variable duration, which in turn leads to challenges for effective scheduling. To address this knowledge gap, we developed

a score to predict ERCP duration using a large amount of data from the unique Gallriks register.

Traditionally ERCP duration is estimated individually by an ERCPist and communicated to a scheduling assistant for each case. This method is resource-intensive and can vary between interventionalists, even more so if the procedure is not necessarily assigned to the planner. The SWEET tool aims to standardize these estimations, making them less dependent on expertise, and ideally more accurate, thereby improving resource allocation. The SWEET tool was developed using Swedish ERCP data. In Sweden, most complex ERCPs are performed centralized in a handful of hospitals, and often, anaesthetic personnel are involved in the procedure. We deliberately did not include the anaesthetic method into the SWEET tool, since it depends on local customs and resources, is at least to some extent arbitrary and might even have reciprocal effects on the procedure time. Our findings might therefore be most applicable, in descending order, in Sweden, Scandinavia, Europe, first world countries, countries with abundant medical resources and predominantly Caucasian population. Still, the Gallriks data used for this study are a unique source that to our knowledge is not available in a similar form anywhere else. Since the data represent almost all ERCPs performed in the whole country, they still might allow to relate to procedures performed in other countries, at least on a proportional relationship, and for flagging procedures at risk for exceptionally long duration. As previously described by von Seth and colleagues, ERCP in PSC takes time [56] – indeed, it is the most time consuming indication for ERCP in Sweden, followed by CP.

The regression analysis presented in this study allow a unique insight into single steps that an ERCP procedure consists of and, due to the various adjustments, how they are interlaced. For instance, we could prove in several ways that an ERCP in a patient with native papilla does not take longer than in a previously sphincterotomized papilla. This is surprising to most ERCP practitioners, but cannulation takes less than 5 minutes in most cases [57]. In contrast to what could be expected, the ERCP duration is longer in our data, if a papilla is not native or if no sphincterotomy is performed (as a proxy for previously performed sphincterotomy), but this difference is equalised when adjusting for the most common therapeutic steps. A native papilla does therefore not seem to prolong the ERCP procedure, and in cases of repeated ERCPs more time is usually spent for therapeutic steps. The anecdotal wisdom that, when placing multiple biliary stents, is advisable to start with the intrahepatic left biliary stents because they

are harder to push, is confirmed by our results showing that left-sided stenting indeed takes longer. There are many more similar findings that could elicit debates and interpretations among ERCP practitioners.

In our observational cohort study evaluating the use of ERCP with MPS for treating painful obstructive CP in highly selected cases no increased complication rate compared to other ERCPs was found. Complete or partial pain relief was achieved in 90% of patients at some point during ERCP treatment, which is slightly higher while the frequency of relapse was equal, than previous studies [49, 50, 52, 54].

Based on the high rate of pain relapse, our findings confirm the recommendation that surgery should be preferred over ERCP in these patients, if eligible [190, 191]. Our study cohort included patients with severe CP and related co-morbidities, many of whom were not suitable for surgery and aggressive ductal dilatation with ERCP was chosen as the first-line treatment. This strategy, while outside guideline recommendations, was based on individual decisions made during multidisciplinary conferences and our results may therefore be influenced by selection bias. This is consistent with the very low rate of conversion to surgery in our cohort. Decisions to perform surgery were likely at least in part driven by IPMN suspicion, as a stricter indication for surgery. Thus, patient selection, study design, local treatment judgment, technical differences, and follow-up time may explain discrepancies between our results and other studies. The outcome measure of the latest study on MPS in CP by Papalavrentios [50] is pain response while stents are in place in 3 patient groups: A.) Single plastic stent only B.) Single and MPS C.) MPS only. This outcome was worst in patients receiving exclusively MPS treatment, and the study title concludes that MPS treatment is not superior to single stent treatment. Although beyond the study's scope, the study's data also showed that the percentage of patients not achieving definitive stent extraction was lower (67% vs. 90%) and the re-stenting rate was higher (58% vs. 38%) if patients were only treated with a single stent. Clinically, if stenting continues to maintain ductal patency, aggressive ductal dilatation with multiple stents might be less important. In contrast, our study data result from an approach, where MPS implantation is practiced with the aim to dilate the duct sufficiently to allow a stent- and pain – free dismission without the need for further continuous ERCP treatment with stent exchanges. An important question is when to stop the ERCP treatment, which was often perpetuated in patients with only a partial response. Our data suggest low chances to achieve full pain relief beyond the 5th ERCP session. The role of ERCP in CP has diminished with the cumulation of evidence favouring surgery [51, 140-

142]. Although ERCP MPS is safe and potentially more effective than single plastic stenting, it will likely remain a niche procedure for selected patients at specialized centres.

5.2 New insights in connection to this PhD

We were able to create the first tool for estimating ERCP duration in this thesis and at the same time, provide insights into duration aspects of procedure steps that have never been described before.

The first description of 2D/3D image fusion during ERCP proved feasibility and usefulness of the technique, while pointing out aspects with limitations.

From our experience with CBCT, we could show that low dose radiation protocols are sufficient to achieve a 3D volume displaying bile duct anatomy, that can be used for navigation during ERCP, while reducing the radiation dose to about 20% of a standard CBCT protocol.

Our study on MPS in CP highlights the need to strongly re-consider surgery after the 5th ERCP session if full pain relief is not achieved as later pain relief by ERCP treatment is unlikely.

5.3 Conclusions

CBCT ERCP procedures result in higher overall radiation exposure compared to traditional exclusively fluoroscopy based ERCP. However, by modifying exposure protocols, radiation doses can be reduced to acceptable levels without diminishing the enhanced intraprocedural guidance provided by cone beam ERCP. In selected cases, that necessitate assessment of complex or multiple anatomical challenges, CBCT potentially could lead to a lower total radiation dose.

ERCP using pre-existing image data with 2D/3D fusion is a viable technique that enhances the understanding of biliary anatomy and aids in lesion visualization. Its potential applications include the evaluation and management of complex intrahepatic and hilar biliary diseases.

The SWEET tool is the first tool for pre-interventional estimation of the duration of an ERCP. It´s use could make ERCP time scheduling more standardized and effective.

ERCP with MPS is safe and effective for initial pain relief in patients with painful obstructive CP, but many patients do not experience complete pain relief or had worsening pain during follow-up.

6 Points of perspective

Interlacing the findings of this PhD project could lead to new projects and insights in the future. Specific research questions in close relation to the studies presented here could be:

- What is the duration of pancreatic ERCP with MPS?

  If the procedure gained popularity, maybe it could one day warrant an inclusion in an updated version of the SWEET tool.

- Is ERCP time and ERCP complexity interlaced with the amount of x-ray exposure?

  Quantitative relations between radiation dose and current pre-ERCP grading systems such as SWEET, ASGE and H.O.U.S.E. could be investigated.

- Which ERCPs will have a high radiation dose?

  Identifying radiation intensive ERCPs in advance could facilitate the use of advanced imaging methods and stringent radiation protection measures, such as x-ray shielding for the anaesthesia team.

- Which ERCPs warrant advanced imaging techniques?

  Relatedly, we could try to identify thresholds for ERCP duration and ERCP radiation dose above which advanced imaging techniques could be especially beneficial. Ideally, the advanced imaging could, beyond improving visibility, help reduce total radiation dose and procedure time by using a single CBCT or fused dataset instead of repeated traditional assessments.

Some of the advanced techniques in ERCP we describe in this thesis could one day become widely used standard practices. The early steps in a field require enthusiasm and effort. Image fusion with manual preparation of 2D/3D image fusion, as presented in this thesis, will never be a standard technique for a large percentage of ERCPs performed. But technical evolution of software solutions is

accelerating, especially with the upcoming of artificial intelligence and machine learning algorithms. 2D/3D and 3D/3D image overlay with automatic fusion algorithms, breath motion compensation, and dynamic adaption of structures dislocated by the endoscope are absolutely feasible, based on current capabilities and resources. Motion artefact compensation is a tool that has been described as useful for CBCT acquisition to improve image quality, and publications on this approach are increasing [192, 193].

While motion compensation might not be necessary in intubated patients that can be held in apnoea for the short period of image acquisition, it may be more relevant to improve image quality in patients not treated in narcosis.

In contrast, for the fusion modality described in paper II, movement motion correction would be appreciated between the fixed fused 3D volume and the continuously moving fluoroscopy image. Given that such a tool is still not offered on any commercially available system today, we are currently collaborating with the manufacturer of our x-ray system in a follow-up project to the study presented here to develope work packages paired to C-arms specifically designed for use in endoscopic procedures.

Two main questions that are coming along with automated capabilities are:

1.) Who is responsible for mistakes if they happen?

The responsibility question is discussed in many fields of technology, in which machines take over skills and this discussion is especially sensible in the medical field. In the long term, there will be machines for specific tasks that make less mistakes than humans on the same task. This will pave the way to imply scenarios of humans and machines working together and make the determination of culpability in the extremely rare cases of failure more of a philosophical than a clinically relevant aspect. From today's perspective, these rare cases may be considered morally as a very unfortunate course. Legally, there will be liability from the physician to the patient. The physician and/or hospital may then seek recourse from the equipment manufacturer.

2.) Is there a business case that is worth investing in the development of this technology?

The business cases will turn out negative for early niche technologies, but costs for development will drop over time, eventually making even development of specific applications for many situations financially viable.

Already today, a multimodal approach is used in selected cases, for instance when a radiologist marks biopsy locations in an imaging dataset which are then fused and projected to an ERCP, as presented in Figure 10. This approach could become more frequently used if it required less specific skill and time. In a further step, AI tools could be used to automatically identify, mark and colour code ductal strictures with worrisome properties. Such marking of strictures could make cytological or even EUS based sampling more objective on a larger scale. In fact, ductal marking, as done manually in Figure 11, can already be achieved automatically by existing algorithms, but currently available versions need adaptions to work well with ERCP purposes.

Additional imaging modalities could be easily included in a multimodal imaging system such as SOC imaging and EUS as the most obvious options, from today's view. This could lead to more reliable allocation of biopsies and surgical dissection lines.

Tracking of devices, that is done with x-ray today, could be replaced by radiation free technologies for real-time 3D image navigation. A technology that could be adapted for this use is the placement of electromagnetic coils along interventional tools to generate a traceable pulsed low-intensity magnetic field, as it is already widely used on the successful Olympus ScopeGuide™ equipment.

The studies presented in this thesis demonstrate that an clinically oriented and open-minded approach can pave the way towards innovative advancements of established techniques such as ERCP and their broader clinical application.

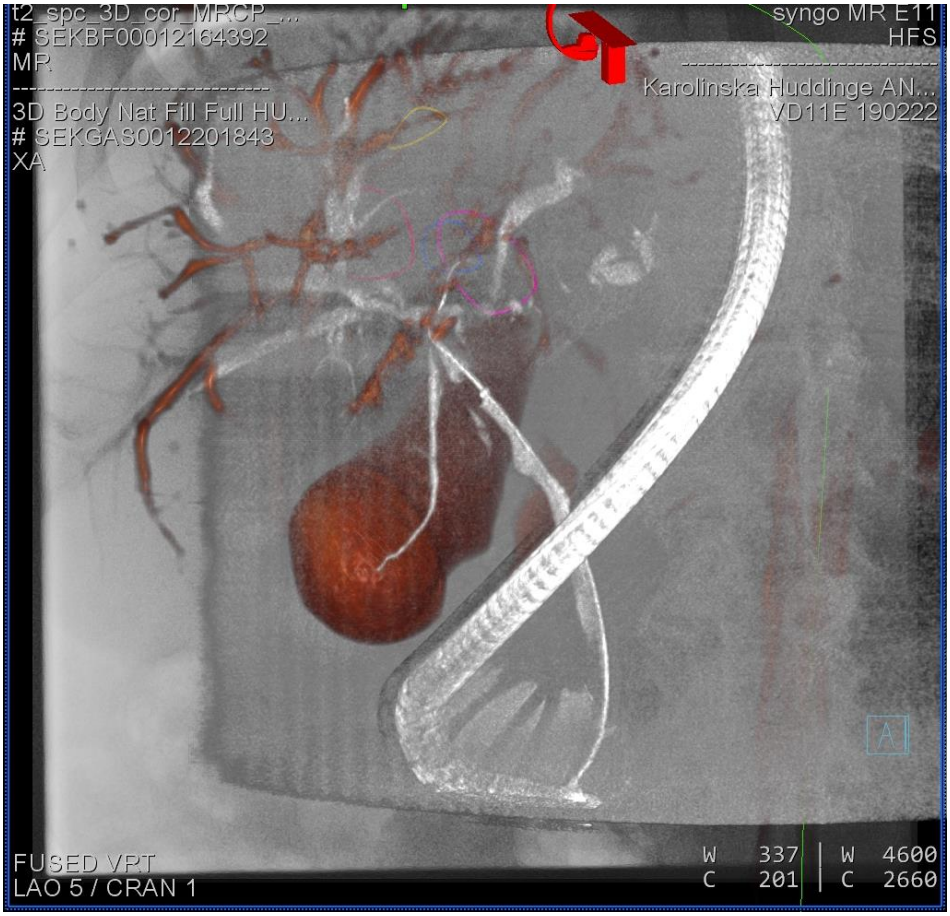

Figure 10. Advanced imaging during ERCP. The red image data are from a pre-interventional MRCP. The MRI dataset has been prepared for 2D/3D fusion with fusion lines (green) and circular markings for targeted ductal sampling. The grey image data come from an intraprocedural CBCT cholangiogram. Both modalities have been used to create a 3D/3D fusion and are blended over the fluoroscopy image. The pull of the duodenoscope on the bowel in the CBCT creates a slight offset and change in angles around the hilum.

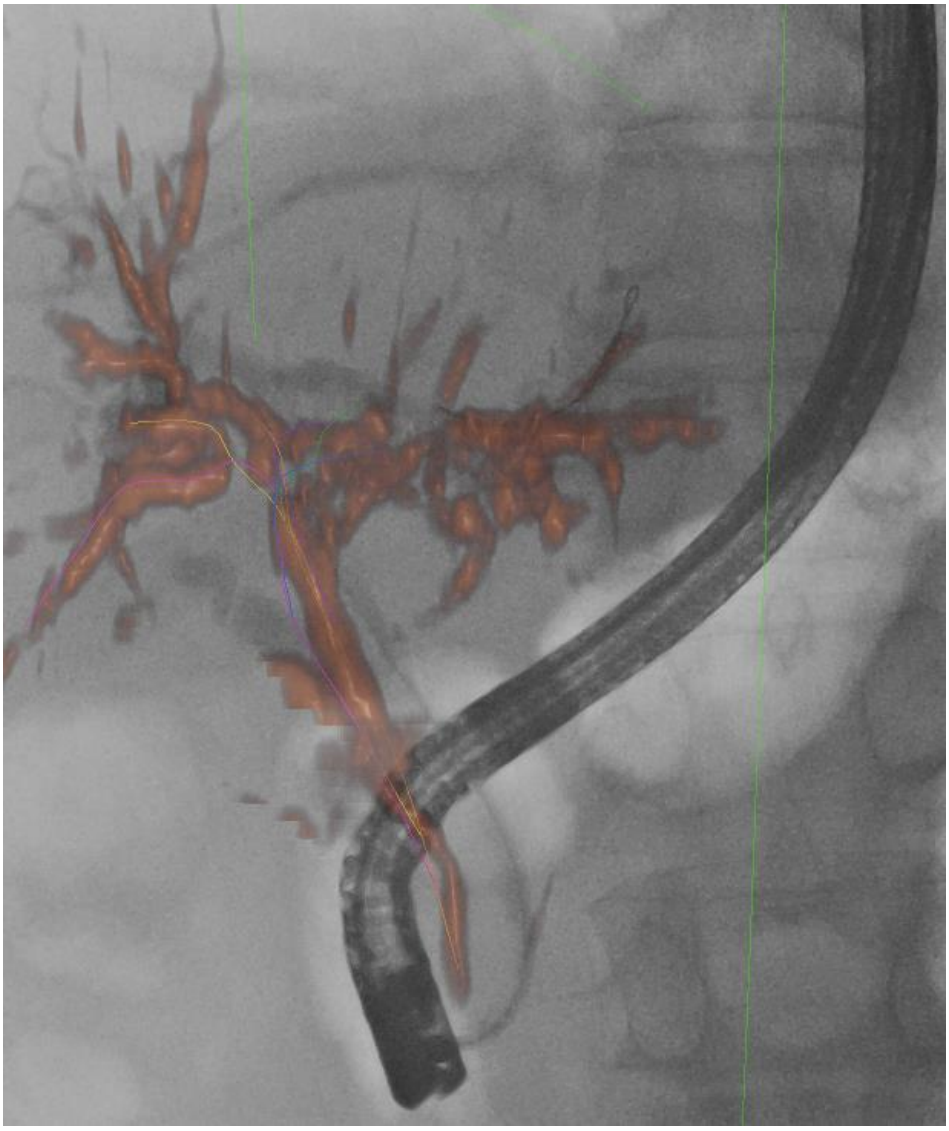

Figure 11. Intraprocedural images of 2D/3D fusion using MRI data from a 160kg patient with primary sclerosing cholangitis and outspoken anatomical changes from hepatic atrophy/hypertrophy. The colour marked bile ducts in the MRCP allow targeted cannulation and sampling and facilitate overcoming the limited x-ray visibility caused by the patient's body mass.

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