Advanced endoscopy in pancreaticobiliary diseases

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Colophon

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GENERAL INTRODUCTION

Endoscopy plays a central role in diagnosis and treatment of diseases of the digestive tract. Approximately 60 years ago, in 1957, two young researchers, Larry Curtiss and Basil Hirschowitz, invented a flexible endoscope that overcame the two major obstacles of visualizing the lumen of the gastrointestinal tract: the curvy anatomy of the gastrointestinal tract and the lack of natural illumination in the lumen. At first, endoscopy was introduced as a technique to visualize the esophagus, but later on it became a technique that enabled visualization of all parts of the digestive tract. It was only in the nineteen-seventies and nineteen-eighties that new endoscopes were developed that enabled the physician to also visualize the biliary system and pancreas. Due to the development of endoscopic retrograde cholangiopancreaticography (ERCP) and endoscopic ultrasound (EUS), the biliary system and pancreatic duct became more easily accessible, with increasing diagnostic and therapeutic options. This has led to a shift from radiological diagnosis to diagnostic endoscopy and from surgical treatment to therapeutic endoscopy in patients with pancreaticobiliary diseases.

During ERCP, a flexible endoscope (i.e. 'duodenoscope') is introduced via the mouth, esophagus and stomach into the first part of duodenum, to the papilla of Vater, which is the entrance to the common bile duct (CBD) and pancreatic duct (PD). The duodenoscope has an accessory channel through which accessory instruments can be advanced into the CBD and PD, after cannulation of the papilla of Vater (**Figure 1**). By means of contrast injection and subsequent fluoroscopy the ductal system can be visualized, and by introducing devices via the accessory channel diseases can be treated under fluoroscopic guidance.

EUS is performed by using an echo-endoscope. This endoscope has an ultrasound transducer at the tip of the scope and has biopsy channels through which a needle can be advanced. Due to the small distance between the transducer and the target area, high resolution images can be obtained resulting in detailed imaging of the surrounding structures. Specifically, the pancreaticobiliary system can be visualized at a high resolution through the gastric or duodenal wall. In addition using special fine biopsy needles targeted samples can be obtained of tissue of interest (**Figure 2**).

As a result of ongoing improvements in ERCP and EUS techniques and development of novel tools, advanced endoscopy has gained an important role in diagnosis and treatment of pancreaticobiliary diseases. This thesis focuses on one of the most important novel developments in advanced pancreaticobiliary endoscopy, cholangiopancreatoscopy, and on optimization of other current diagnostic and therapeutic endoscopic strategies in biliary and pancreatic diseases.

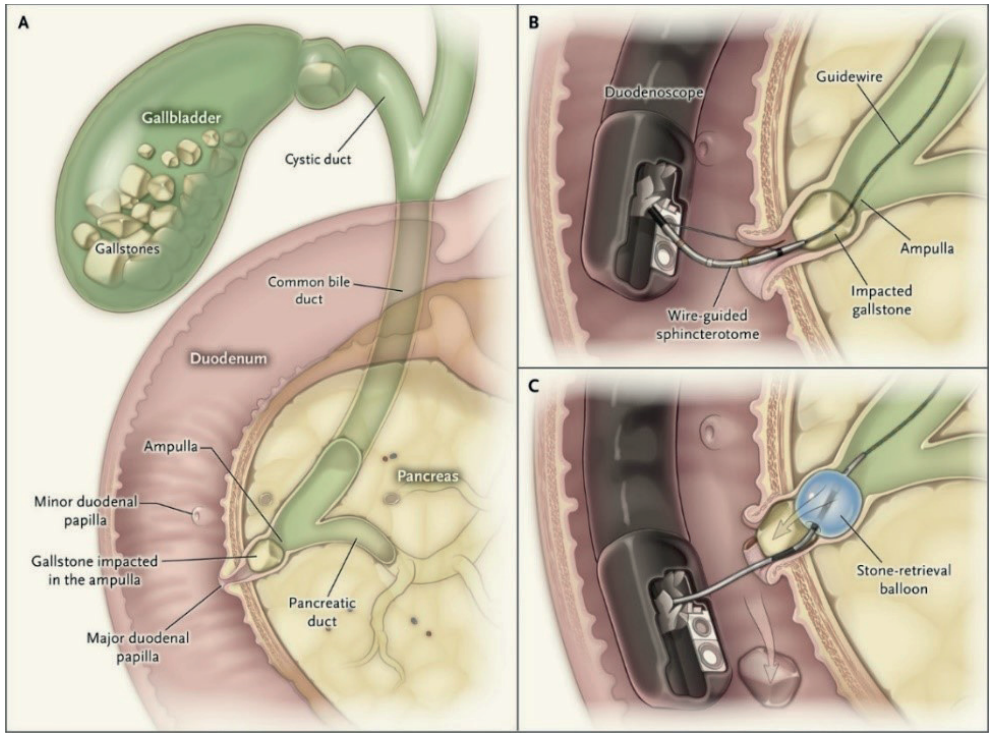

Figure 1. Endoscopic retrograde cholangiopancreaticography (ERCP). A. Illustration showing anatomy of the bile duct and pancreatic duct, in relation to the duodenum. B. & C. Illustration of accessory tools introduced via the papilla of Vater to perform treatment (in this case bile duct stone removal). (Reproduced with permission from (1), Copyright Massachusetts Medical Society).

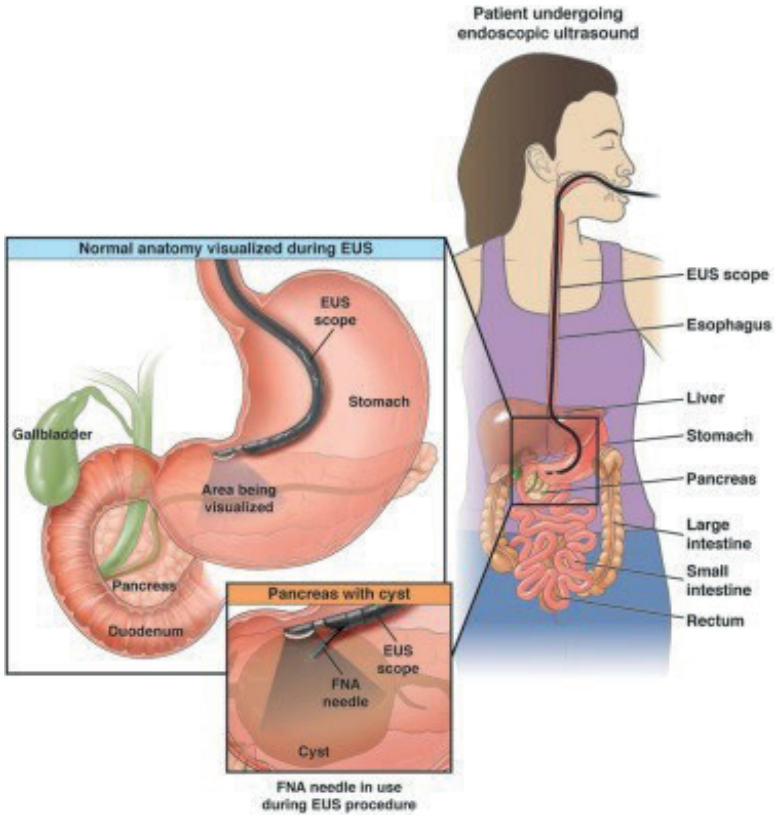

Figure 2. Echo-endoscope visualizing the pancreas, through the gastric wall. A fine needle is used to puncture a cystic lesion in the pancreatic body. (This figure was published in Clinical Gastroenterology and Hepatology, Volume 17, AGA Patient Education Section, Endoscopic Ultrasound, p38., Copyright Elsevier (2019) (2)).

Cholangiopancreatoscopy

Technique

Direct intraductal visualization of the pancreaticobiliary system by peroral cholangiopancreatoscopy was first described in the 1970s (3). Two techniques were available; direct or indirect peroral cholangiopancreatoscopy. Direct cholangioscopy uses conventional endoscopes, mainly pediatric or transnasal esophagogastroduodenoscopes, to directly enter the CBD. However, advancing the ultraslim gastroscope into the CBD is technically challenging, due to for example gastric looping, requirement of a large sphincterotomy, and instability of the endoscope once introduced in the CBD. Therefore, this system has failed to achieve widespread adoption in daily practice (4).

The first indirect cholangiopancreatoscopy system that was available was the so called dual-operator ''mother-baby" peroral cholangiopancreatoscopy. This technique uses a

dedicated ultra slim endoscope with a fiber-optic probe (''baby'' scope) that is advanced into the CBD or PD through the working channel of a duodenoscope (''mother'' scope). This technique requires two operators to control the two different scopes simultaneously. Wide clinical acceptance was never achieved because of suboptimal image quality, fragility of the devices and the need for two operators. These disadvantages were overcome by the introduction of the first single-use single-operator cholangiopancreatoscopy system (SOC) in 2007 (Spyglass Direct Visualization System, Boston Scientific Inc., Natick, Massachusetts, USA). The cholangiopancreatoscope is advanced through the working channel of a duodenoscope and is secured to the duodenoscope handle, enabling the endoscopist to control both scopes simultaneously (4,5). Further improvement led to introduction of a digital imaging version in 2015 (d-SOC) (Spyglass DS Direct Visualization system) and the newest version in 2018 (Spyglass DS II Direct Visualization system). The digital optics together with improved suction and irrigation abilities of the system and a wider field of view resulted in a significantly improved visualization. This has led to an increased use of cholangiopancreatoscopy in clinical practice for diagnostic and therapeutic indications and in a growing body and quality of research in this field.

Clinical applications

The major advantages of cholangiopancreatoscopy over ERCP and EUS are the ability to directly visualize the intraductal mucosa, enabling visual assessment of intraductal lesions, and the ability to introduce instruments into the CBD or PD through a dedicated access channel of these single-use single-operator cholangiopancreaticoscopes, allowing for targeted diagnostic or therapeutic interventions under direct visualization, such as taking targeted biopsies or intraductal lithotripsy.

The European Society of Gastrointestinal Endoscopy (ESGE) and the American Society for Gastrointestinal Endoscopy (ASGE) have provided technology reviews on intraductal pancreaticobiliary imaging (4,5). These reviews provide an overview of the available techniques for intraductal imaging, including cholangiopancreatoscopy, and diagnostic and therapeutic indications of cholangiopancreatoscopy are described based on currently available literature. In addition, several systematic reviews and meta-analyses have been published summarizing the most common indications of cholangiopancreatoscopy. However, due to limited high quality (prospective or randomized) studies, an international consensus guideline including recommendations on equipment, technique and clinical indications is lacking.

Biliary indications

In current clinical practice, SOC is primarily used for the treatment of difficult bile duct stones and evaluation of (indeterminate) biliary strictures. Much less, SOC is used to determine the extent of cholangiocarcinoma (CCA), palliative therapy of biliary malignancy and selective cannulation of intrahepatic ducts (4).

Difficult bile duct stones are stones that cannot be removed using conventional techniques, i.e. ERCP with endoscopic sphincterotomy (ES) and stone extraction using a balloon or basket. Several contributing factors to difficult removal have been described, such as large stones (>15 mm), strictures, altered anatomy due to surgery, significant ductal

angulation or impacted stones (6,7). Using SOC, intraductal lithotripsy can be performed, using either laser lithotripsy (LL) or electrohydraulic lithotripsy (EHL). This is reported to be a safe and effective tool for removal of difficult bile duct stones, with complete ductal clearance of extrahepatic stones in 71-100% of patients (4,5), but lower rates reported for intrahepatic stones (7), with a higher adverse event rate in the latter (8). Advantages of SOC for removal of difficult bile duct stones as compared to conventional techniques include a lower number of lithotripsy sessions, better assessment of bile duct clearance with regard to residual stones, and the ability to treat strictures simultaneously (5,9).

Indeterminate biliary strictures present a diagnostic challenge and are defined as strictures of indeterminate nature after previous diagnostic work-up (i.e. laboratory investigations, cross-sectional imaging and/or EUS- or ERCP-guided tissue sampling), or suspicion of malignancy despite previous benign histopathology results. In addition, benign conditions such as primary sclerosing cholangitis (PSC) and IgG4-related cholangitis may mimic malignant disease, posing added diagnostic difficulty in making a benign or malignant diagnosis. Unfortunately, diagnostic methods such as ERCP with brush cytology or intraductal biopsies have a poor sensitivity for diagnosing malignancy. A comparative systematic review and meta-analysis regarding fluoroscopy-guided brush cytology and intraductal biopsies reported sensitivity rates of 45% and 48%, respectively, increasing to only 59% when combined (10). The use of SOC in this setting may improve detection of malignancy by identification of endoscopic findings that are suggestive of malignancy and by taking SOC-guided targeted biopsies. Overall, high diagnostic accuracy rates have been reported for the visual diagnosis of malignant biliary strictures using SOC, with sensitivity, specificity and accuracy rates ranging from 78 to 100%, 78 to 98%, and 80 to 97%, respectively, with slightly higher rates reported for digital SOC (d-SOC) (11-13). With regard to SOC-guided biopsies, rates that have been reported range between 49-100%, 82-100% and 55-100%, respectively (11,12). A comparative study by Draganov et al. reported significantly higher sensitivity and accuracy rates for SOC-guided biopsies as compared to fluoroscopy-guided biopsies and brush cytology (77% and 85%, 29% and 54%, and 6% and 39%, respectively) (14). In summary, diagnostic accuracy rates reported for visual impression and SOC-guided targeted biopsies exceed rates that have been reported for fluoroscopy-guided brush cytology and intraductal biopsies. In addition, diagnostic accuracy rates for the visual impression during SOC are even higher than those reported for SOC-guided biopsies, suggesting that the visual impression is better at detecting malignancy than tissue examination is. Although promising, future studies are needed to further define and classify cholangioscopic features consistent with benign and malignant strictures, as it has already been shown that features may overlap (15). Furthermore, due to its relative novelty, a consensus should be reached as to the actual appearance and definition of the individual features, as two studies by Sethi et al. showed that there is poor interobserver agreement (IOA) with regard to cholangioscopic features, even among expert endoscopists (16,17).

Pancreatic indications

With regard to pancreatic indications, SOC is primarily used for treatment of pancreatic duct stones in patients with chronic pancreatitis (CP) and for evaluation of PD strictures and suspected intraductal papillary mucinous neoplasm (IPMN) (4,5).

In patients with CP, obstruction of the PD is often caused by strictures (47%), stones (18%) or a combination of the two (32%) (18). Obstruction of the PD may lead to intraductal hypertension and parenchymal pressure and ischemia, causing severe abdominal pain. In current clinical practice, treatment of patients with symptomatic CP follows a step-up approach, where medical therapy is applied first and endoscopic therapy as second step after failure of medical therapy (19). Endoscopic therapy is aimed at pain relief, mainly by restoring ductal outflow by treatment of strictures or stone removal. Small stones can usually be removed during ERCP using a basket or balloon. For stones >5 mm, extracorporeal shockwave lithotripsy (ESWL) is recommended as first-line endoscopic treatment option (19,20), with stone fragmentation using an electromagnetic lithotripter, usually performed in multiple sessions, followed by removal of stone fragments during subsequent ERCP. For this technique, however, dedicated equipment and expertise are required, limiting the availability of ESWL. According to meta-analyses, successful stone fragmentation is reported in 38-100% of patients, requiring 1-4 sessions (21,22). Currently, SOC with intraductal lithotripsy (using either LL or EHL) is only recommended after failure of ESWL and ERCP or when ESWL is unavailable (20). Overall, complete or partial ductal clearance using SOC with intraductal lithotripsy is achieved in 43-100% of patients, which is comparable to ESWL performance (23-25), with higher success rates reported for stones located in the head or neck of the pancreas. Clinical success, which is defined as reduced abdominal pain, less opiate usage and/or less hospitalization days related to CP, is achieved in 74-95% of patients (24-27). To date, data on technical and clinical success of SOC-guided lithotripsy come from small, retrospective studies, which only reported results regarding second-line therapy, after failed ESWL. An advantage of SOC-guided lithotripsy might be that stones can be fragmented and removed during the same session and that concomitant strictures can be treated simultaneously. In addition, SOC-guided lithotripsy can be performed in any hospital with an ERCP facility, provided that an expert ERCPist is available with ample expertise in SOC and SOC-guided lithotripsy. There are currently no data available regarding technical and clinical success of SOC-guided lithotripsy when used as first-line treatment of symptomatic CP with stones located in the head or the neck of the PD.

IPMN is among the most important precancerous lesions of the pancreas and is characterized by intraductal papillary proliferation of mucin producing cells resulting in cystic dilation of the PD (28). IPMN can be divided into three different types, based on anatomical location; branch duct IPMN (BD-IPMN), mixed-type IPMN (MT-IPMN), and main duct IPMN (MD-IPMN). Of these, MD-IPMN is at highest risk of developing malignancy. Therefore, determining the diameter and the presence of lesions in the main pancreatic duct (MPD) is important, as MD-IPMN is often considered to be an indication for surgery. Currently, the diagnostic work-up of IPMN consists of magnetic resonance cholangiopancreatography (MRCP), computed tomography (CT), or EUS with fine-needle aspiration (FNA). In addition, ERCP with intraductal biopsies and/or pancreatic fluid cytology can be performed. Nevertheless, determining the presence of high-grade dysplasia or invasive carcinoma and the extent of the lesion can be challenging. As a result, setting the right indication for surgery remains difficult as well as determining the extent of surgery. In an attempt to optimize the diagnostic work-up of IPMN, SOC has been increasingly used. Similar to evaluation of indeterminate biliary strictures, SOC

enables intraductal visualization and has potential benefit in identification of high risk or worrisome features, performance of SOC-guided targeted biopsies and determining the intra-ductal extent of the lesion. However, most data come from retrospective series with varying study designs. Therefore, the exact role of SOC in the diagnostic algorithm of IPMN remains unclear and needs to be specified.

Optimization of endoscopic strategies in biliary and pancreatic diseases

The role of advanced endoscopy in diagnosis and treatment of biliary and pancreatic diseases has become increasingly important over the past decades. As mentioned before diagnostic endoscopy has gained a more prominent role as compared to radiological diagnosis, and therapeutic endoscopy has gained a more prominent role as compared to primary surgical treatment. Among the most important indications for ECRP and EUS in pancreaticobiliary diseases are treatment of biliary and pancreatic calculi or strictures, biliary or pancreatic drainage, delineation of IPMN or CCA, or tissue sampling from pancreatic or biliary lesions. Furthermore, advanced endoscopy has gained an important role in the treatment of acute pancreatitis due to several large multicenter trials that have shown favorable outcomes for endoscopic treatment compared to surgical treatment (29-31). Therefore, this part of the thesis mainly focuses on acute pancreatitis.

Acute pancreatitis

Aetiology and diagnostic approach

The most common cause of acute pancreatitis (AP) is gallstone disease in 40-70% of patients, followed by alcohol abuse (32). Less common causes include hypertriglyceridemia, post-ERCP complication, genetic risk, medications, pancreatic duct injury or anatomic or physiologic pancreatic anomalies, such as pancreas divisum.

After diagnosis of AP, the aetiology should be determined for adequate treatment. Medical history (i.e. previous AP episode, known gallstone disease, alcohol intake, medication and drug use, trauma or recent ERCP), physical examination, laboratory serum tests (i.e. liver enzymes, triglycerides, or calcium) and imaging are used to determine the aetiology. In patients with a suspected biliary cause of AP, the current diagnostic work-up consists of laboratory tests and abdominal ultrasound to evaluate the presence of stones or sludge in the CBD. However, diagnostic accuracy rates for detection of CBD stones by means of these modalities is reported to be low (33). EUS is suggested to be the most reliable diagnostic tool to detect CBD stones (34). A recent systematic review has shown that performance of EUS prior to ERCP could prevent patients from undergoing an ERCP for suspected obstructing CBD stones, without a negative effect on the clinical course of AP (35). Currently, EUS is only recommended in case the aetiology is considered to be idiopathic after negative routine diagnostic work-up, and should be performed to evaluate the presence of microlithiasis in the CBD, CP or neoplasms (36).

Treatment

Initial treatment of AP consists of adequate pain control, fluid resuscitation using Ringer's lactate, and nutritional support in patients with predicted severe AP who fail to thrive

after 72 hours (37). In addition, it is important to address and treat the underlying cause. For example, medication or drugs that initiated the AP should be discontinued, patients with known alcohol abuse should receive counselling, and triglyceride or calcium levels should be normalized.

In patients with acute biliary pancreatitis (ABP), most stones pass through the papilla of Vater into the duodenum. However, in a small proportion of patients, stones are retained and cause persistent obstruction of the CBD and possibly the PD. According to the guidelines, immediate ERCP with ES is only indicated in case of concomitant cholangitis and is not recommended to perform in patients with predicted mild ABP (36,38). There is however no consensus as to whether early ERCP with ES would be beneficial for patients with predicted severe ABP without cholangitis. A randomized controlled trial (RCT), the APEC-trial, performed by the Dutch Pancreatitis Study Group (DPSG), has addressed this question. This study compared early ERCP with ES to conservative treatment in patients with predicted severe ABP without cholangitis, with regard to major complications and mortality. This study showed no significant difference between the two groups with regard to occurrence of major complications or mortality (39). However, in these patients suspicion of a biliary origin was based on alanine-aminotransferase (ALAT) levels and CBD diameter and no EUS was performed prior to ERCP performance. As aforementioned, EUS is suggested to be the most reliable tool for detection of stones or sludge in the CBD. Subsequently, EUS may allow to proceed to early ERCP with ES only in patients with confirmed stones or sludge who may potentially benefit from the procedure, but withhold patients from this intervention when EUS is negative. Finally, after recovery cholecystectomy should be performed to prevent recurrent ABP.

With regard to pancreatic anomalies as a cause of AP, pancreas divisum is the most common pancreatic anomaly, present in 2-10% of the general population (40,41). In pancreas divisum, the ventral and dorsal pancreatic duct have failed to fuse during embryogenesis, resulting in drainage of pancreatic excretions predominantly through the duct of Santorini and minor papilla (42). Although the vast majority of patients with pancreas divisum are asymptomatic, in approximately 5% of patients it causes recurrent episodes of AP or flares of CP, with subsequent risk of pancreatitis-associated complications such as chronic abdominal pain, walled-off pancreatic necrosis (WOPN) or pseudocysts, or pancreatic insufficiency. These patients may benefit from treatment, either surgical or endoscopic, which is aimed at improving ductal outflow. Regarding treatment options, a systematic review reported similar results for surgical and endoscopic therapy with regard to complete or partial pain relief (43). As endoscopic therapy is less invasive than surgery, this might be a favourable first-line approach, reserving surgery as second-line therapy after failure of endoscopic therapy. Endoscopic therapy consists of ES and temporary stent placement in the duct of Santorini of the minor papilla. However, being a relatively uncommon cause of AP, only limited data is available regarding the short-term and long-term clinical success and the occurrence of treatment-related adverse events. Therefore, to date, the exact role of endoscopic therapy in the management of symptomatic pancreas divisum remains unclear.

Endoscopic management of acute necrotizing pancreatitis

In the majority of patients with AP the disease will have a mild course with rapid favourable recovery. However, approximately 20% of patients with AP will develop acute necrotizing pancreatitis (ANP), with necrosis of the pancreatic parenchyma and/or peripancreatic tissue. About 30% of patients with ANP will develop infected necrosis, which is associated with high mortality rates of between 15 and 30% (44-46). Therefore, treatment of infected ANP is virtually always necessary to prevent ongoing infection and sepsis-related multi-organ failure.

Regarding treatment of ANP, the ESGE guideline only recommends invasive treatment after previous conservative treatment, in case of ANP with proven or clinically suspected infected necrosis, persistent organ failure, failure to thrive, or sterile necrosis with organ compression or persistent pain (37). Recently, treatment of infected ANP has shifted from early open surgery to minimally-invasive techniques following a step-up approach. Using such an approach, first endoscopic transluminal drainage or percutaneous drainage is performed, after initial treatment with antibiotics. As second step, in case of insufficient improvement after drainage, endoscopic necrosectomy or video-assisted retroperitoneal debridement (VARD) can be performed. By first performing endoscopic or percutaneous drainage, a considerable proportion of patients (35-70%) can be adequately treated, avoiding the need for additional necrosectomy (30,47-49).

Endoscopic drainage can either be performed transmurally via the stomach or duodenum or transpapillary via the PD. Collections abutting the stomach or duodenum are better candidates for transmural drainage, whereas small collections that are in communication with the MPD are better candidates for transpapillary drainage. Transmural drainage is performed by creating a fistula between the collection and gastric or duodenal lumen. Under EUS-guidance the collection is punctured using an FNA needle, with subsequent balloon dilation and stent placement with either multiple plastic double-pigtail stents or a metal stent (i.e. a lumen-apposing metal stent (LAMS) or a fully-covered self-expendable metal stent (FC-SEMS)).

Endoscopic necrosectomy can be performed by entering the cystic cavity through the fistula that is maintained by the previously placed plastic pigtail stents after subsequent balloon dilation of the tract up to 18 mm or through a lumen opposing metal stent (15 or 20 mm) that deployed over the guidewire to ensure drainage of the collection. A wide variety of instruments is used to perform endoscopic necrosectomy, including retrieval baskets, snares, or biopsy forceps. These instruments were not primarily designed for endoscopic necrosectomy and therefore carry several limitations, such as lack of sufficient grip on the necrotic tissue and poor endoscopic visualization in the cavity resulting in time-consuming procedures with often unsatisfactory results. These limitations jeopardize the effectiveness of endoscopic necrosectomy and often necessitate repeat procedures in order to clear the cavity. A mean of 4 procedures was reported in a meta-analysis by Puli et al. (50).

Duodenal perforation after biliary stenting

Complications of ERCP include post-ERCP pancreatitis, cholangitis, bleeding or perforation (51). However, as ECRP is increasingly used in complex patients, more rare complications might become more important. As mentioned before, restoring biliary drainage in case of a biliary obstruction is now an important indication for ERCP. Specifically, transpapillary drainage using plastic stents is a well-established treatment for biliary obstruction due to strictures or cholelithiasis. Endoscopic stent placement may be complicated by the occurrence of stent occlusion necessitating repeat ERCP with stent placement, or by stent migration. Stent migration is reported to occur in 5-10% of patients (52-55). Luckily, the vast majority of stents that have migrated distally pass through the digestive tract spontaneously. Some distally migrated stents however may cause erosion or ulcers on the contralateral duodenal wall by mechanical friction. This may in turn lead to pressure necrosis resulting in perforation of the duodenal wall. Stent migration-induced duodenal wall perforation (SMDP) is a rare, but potentially life-threatening complication, associated with intra-abdominal or retroperitoneal abscesses or sepsis (56). Therefore, early recognition and adequate treatment is mandatory. However, SMDP has only been reported in case reports and small case series and therefore the actual prevalence and possible risk factors remain unclear.

AIMS AND OUTLINE OF THIS THESIS

Based on the above given overview of the various applications of advanced endoscopic techniques in pancreaticobiliary diseases, the available evidence but especially the gaps that still remain in this research, the following aims and focus of the present thesis were chosen.

Aims

The primary aim of this thesis was to investigate the clinical value of a relatively new endoscopic technique, i.e. SOC, for use in diagnosis and treatment of pancreaticobiliary diseases. The secondary aim was to contribute to the body of evidence on existing diagnostic and therapeutic endoscopic strategies in biliary and pancreatic diseases.

Outline of this thesis

This thesis is divided into four parts. **Part I** contains the general introduction, aims and outline of this thesis. In **Chapter 1** a general introduction is given including existing advanced endoscopic techniques (i.e. ERCP, EUS, and SOC), aetiology of and diagnostic approach to acute pancreatitis, treatment of acute pancreatitis and its complications, and complications of biliary stenting. Also, the aims and outline of this thesis are described.

Part II of this thesis focuses on the feasibility, use and clinical value of SOC. Part II starts with a European survey on the clinical practice patterns of indirect SOC, with the aim to investigate the techniques used and main indications (**Chapter 2**).

One of the most important biliary indications for SOC is the evaluation of indeterminate biliary strictures. Previous studies have shown promising results as to diagnosing malignant

strictures, with higher diagnostic accuracy rates reported for the visual diagnosis as compared to SOC-guided targeted biopsies. However, study populations may not always have been representative, for example including a low number of patients with primary sclerosing cholangitis (PSC), in whom differentiation of strictures is notoriously difficult. In addition, in most studies the endoscopists were not blinded to patients' medical history and outcomes of previous investigations. **Chapter 3** describes a retrospective cohort study investigating the current diagnostic accuracy and interobserver agreement (IOA), in a study population with a high pre-test probability of having CCA, while blinding the reviewing endoscopists to all clinical information.

The most common pancreatic indication for SOC is treatment of pancreatic duct stones in patients with symptomatic CP. In **Chapter 4** an overview is given of the endoscopic treatment options for pain in patients with CP. Currently, ESWL is the recommended first-line therapy for patients with symptomatic CP and stones of >5 mm in the head or neck of the pancreas. **Chapter 5** describes a prospective consecutive case series investigating the feasibility and clinical success of SOC with intraductal lithotripsy, i.e. EHL, as first-line treatment option, without prior ESWL.

In addition to treatment of pancreatic duct stones, SOC is now increasingly used in the diagnostic algorithm of IPMN. **Chapter 6** describes a meta-analysis of studies investigating the diagnostic yield, safety and clinical utility of SOC in the management of IPMN.

Part III of this thesis focuses on optimizing endoscopic diagnosis and treatment of AP. The most common cause of AP is gallstones and diagnosis can be established by means of laboratory testing and abdominal ultrasound. However, these modalities suffer from moderate accuracy rates. EUS is considered to be a more sensitive tool for detecting bile duct stones or biliary sludge. In case of predicted severe AP and presence of cholangitis, urgent ERCP with ES is indicated. It is however unknown if patients with predicted severe biliary AP without cholangitis will benefit from urgent ERCP. **Chapter 7** describes a multicenter prospective study, designed as third treatment arm to a randomized controlled trial, investigating the clinical value of urgent EUS-guided ERCP with ES in patients with predicted severe biliary AP without cholangitis, with regard to the occurrence of major complications and mortality.

A less common, but clinically relevant cause of AP is pancreas divisum, an anatomical anomaly. A subgroup of patients with pancreas divisum presents with recurrent AP or chronic abdominal pancreatic-type pain or even progresses to CP. In these patients endoscopic therapy is often applied, including ES and/or stent placement in the pancreatic duct. However, due to its low incidence there is limited data to support this strategy. In **Chapter 8** a multicenter retrospective cohort study is described investigating the short-term and long-term efficacy and safety of endoscopic therapy in these patients.

Several instruments are available to perform endoscopic necrosectomy, such as retrieval baskets, snares or biopsy forceps. However, these instruments are not specifically designed for use in endoscopic necrosectomy, resulting in inefficient removal of necrotic debris and time-consuming procedures. The EndoRotor® Powered Endoscopic Debridement™ (PED)

System (Interscope, Inc., Northbridge, MA, USA) is a new dedicated instrument, designed to simultaneously resect and remove necrotic debris within walled-off pancreatic necrosis. A pilot study showed that less necrosectomy procedures were required as compared to previously reported numbers when conventional techniques were used, and that no procedure-related adverse events occurred. In **Chapter 9** an international multicenter prospective device trial is described further investigating the safety and efficacy of the EndoRotor® PED™ System.

In **Chapter 10** a retrospective cohort study is presented, evaluating the prevalence, clinical course and possible risk factors for stent migration-induced duodenal perforation (SMDP). SMDP is considered to be a rare, but potentially life-threatening complication of transpapillary biliary plastic stent placement used as treatment for bile duct obstruction caused by strictures or cholelithiasis. However, data come from case reports or small case series and therefore the actual prevalence remains unknown, as well as possible risk factors. This chapter aims to enlarge the available information.

Part IV consists of the summary, discussion and future perspectives of this thesis (**Chapter 11**) and the Dutch summary (**Chapter 12**).

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Part II

Cholangiopancreatoscopy

Chapter 2

Clinical practice patterns in indirect peroral cholangiopancreatoscopy: outcome of a European survey

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ABSTRACT

Background and aim: Indirect peroral cholangiopancreatoscopy (IPOC) is a relatively new diagnostic and therapeutic tool for biliopancreatic diseases. This international survey aimed to evaluate clinical practice patterns in IPOC amongst endoscopists in Europe.

Methods: An online survey was developed comprising 66 questions on the use of IPOC. Questions were grouped into 4 domains. The survey was sent to 369 endoscopists who perform IPOC.

Results: 86 respondents (23.3%) from 21 different countries across Europe completed the survey. The main indications for cholangioscopy were determination of biliary strictures (85 (98.8%)) and removal of common bile duct or intrahepatic duct stones (79 (91.9%)), accounting for an estimated use of 40% (interquartile range (IQR) 25-50) and 40% (IQR 30-60), respectively, of all cases undergoing cholangioscopy. Pancreatoscopy is mainly used for removal of pancreatic duct stones (68/76 (89.5%)), accounting for an estimated use of 76.5% (IQR 50-95) of all cases undergoing pancreatoscopy. Only 13/85 respondents (15.3%) had an institutional standardized protocol for targeted cholangioscopy-guided biopsy sampling. IPOC with lithotripsy was used as first-line treatment in selected patients with bile duct stones or pancreatic stones by 24/79 (30.4%) and 53/68 (77.9%) respondents, respectively.

Conclusion: This first European survey on the clinical practice of IPOC demonstrates a wide variation in experience, indications, and techniques. These results emphasize the need for prospective studies and development of an international consensus guideline to standardize the practice and quality of IPOC.

INTRODUCTION

Indirect peroral cholangiopancreatoscopy (IPOC) is a relatively new technique that was first described in the 1970s, but with an increasing role in the management of biliopancreatic diseases over the last 15 years (1). IPOC has enabled the endoscopists to directly visualize the intraductal mucosa. Together with the development of dedicated accessories, this has led to an increased diagnostic and therapeutic capability, by assisting in differentiating of malignant and benign lesions, taking targeted intraductal biopsies, and delineating intraductal tumors. Moreover, fragmentation of (difficult) bile duct or pancreatic duct stones can now be performed under direct visualization. The European Society of Gastrointestinal Endoscopy (ESGE) and the American Society for Gastrointestinal Endoscopy (ASGE) have provided technology reviews on intraductal biliopancreatic imaging (2,3), presenting an overview of the currently available techniques and instruments for intraductal imaging. Furthermore, diagnostic and therapeutic indications have been described based on the currently available literature. However, despite the technology reviews of the ESGE and ASGE, a clinical practice guideline or standardized protocol for IPOC is lacking. As IPOC is increasingly used in daily practice and technical improvements continue to be made, development of an international clinical guideline is crucial. Unfortunately, only a limited number of high quality studies are available in this field. As a result, current practice mainly relies on expert opinion and personal preference. In the process of developing a guideline, knowledge of current clinical practice in the performance of IPOC is necessary. Therefore, the aim of this survey was to evaluate the current clinical practice of IPOC in Europe, with regard to applied techniques and main indications.

METHODS

Study design

A European online survey was conducted among endoscopists who perform cholangioscopy and/or pancreatoscopy. The survey was sent to members of the European Cholangioscopy Group (see **Supplementary material**), which is an international research group established in 2018, with currently 37 members who are expert pancreaticobiliary endoscopists, from 10 different countries. In addition, the survey was sent to members of the German Spyglass User Group (see **Supplementary material**), authors working in European hospitals who have published on IPOC in the past 5 years of whom contact details were available online, and to Spyglass users who had given consent to Boston Scientific Inc. (Marlborough, Massachusetts, USA) for commercial use of their contact details.

The survey questions were developed by the core study team P.M.C.S., P.J.F.dJ., M.J.B., and V.C.), and were tested for content and clarity by a native English speaker (G.J.M.W.) and three other authors (M.E., A.J.D., and M.U). The survey consisted of 66 questions, divided into 4 domains:

1) experience in endoscopic retrograde cholangiopancreatography (ERCP), cholangioscopy, and pancreatoscopy;
2) equipment and technique;
3) indications for cholangioscopy; and
4) indications for pancreatoscopy.

An online survey was built using LimeSurvey, Version 2.06 LTS. The contents of this survey are provided in the supplementary Appendix. Invitations were sent through e-mail in September 2019, with reminders sent in October and November 2019.

Statistical analysis

Only completed surveys were used for statistical analysis. Descriptive statistics were used to analyze the data, using median and interquartile range (IQR) for non-normally distributed continuous variables, and frequencies and percentages (%) for categorical variables. The statistical analyses were performed using the statistical software package SPSS version 25 (IBM Corp, Armonk, New York, USA).

RESULTS

The survey was sent to 369 endoscopists who perform cholangioscopy and/or pancreatoscopy. In total, 86 endoscopists (23.3%) completed the survey, 25% of whom were affiliated to the European Cholangioscopy Group or German Spyglass User Group. Responses were received from 21 countries and 71 different hospitals. Demographic details are shown in **Table 1s**.

Endoscopic experience

The majority of the respondents were very experienced in ERCP, with a lifetime experience of over 1000 procedures (68 (79.1%)). Experience in IPOC was much more variable (**Figure 1**), with a greater lifetime experience in cholangioscopy than in pancreatoscopy, and also a higher number of cholangioscopy procedures performed on average per year over the past 5 years compared with pancreatoscopy procedures. Experience in pancreatoscopy showed that 6/86 (7.0%) had performed >100 procedures, but the majority of respondents (58/86 (67.4%)) had performed no more than 25 pancreatoscopies.

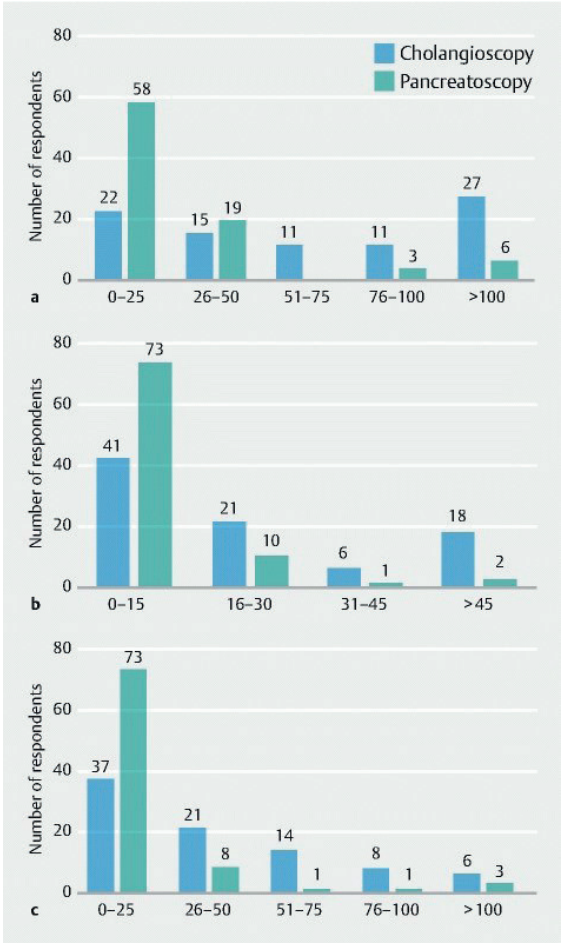

Figure 1. Experience in indirect peroral cholangiopancreatoscopy. ***a*** Total lifetime number of cholangioscopies and pancreatoscopies performed by the respondents. ***b*** Average number of cholangioscopies and pancreatoscopies performed by the respondents per year over the past 5 years. ***c*** Total number of cholangioscopies and pancreatoscopies performed per year in the hospitals of the respondents.

Equipment and technique

The vast majority of respondents used the second-generation SpyGlass DS Visualization System (82 (95.3%)). Compared with ERCP without IPOC, general anesthesia with endotracheal intubation was used more frequently than other sedation techniques for ERCP with IPOC. Antibiotic prophylaxis prior to or during cholangioscopy was routinely administered by most respondents (76.7%). Intraprocedurally, access to the biliary tree and to the pancreatic duct (PD) was achieved via over-the-wire insertion by the majority of the respondents (60 (69.8%) and 75 (87.2%), respectively). The remaining respondents performed direct access by free-hand cannulation. These results are presented in **Table 1**.

Table 1. Equipment and technique used by the respondents (n=86)

	n (%)
The main type of cholangiopancreatoscope used (multiple options possible)	
• The SpyGlass Direct Visualization System (first-generation)[1]	11 (12.8)
• The SpyGlass DS Direct Visualization System[1]	82 (95.3)
• CHF-BP30[2]	1 (1.2)
• Polyscope[3]	1 (1.2)
Number of operators	
• Single	76 (88.4)
• Double	10 (11.6)
Preferred patient position during IPOC	
• Supine	32 (37.2)
• Prone	40 (46.5)
• Left lateral	14 (16.3)
The most common type of sedation used for ERCP *without* IPOC	
• Conscious sedation	24 (27.9)
• Nurse administered propofol sedation	23 (26.7)
• Propofol administered by anaesthesiologist	18 (20.9)
• General anaesthesia with endotracheal intubation	21 (24.4)
The most common type of sedation used for ERCP *with* IPOC	
• Conscious sedation	6 (7.0)
• Nurse administered propofol sedation	21 (24.4)
• Propofol administered by anaesthesiologist	24 (27.9)
• General anaesthesia with endotracheal intubation	35 (40.7)
IPOC is scheduled as an	
• Outpatient procedure, discharge on the same day	30 (34.9)
• Inpatient procedure, at least one night hospital stay	56 (65.1)
Routinely administration of prophylactic antibiotics in patients undergoing IPOC	66 (76.7)
Access to the biliary tree is usually obtained by	
• Over the wire insertion	60 (69.8)
• Direct access	26 (30.2)
Access to the pancreatic duct is usually obtained by	
• Over the wire insertion	75 (87.2)
• Direct access	11 (12.8)
Type of medium used to improve visualization	
• Sterile saline	76 (88.4)
• Water	7 (8.1)
• Carbon dioxide (CO_2)	3 (3.5)

IPOC, indirect peroral cholangiopancreatoscopy; ERCP, endoscopic retrograde cholangiopancreatography.
[1]Boston Scientific, Marlborough, Massachusetts, USA., [2]Olympus, Tokyo, Japan., [3]PolyDiagnost GmbH, Hallbergmoos, Germany.

Indications for cholangioscopy

The three indications accounting for the most frequently performed procedures in daily clinical practice as reported by the respondents were:

1) removal of common bile duct (CBD) or intrahepatic stones (40% of procedures);
2) determination of biliary strictures (40% of procedures); and
3) delineation of known cholangiocarcinoma (CCA; 10% of procedures).

The results are shown in **Table 2**.

Table 2. Indications for cholangioscopy (n=86)

Biliary indication	Respondents, n (%)	Use in daily clinical practice, median, (IQR), %
Determination of biliary strictures	85 (98.8)	40 (25 – 50)
Removal of CBD or intrahepatic duct stones	79 (91.9)	40 (30 – 60)
Selective segment cannulation	57 (66.3)	5 (3.5 – 10)
Delineation of CCA	45 (52.3)	10 (5 – 17.5)
Removal of cystic duct stones	45 (52.3)	5 (3 – 7)
Removal of foreign bodies within the bile duct	43 (50.0)	5 (2 – 5)
Stricture negotiation	38 (44.2)	5 (3 – 8)
Recanalization of postoperative biliary disconnection	23 (26.7)	3 (1 – 5)
Transpapillary gallbladder drainage for acute cholecystitis	5 (5.8)	1 (1 – 3)
Access to biliodigestive anastomosis after Whipple's resection	1 (1.2)	2
Transgastric access to the bile duct	1 (1.2)	38

IQR, interquartile range; CBD, common bile duct; CCA, cholangiocarcinoma.

Bile duct stones

In total, 79/86 respondents (91.9%) used IPOC for removal of CBD and intrahepatic duct stones. The results are summarized in **Table2s**. In the treatment strategy, only one-third of respondents (30.4%) used IPOC with lithotripsy as first-line treatment without prior ERCP with conventional stone extraction techniques. In general, the mean number of IPOC procedures reported to be required to achieve stone clearance was 1 or 2 (46.8% and 48.1%, respectively). Two types of lithotripsy tools were available to respondents: electrohydraulic lithotripsy (EHL) by 64.6% and laser lithotripsy by 20.3% of users. Both tools were used by 15.2% of users.

IPOC for bile duct stone removal was most frequently used for stones located in the proximal CBD (93.7%) and in the hilum (92.4%), but was also used for stones located in the distal CBD (73.4%), left and right intrahepatic ducts (86.1% and 88.6%, respectively), and the cystic duct (64.6%). In cases with failed bile duct stone removal using IPOC with lithotripsy, this was mostly reported to be due to difficult fragmentation using EHL or laser lithotripsy (57.0%). Other frequently reported reasons included a stricture distal to the stone (48.1%), difficult stone location (46.8%), or the size of the stone (50.6%). Difficult stone locations were mostly the intrahepatic left and right ducts (75.7% and 64.9%, respectively).

Determination of biliary strictures

In total, 85/86 respondents (98.8%) used IPOC for determination of biliary strictures. For optimal intraductal visualization, the vast majority (92.9%) used white light and only a minority (7.1%) used white light in combination with chromoendoscopy (with vital staining). All respondents reported taking targeted biopsies under cholangioscopic visualization; however, only 63.5% of respondents reported taking cholangioscopic

targeted biopsies routinely in all patients. The remaining respondents did this in at least 50% of patients (29.4%) or in less than 50% of patients (7.1%). Furthermore, even though all respondents reported taking cholangioscopic targeted biopsies, only 15.3% reported having an institutional protocol available for targeted cholangioscopy-guided tissue sampling. Nevertheless, the vast majority of respondents took at least three biopsies (96.5%) and the majority (82.4%) took bite-on-bite biopsies from the identified lesions. After cholangioscopy-guided biopsies had been taken, about half of the respondents (48.2%) performed additional fluoroscopy-guided brush cytology. Finally, rapid onsite evaluation of touch imprint cytology (ROSE-TIC) or fluorescence in situ hybridization analysis was available to only a minority of respondents (2.4% and 9.4%, respectively). The results are shown in **Table3s**.

Delineation of CCA

IPOC for the preoperative delineation of CCA was used by 45/86 respondents (52.3%). A total of 42 respondents (93.3%) used IPOC with delineation as part of the preoperative diagnostic work-up protocol, all prior to surgery and not during surgery, with 69.0% relying on both visual characteristics and mapping biopsies.

With regard to clinical relevance, the majority of respondents reported that only in a small proportion of patients was the surgical approach altered by cholangioscopic findings preoperatively: in 0–20% of the patients according to 31.1% and in 21%–40% of the patients according to 42.2% of respondents. The results are presented in **Table4s**.

Indications for pancreatoscopy

A total of 10 respondents recorded that they did not perform pancreatoscopy, resulting in 88.4% of respondents (n=76) performing pancreatoscopy. The three indications accounting for the most frequently performed procedures in daily clinical practice were:

1) removal of pancreatic duct (PD) stones (76.5% of procedures);
2) determination of pancreatic strictures (30% of procedures); and
3) delineation of intraductal papillary mucinous neoplasms (IPMN; 20% of procedures).

These results are shown in **Table 3**.

Table 3. Indications for pancreatoscopy (n=76)

Pancreatic indication	Respondents, n (%)	Use in daily clinical practice, median (IQR), %
Removal of pancreatic duct stones	68 (89.5)	76.5 (50 – 95)
Determination of indeterminate pancreatic strictures	41 (53.9)	30 (15 – 40)
Delineation of IPMN	35 (46.1)	20 (10 – 40)
Removal of foreign bodies within the pancreatic duct	27 (35.5)	5 (5 – 20)
Dilatation of the Wirsung duct	1 (1.3)	6

IQR, interquartile range; IPMN, intraductal papillary mucinous neoplasm.

Pancreatic duct stones

In total, 68/76 respondents (89.5%) used IPOC for removal of PD stones. In the treatment algorithm of PD stones, 77.9% used IPOC with lithotripsy as first-line treatment, without prior extracorporeal shock wave lithotripsy (ESWL). However, 89.7% of users first performed conventional ERCP with sphincterotomy before performing IPOC lithotripsy. For PD stone removal, the majority of respondents used EHL (70.6%), 17.6% used laser lithotripsy, and 11.8% used both tools for PD stone fragmentation. IPOC for PD stone removal was mostly used for stones located in the head or the neck of the pancreas (97.1% and 75.0%, respectively). Half of the respondents (50.0%) reported successful PD stone removal in a single IPOC session. Where multiple sessions were required to achieve complete stone removal, this was due to a large stone size (67.6%), difficult stone location (52.9%), a stricture distal to the stone(s) (52.9%), or difficult stone fragmentation with EHL or laser lithotripsy (67.6%). Finally, after IPOC with lithotripsy, 89.7% reported placing a PD stent to provide drainage of pancreatic fluid. All responses are shown in **Table5s**.

Delineation of IPMN

IPOC for the delineation of main duct IPMN was used by 35/76 respondents (46.1%). Similarly to the use of IPOC in the preoperative work-up of CCA, IPOC was part of the preoperative diagnostic work-up of IPMN by 80.0% of respondents, with 71.4% relying on both visual characteristics and mapping biopsies for determining the extent of IPMN. The surgical approach was altered in less than half of the patients: in only 0–20% of the patients according to 42.9% and in 21%–40% of the patients according to 46.4% of respondents. These results are presented in **Table6s**.

DISCUSSION

This is the first European survey to investigate current clinical practice patterns of IPOC among endoscopists experienced in ERCP. The results showed that there was wide variation in both experience and use of IPOC. IPOC was most frequently used for biliary indications, mainly evaluation of biliary strictures and stone removal, which together accounted for a median of 80.0% of the indications that IPOC was used for in daily clinical practice.

According to this survey, the evaluation of biliary strictures was one of the main indications for cholangioscopy. Previous studies have shown very good results regarding the diagnostic accuracy of visual characteristics for determining the etiology of strictures, but considerable interobserver variation exists among endoscopists (4, 5). Morphological features of malignant and inflammatory disease may overlap significantly and not be exclusive or clearly discriminative, even for experienced endoscopists. As such, the widely used phrase "tissue is the issue" remains central. Kalaitzakis et al. showed that obtaining more than four biopsies compared with fewer than four biopsies resulted in a higher adequacy rate of the tissue samples (90% vs. 64%; P =0.037) (6). In addition, Gerges et al. showed that an accuracy rate of 66% can be achieved by taking at least three biopsies (7). In the current survey, we found that only 15.3% of respondents had an institutional protocol for taking cholangioscopy-guided biopsies. However, 96.5% took at least three

biopsies, which should increase accuracy rates of the specimen samples according to the literature. Furthermore, techniques for optimizing tissue yield vary widely, with some endoscopists performing bite-on-bite biopsies, and others obtaining an additional brushing after IPOC-directed biopsies. Very few respondents performed ROSE-TIC analysis. This technique has shown promising results in two studies, in which ROSE-TIC used for the diagnosis of indeterminate biliary strictures and pancreaticobiliary lesions showing sensitivity and specificity rates of 97%–100% and 88%–89%, respectively (8, 9). Optimizing visually directed pathological sampling may be the most important current task for cholangioscopic assessment of biliary strictures. Prospective studies are needed in order to inform the development of an international cholangioscopy-guided biopsy protocol aimed at improving diagnostic accuracy rates.

An interesting finding of this survey was the relatively common use of IPOC in clinical practice for preoperative determination of the extent ("mapping") of IPMN and/or CCA. The timing in clinical work-up for both indications is debatable. To the best of our knowledge, there is no guideline available recommending the timing and use of cholangioscopy in the preoperative work-up of CCA. For IPMN, the European Study Group of Cystic Tumours of the Pancreas has written an evidence-based guideline on pancreatic cystic neoplasms and recommended that pancreatoscopy may be used in selected cases to provide information on the location and extent of main duct IPMN, with higher accuracy rates reported for main duct IPMN compared with branch duct IPMN (88% and 67%, respectively) (10). Interestingly, according to the current survey, despite the lack of international recommendations, cholangioscopy was more frequently used for delineation of CCA (52.3%), with 93.3% of these respondents using it as part of the preoperative work-up, compared with pancreatoscopy for delineation of IPMN (46.1%), where 80% used it as preoperative work-up. Also noteworthy is that approximately half of the respondents that used IPOC in preoperative work-up (42.2% and 46.4%, respectively) reported that the surgical approach was altered in 21%–40% of patients, based on preoperative cholangioscopic or pancreatoscopic findings. This seems to be a considerable proportion of patients and is in line with the results of two recently published studies (11, 12). Tyberg et al. reported that the surgical approach was altered based on preoperative IPOC in 34% of patients in total. In 8/13 patients with IPMN the surgical approach changed: less extensive surgery in 4 patients and more extensive surgery in 4 patients. Furthermore, in 32/105 patients with presumed CCA, the surgical approach changed: less extensive surgery in 6 patients and avoidance of surgery in 26 patients, 14 of whom were found to have benign disease and 12 of whom were determined to be irresectable (11). Pereira et al. reported that the anatomical classification of CCA was altered based on cholangioscopic findings in 42% of patients, resulting in a changed surgical approach in 21% (n=4): more extensive surgery in 2 patients and avoidance of surgery due to irresectability in 2 patients (12). In both studies, a combination of visual assessment of the lesions and biopsy findings was used for preoperative assessment and led to identification of benign disease or a more extensive intraductal disease. Given the relatively high proportion of patients in whom the surgical approach was altered, this could be a very promising indication for IPOC, both to aid in the differentiation of cancerous from noncancerous lesions and for determination of lesion extent. However, given the risk of inducing cholangitis or post-ERCP pancreatitis preoperatively, possibly postponing surgical treatment in these patients, a decision to perform cholangiopancreatoscopy should be made after multidisciplinary discussion in a

team with radiologists, surgeons, and gastroenterologists. In these two previous studies, the rates of cholangitis or post-ERCP pancreatitis were 0-7% and 2.5%-11.6%, respectively (11, 12). Currently, data on preoperative use of IPOC for CCA and IPMN are still scarce, and therefore investigating the clinical utility and adverse event rate of preoperative delineation in prospective studies might be useful to determine the exact role, as it could lower the treatment burden for patients and lead to decreased health care costs for the treatment of patients with CCA or IPMN.

Another important finding of this survey involved the role of pancreatoscopy-guided lithotripsy in the treatment algorithm of symptomatic PD stones. Although the ESGE guideline recommends ESWL as first-line therapy for PD stones of >5mm, and to consider pancreatoscopic lithotripsy in cases of ESWL failure (13), 77.9% of our experienced endoscopists performed pancreatoscopy-guided lithotripsy without prior ESWL. Although there is no prospective literature available on the technical and clinical success of pancreatoscopy with EHL or laser lithotripsy as first-line treatment in patients with intraductal stones, very high success rates have been reported as second-line therapy (14). The advantages of performing this treatment is that successful fragmentation can be achieved in a mean of two lithotripsy procedures (14) and that strictures can be treated simultaneously. Compared with ESWL, it also allows not only stone fragmentation but also stone fragment removal at the same time. This could result in a lower total number of procedures, thereby reducing patient burden and costs. However, prospective studies are needed to investigate the technical and clinical success of pancreatoscopy-guided lithotripsy as a first-line treatment option, ideally followed by a randomized controlled trial directly comparing EHL or laser lithotripsy with ESWL.

Similarly to pancreatoscopy-guided lithotripsy, a considerable proportion of the respondents (30.4%) reported using cholangioscopy-guided lithotripsy as a first-line treatment option in selected cases without prior ERCP with conventional extraction techniques (i.e. basket or balloon). Again, this is not recommended by the ESGE guideline and cholangioscopy-guided lithotripsy is only recommended in cases of difficult bile duct stones (15). Although not specified in this survey, "selected cases" might be patients with one or multiple risk factors for difficult bile duct stone removal. As second-line treatment after ERCP with conventional extraction techniques, cholangioscopy-guided lithotripsy has shown promising results regarding technical and clinical success (99% and 92%, respectively) for treatment of difficult bile duct stones in a recently published study by Minami et al. (16). To the best of our knowledge, there are no studies available on technical and clinical success of IPOC-guided lithotripsy as a first-line treatment option. An advantage of this treatment strategy might be to prevent patients from undergoing repeated ERCP procedures without successful removal, with concomitant risk of ERCP-related complications. However, a diagnostic algorithm should be conducted to select the most appropriate patients who might benefit from a cholangioscopy-first treatment, and subsequently technical and clinical success needs to be investigated.

A striking finding was that, even though the majority of respondents administered intravenous antibiotics during the investigation, 23.3% did not. A retrospective study by Sethi et al. found a higher rate of cholangitis in patients undergoing ERCP with IPOC compared with patients undergoing ERCP without IPOC (17). More recently, Thosani et al.

found that bacteraemia was specifically related to IPOC, and not ERCP, in 13.9% of patients (18). Othman et al. also found bacteremia to be present in 9% of patients post-IPOC, with a higher rate of bacteremia in patients in whom biopsy sampling was performed compared with patients without sampling (P =0.011) (19). A definitive explanation for increased bacteremia and cholangitis has not been established, but the necessity of fluid irrigation (saline or water), perhaps into poorly drained biliary segments, under increased ductal pressure, is likely to play an important role. Given the increased risk of bacteremia and cholangitis, the ESGE technology review has already stated that administration of antibiotics in patients undergoing IPOC is considered to be important (3), and therefore it would also be vital that this is included in an international clinical practice guideline to standardize use of antibiotic prophylaxis in this subgroup of patients undergoing ERCP.

Finally, also noteworthy is that there was considerable variation in the type of sedation used for ERCP without IPOC and ERCP with IPOC. For ERCP without IPOC the most common type of sedation used was almost equally divided between conscious sedation, nurse-administered propofol sedation or propofol sedation administered by an anesthesiologist, and general anesthesia with endotracheal intubation. However, when ERCP was performed with IPOC, propofol administered by an anesthesiologist or general anesthesia with endotracheal intubation were the two most commonly used types of sedation (27.9% and 40.7%, respectively). This may be due to the fact that IPOC procedures are often lengthy and may be technically difficult to perform. Administration of enhanced anesthesia possibly makes IPOC procedures more comfortable for patients, which in turn makes the procedure easier for the endoscopist to perform.

A strength of this study is that we were able to reach a wide variety of endoscopists in many different countries. Unfortunately, in many countries we received a completed survey from only one endoscopist. Therefore, we were not able to analyze the difference in use between countries and regions. However, we were able to provide a general overview of the clinical practice patterns of IPOC throughout Europe. Another limitation of the survey is that strict privacy laws restricted our ability to contact endoscopists directly to invite them to participate in the survey. For example, we were not permitted to directly contact SpyGlass users who had given consent to Boston Scientific Inc. for commercial use of their contact details and were dependent on distribution of the survey through local representatives. This could have led to the low response rate (23.3%), which could be seen as a limitation of this paper with regard to providing a general overview of European clinical practice. However, we were able to collect responses from experienced endoscopists and therefore deem our results representative of current clinical practice. Nevertheless, it is not possible to be certain from this survey whether the study respondents represent usual IPOC practice in Europe.

In conclusion, this first European survey on clinical practice patterns of IPOC provides an overview of current clinical use of IPOC. The results demonstrated consensus in its role for the most common indications (assessment of biliary strictures and management of difficult biliary stones), but considerable variation in its overall role and in areas of clinical practice (e.g. pancreatic disease). There is an urgent need for standardization of indications and technical performance in an international consensus position statement.

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SUPPLEMENTARY MATERIAL

Table 1s. Demographic details

Country (n = 21)	Number of hospitals (n = 71)	Number of respondents (n=86)
Austria	1 (1.4%)	1 (1.2%)
Belgium	1 (1.4%)	1 (1.2%)
Bulgaria	1 (1.4%)	1 (1.2%)
Croatia	1 (1.4%)	1 (1.2%)
Czech Republic	1 (1.4%)	1 (1.2%)
Finland	6 (8.5%)	10 (11.6%)
France	6 (8.5%)	6 (7%)
Germany	13 (18.3%)	14 (16.3%)
Greece	3 (4.2%)	3 (3.5%)
Hungary	1 (1.4%)	1 (1.2%)
Italy	7 (9.9%)	8 (9.3%)
Lithuania	1 (1.3%)	2 (2.3%)
Norway	2 (2.8%)	3 (3.5%)
Poland	2 (2.8%)	2 (2.3%)
Russia	1 (1.4%)	1 (1.2%)
Slovenia	1 (1.4%)	1 (1.2%)
Spain	2 (2.8%)	3 (3.5%)
Sweden	4 (5.6%)	6 (7%)
Switzerland	1 (1.4%)	1 (1.2%)
The Netherlands	6 (8.4%)	9 (10.5%)
The United Kingdom	10 (14.1%)	11 (12.8%)

Table 2s. Bile duct stones

	N=79
Use of IPOC with lithotripsy as the first treatment option, without prior ERCP with conventional stone extraction techniques, in selected cases	24 (30.4%)
Use of IPOC with lithotripsy is usually for stone removal after failed prior ERCP with conventional stone extraction techniques	78 (98.7%)
Use of IPOC for confirmation of bile duct clearance after ERCP with conventional stone extraction techniques	20 (25.3%)
The mean number of ERCPs prior to IPOC for stone removal	
• 0	4 (5.1%)
• 1	30 (38%)
• 2	40 (50.6%)
• 3	5 (6.3%)
The mean number of IPOCs to obtain stone clearance	
• 1	37 (46.8%)
• 2	38 (48.1%)
• 3	3 (3.8%)
• ≥4	1 (1.3%)
The type of lithotripsy tool used for removal of bile duct stones	
• Electrohydraulic lithotripsy	51 (64.6%)
• Laser lithotripsy	16 (20.3%)
• Both	12 (15.2%)
The type of lithotripsy tool preferred to use for removal of bile duct stones is (not necessarily available in the hospital):	
• Electrohydraulic lithotripsy	56 (70.9%)
• Laser lithotripsy	23 (29.1%)
Cholangioscopy for bile duct stone removal is used for stones located in the (multiple options possible)	
• Distal common bile duct (distal to insertion of cystic duct)	58 (73.4%)
• Proximal common bile duct (proximal to insertion of cystic duct)	74 (93.7%)
• Hilum	73 (92.4%)
• Left intrahepatic bile ducts	68 (86.1%)
• Right intrahepatic bile ducts	70 (88.6%)
• Cystic duct	51 (64.6%)
Failure of biliary stone removal is usually due to (multiple options possible)	
• Stricture distal to the location of stones	38 (48.1%)
• Difficult stone location	37 (46.8%)
• Size of the stone	40 (50.6%)
• The number of stones	23 (29.1%)
• Difficult fragmentation of the stone with EHL/ laser lithotripsy	45 (57%)
In case of difficult stone location, this is usually in (multiple options possible)	**N=37**
• Distal common bile duct (distal to insertion of cystic duct)	5 (13.5%)
• Proximal common bile duct (proximal to insertion of cystic duct)	5 (13.5%)
• Hilum	8 (21.6%)
• Left intrahepatic bile ducts	28 (75.7%)
• Right intrahepatic bile ducts	24 (64.9%)
• Cystic duct	15 (40.5%)
After failure of stone removal by cholangioscopy	
• A repeat ERCP with IPOC is scheduled	62 (78.5%)
• A percutaneous transhepatic drain is placed	0 (0%)
• Patient is scheduled for ESWL	4 (5.1%)
• Patient is referred to the surgeon	12 (15.2%)
• A percutaneous transhepatic drain is placed	1 (1.3%)

Table 3s. Indeterminate biliary strictures

	N=85
Visualization of biliary strictures is performed by	
• White light	79 (92.9%)
• White light with digital chromo-endoscopy (narrow band imaging (NBI))	5 (5.9%)
• White light with chromo-endoscopy with vital staining	1 (1.2%)
Difficulty of failure of visualization of the target area is usually due to (multiple options possible)	
• The anatomical location of the stricture	69 (81.2%)
• Technical failure of IPOC	41 (48.2%)
In case of failure due to a difficult anatomical location of the stricture, the most frequent location is (multiple options possible)	**N=69**
• Distal common bile duct (distal to insertion of cystic duct)	30 (43.5%)
• Proximal common bile duct (proximal to insertion of cystic duct)	3 (4.3%)
• Hilum	10 (14.5%)
• Left intrahepatic bile ducts	40 (58%)
• Right intrahepatic bile ducts	32 (46.4%)
In case of failure due to technical aspects of IPOC, this is usually due to (multiple options possible)	**N=41**
• Inability to pass the stricture with the cholangioscope	26 (63.4%)
• Insufficient cholangioscopic image or video quality	16 (39%)
• Insufficient irrigation resulting in an unclear view	9 (22%)
In case of inability to pass the stricture with the cholangioscope, the stricture is usually subsequently dilated	**N=26** 21 (80.8%)
Videos and/or images are routinely recorded from each identified lesion	75 (88.2%)
Targeted biopsies taken under cholangioscopic visualization	
• Yes, all biopsies are taken under cholangioscopic visualization in every patient	54 (63.5%)
• Yes, biopsies are taken under cholangioscopic visualization, in ≥50% of the patients	25 (29.4%)
• Yes, biopsies are taken under cholangioscopic visualization, in <50% of the patients	6 (7.1%)
Institutional standardized protocol available for targeted cholangioscopy-guided biopsy sampling	13 (15.3%)
Cholangioscopy-guided biopsies are taken from adjacent normal appearing biliary mucosa	14 (16.5%)
Performance of cholangioscopy-guided bite-on-bite biopsies	
• Yes, always multiple bite-on-bite biopsies form each identified lesion	25 (29.4%)
• Yes, at least one bite-on-bite from each identified lesion	15 (17.6%)
• Yes, however not in every identified lesion	30 (35.3%)
• No	15 (17.6%)
The mean number of cholangioscopy-guided biopsies taken per identified lesion	
• 1-2	3 (3.5%)
• 3-4	27 (31.8%)
• 5-6	35 (41.2%)
• > 6	20 (23.5%)
Performance of additional fluoroscopy-guided brush cytology before or after performance of targeted cholangioscopy-guided biopsies	
• Yes, before targeted cholangioscopy-guided biopsy sampling	14 (16.5%)
• Yes, after targeted cholangioscopy-guided biopsy sampling	41 (48.2%)
• No, in case cholangioscopy-guided biopsies are taken, no additional brush cytology is performed	30 (35.3%)
Performance of rapid onsite evaluation of touch imprint cytology (ROSE-TIC) for onsite evaluation of pathology	2 (2.4%)
Routinely performance of FISH analysis on biopsies	8 (9.4%)

Table 4s. Preoperative delineation of CCA

	N=45
IPOC for delineation of CCA is part of the preoperative diagnostic workup protocol	
• Yes, performed in all patients with CCA	10 (22.2%)
• Yes, performed in some patients with CCA	32 (71.1%)
• No	3 (6.7%)
Cholangioscopic delineation of CCA is performed	**N=42**
• Prior to surgery	42 (100%)
• During surgery	0 (0%)
Cholangioscopic delineation of CCA is performed mainly for	
• Distal CCA	7 (15.6%)
• Perihilar CCA	42 (93.9%)
• Intrahepatic CCA	9 (20%)
Preoperative delineation of CCA is determined by	**N=42**
• Visual characteristics solely	13 (31%)
• Visual characteristics and mapping biopsies	29 (69%)
• Mapping biopsies solely	0 (0%)
In the respondents' experience, preoperative delineation of CCA with IPOC results in an altered surgical approach in	**N=42**
• 0-20% of the patients	14 (31.1%)
• 21-40% of the patients	19 (42.2%)
• 41-60% of the patients	5 (11.1%)
• 61-80% of the patients	3 (6.7%)
• 81-100% of the patients	1 (2.2%)

Table 5s. Pancreatic duct stones

	N=68
IPOC with lithotripsy is used without prior ESWL performance	53 (77.9%)
IPOC with lithotripsy is performed after a prior conventional ERCP with sphincterotomy (separately performed)	61 (89.7%)
IPOC is usually performed after failed ESWL	25 (36.8%)
The type of lithotripsy procedure used for removal of pancreatic duct stones	
• Electrohydraulic lithotripsy	48 (70.6%)
• Laser lithotripsy	12 (17.6%)
• Both	8 (11.8%)
The type of lithotripsy preferred for removal of pancreatic duct stones is (not necessarily available in the hospital):	
• Electrohydraulic lithotripsy	50 (73.5%)
• Laser lithotripsy	18 (26.5%)
IPOC-guided lithotripsy for stone removal is used for pancreatic stones located in the (multiple options possible)	
• Head	66 (97.1%)
• Neck	51 (75%)
• Body	33 (48.5%)
• Tail	7 (10.3%)
Removal of the majority of stones in one IPOC session	34 (50%)
Need for multiple IPOC sessions to obtain complete stone clearance, is due to (multiple options possible)	**N=34**
• Size of the stone	23 (67.6%)
• Difficult stone location	18 (52.9%)
• Stricture distal to location of stones	18 (52.9%)
• Difficult stone fragmentation with EHL/ laser lithotripsy	23 (67.6%)
• Technical limitations or failure. If yes, specify Click here to enter text.	5 (14.7%)
The size of the stone is, in case of multiple IPOC sessions required	**N=23**
• 6-10 mm	15 (65.2%)
• >10 mm	8 (34.8%)
Stone location, in case of multiple IPOC sessions required (multiple options possible)	**N=18**
• Head	7 (38.9%)
• Neck	10 (55.6%)
• Body	6 (33.3%)
• Tail	5 (27.8%)
A plastic stent is placed to provide drainage of pancreatic fluid	61 (89.7%)

Table 6s. Preoperative delineation of IPMN

	N=35
IPOC for delineation of IPMN is part of the preoperative diagnostic work up protocol	
• Yes, performed in all patients	2 (5.7%)
• Yes, performed in some patients	26 (74.3%)
• No	7 (20%)
Pancreatoscopic delineation of IPMN is performed	**N=28**
• Prior to surgery	22 (89.3%)
• During surgery	3 (10.7%)
Preoperative delineation of IPMN is determined by	**N=28**
• Visual characteristics solely	7 (25%)
• Visual characteristics and mapping biopsies	20 (71.4%)
• Mapping biopsies solely	1 (3.6%)
In the respondents' experience, preoperative delineation of IPMN with IPOC results in an altered surgical approach in	**N=28**
• 0-20% of the patients	12 (42.9%)
• 21-40% of the patients	13 (46.4%)
• 41-60% of the patients	2 (7.1%)
• 61-80% of the patients	1 (3.6%)

APPENDIX

QUESTIONAIRE

International survey on the current clinical practice of indirect peroral cholangiopancreatoscopy

1. EXPERIENCE IN ERCP

1. The total lifetime number of endoscopic retrograde cholangiopancreatographies (ERCP) I have performed is:
   - ☐ 0-250
   - ☐ 251-500
   - ☐ 501-750
   - ☐ 751-1000
   - ☐ >1000

2. The average number of ERCPs I have performed per year over the past five years is:
   - ☐ 0-50
   - ☐ 51-100
   - ☐ 101-200
   - ☐ >200

3. The total number of ERCPs performed per year in our hospital is:
   - ☐ 0-250
   - ☐ 251-500
   - ☐ 501-750
   - ☐ 751-1000
   - ☐ >1000

4. The total lifetime number of indirect peroral cholangioscopies I have performed is:
   - ☐ 0-25
   - ☐ 26-50
   - ☐ 51-75
   - ☐ 76-100
   - ☐ >100

5. The average number of indirect peroral cholangioscopies I have performed per year over the past five years is:
   - ☐ 0-15
   - ☐ 16-30
   - ☐ 31-45
   - ☐ >45

6. The total number of indirect peroral cholangioscopies performed per year in our hospital is:
   - ☐ 0-25
   - ☐ 26-50
   - ☐ 51-75
   - ☐ 76-100
   - ☐ >100

7. The total lifetime number of indirect peroral pancreatoscopies I have performed is:
   - ☐ 0-25
   - ☐ 26-50
   - ☐ 51-75
   - ☐ 76-100
   - ☐ >100

8. The average number of indirect peroral pancreatoscopies I have performed per year over the past five years is:
   - ☐ 0-15
   - ☐ 16-30
   - ☐ 31-45
   - ☐ >45

9. The total number of indirect peroral pancreatoscopies performed per year in our hospital is:
   - ☐ 0-25
   - ☐ 26-50
   - ☐ 51-75
   - ☐ 76-100
   - ☐ >100

2. EQUIPMENT AND TECHNIQUE

10. The main type of cholangiopancreatoscope I use is:
    - ☐ The SpyGlass Direct Visualization System (first-generation) (Boston Scientific)
    - ☐ The SpyGlass DS Direct Visualization System (Boston Scientific)
    - ☐ CHF-BP30 (Olympus)
    - ☐ FCP-9P (Pentax)
    - ☐ Polyscope (PolyDiagnost)
    - ☐ Other: Click here if you want to enter text

11. Number of operators:
    - ☐ Single
    - ☐ Double

12. Preferred patient position during IPOC:
    - ☐ Supine
    - ☐ Prone
    - ☐ Left lateral

13. The most common type of sedation used for ERCP *without* IPOC in our clinic is:
    - ☐ Conscious sedation
    - ☐ Nurse administered propofol sedation
    - ☐ Propofol administered by anesthesiologist
    - ☐ General anesthesia with endotracheal intubation

14. The most common type of sedation used for ERCP *with* IPOC in our clinic is:
    - ☐ Conscious sedation
    - ☐ Nurse administered propofol sedation
    - ☐ Propofol administered by anesthesiologist
    - ☐ General anesthesia with endotracheal intubation

15. IPOC is scheduled as an:
    - ☐ Outpatient procedure, discharge on the same day
    - ☐ Inpatient procedure, at least one night hospital stay

16. Are prophylactic antibiotics routinely administered in patients undergoing IPOC?
    - ☐ Yes
    - ☐ No

17. Access to the biliary tree is usually obtained by:
    - ☐ Over the wire insertion
    - ☐ Direct access

18. Access to the pancreatic duct is usually obtained by:
    - ☐ Over the wire insertion
    - ☐ Direct access

19. Type of medium used to improve visualization:
    - ☐ Sterile saline
    - ☐ Water
    - ☐ Carbon dioxide (CO2)
    - ☐ Other

3. INDICATIONS FOR CHOLANGIOSCOPY

20. I use IPOC for (*multiple options possible*):
(please put between parentheses the percentage the indication accounts for in your daily clinical practice. The numbers need to add up to 100%)
- ☐ Determination of (indeterminate) biliary strictures (… %).
- ☐ Removal of common bile duct or intrahepatic duct stones (… %).
- ☐ Removal of cystic duct stones (… %).
- ☐ Preoperative delineation of cholangiocarcinoma (CCA) (… %).
- ☐ Transpapillary gallbladder drainage for acute cholecystitis (… %).
- ☐ Removal of foreign bodies within the bile duct (… %).
- ☐ Selective segment cannulation (… %).
- ☐ Stricture negotiation (… %).
- ☐ Recanalization of postoperative biliary disconnection (… %).
- ☐ Other Click here if you want to enter text (… %).

Biliary strictures

21. Visualization of biliary strictures is performed using:
- ☐ White light
- ☐ White light in combination with digital chromo endoscopy, for example narrow band imaging (NBI)
- ☐ White light in combination with chromo endoscopy with vital staining

22. Difficulty or failure of visualization of the target area is usually due to (*both options possible*):
- ☐ The anatomical location of the target area (*please answer question 23*)
- ☐ Technical aspects of IPOC (*please answer question 24*)

23. In case of failure due to a difficult anatomical location of the stricture, the most frequent location is (*multiple options possible*):
- ☐ Distal common bile duct (distal to insertion of cystic duct)
- ☐ Proximal common bile duct (proximal to insertion of cystic duct)
- ☐ Hilum
- ☐ Left intrahepatic bile ducts
- ☐ Right intrahepatic bile ducts

24. In case of failure due to technical aspects of IPOC, this is usually due to (*multiple options possible*):
- ☐ Inability to pass the stricture with the cholangioscope
- ☐ Insufficient cholangioscopic image or video quality
- ☐ Insufficient irrigation resulting in an unclear view

25. In case of inability to pass the stricture with the cholangioscope, is the stricture usually dilated subsequently?
- ☐ Yes
- ☐ No

26. Videos and/or images are routinely recorded from each identified lesion:
    - ☐ Yes
    - ☐ No

27. Are targeted biopsies taken under cholangioscopic visualization?
    - ☐ Yes, all biopsies are taken under cholangioscopic visualization in every patient
    - ☐ Yes, biopsies are taken under cholangioscopic visualization, in ≥*50%* of the patients
    - ☐ Yes, biopsies are taken under cholangioscopic visualization, in <*50%* of the patients
    - ☐ None of the biopsies are taken under cholangioscopic visualization (*go to question 32*)

28. Is there an institutional standardized protocol available for targeted cholangioscopy-guided biopsy sampling?
    - ☐ Yes
    - ☐ No

29. Do you take cholangioscopy-guided biopsies from adjacent normal appearing biliary mucosa?
    - ☐ Yes
    - ☐ No

30. Do you take cholangioscopy-guided bite-on-bite biopsies?
    - ☐ Yes, always multiple bite-on-bite biopsies form each identified lesion
    - ☐ Yes, at least one bite-on-bite from each identified lesion
    - ☐ Yes, however not in every identified lesion
    - ☐ No

31. The mean number of cholangioscopy-guided biopsies taken per identified lesion:
    - ☐ 1-2
    - ☐ 3-4
    - ☐ 5-6
    - ☐ > 6

32. Is additional fluoroscopy-guided brush cytology performed before or after targeted cholangioscopy-guided biopsy taking?
    - ☐ Yes, *before* targeted cholangioscopy-guided biopsy sampling
    - ☐ Yes, *after* targeted cholangioscopy-guided biopsy sampling
    - ☐ No, in case cholangioscopy-guided biopsies are taken, no additional brush cytology is performed

33. Is rapid onsite evaluation of touch imprint cytology (ROSE-TIC) performed for onsite evaluation of pathology?
    - ☐ Yes
    - ☐ No

34. Is FISH analysis routinely performed on biopsies?
    - ☐ Yes
    - ☐ No

Bile duct stones

35. In selected cases, IPOC with lithotripsy is used as the first treatment option, without prior ERCP with conventional stone extraction techniques:
    - ☐ Yes
    - ☐ No

36. IPOC with lithotripsy is usually used for stone removal after failed prior ERCP with conventional stone extraction techniques:
    - ☐ Yes
    - ☐ No

37. IPOC is used for confirmation of bile duct clearance after ERCP with conventional stone extraction techniques:
    - ☐ Yes
    - ☐ No

38. The mean number of ERCPs prior to IPOC for stone removal is:
    - ☐ 0
    - ☐ 1
    - ☐ 2
    - ☐ 3
    - ☐ 4

39. The mean number of IPOCs to obtain stone clearance is:
    - ☐ 1
    - ☐ 2
    - ☐ 3
    - ☐ ≥4

40. The type of lithotripsy tool I use for removal of bile duct stones is:
    - ☐ Electrohydraulic lithotripsy
    - ☐ Laser lithotripsy
    - ☐ Both

41. The type of lithotripsy tool I prefer to use for removal of bile duct stones is (not necessarily available in your hospital):
    - ☐ Electrohydraulic lithotripsy
    - ☐ Laser lithotripsy

42. Cholangioscopy for bile duct stone removal is used for stones located in the (*multiple options possible*):
    - ☐ Distal common bile duct (distal to insertion of cystic duct)
    - ☐ Proximal common bile duct (proximal to insertion of cystic duct)
    - ☐ Hilum
    - ☐ Left intrahepatic bile ducts
    - ☐ Right intrahepatic bile ducts
    - ☐ Cystic duct

43. Failure of biliary stone removal is usually due to:
    - ☐ Stricture distal to the location of stones
    - ☐ Difficult stone location (*go to question 44*)
    - ☐ Size of the stone
    - ☐ The number of stones
    - ☐ Difficult fragmentation of the stone with EHL/ laser lithotripsy
    - ☐ Other: .....

44. In case of difficult stone location, this is usually in:
    - ☐ Distal common bile duct (distal to insertion of cystic duct)
    - ☐ Proximal common bile duct (proximal to insertion of cystic duct)
    - ☐ Hilum
    - ☐ Left intrahepatic bile ducts
    - ☐ Right intrahepatic bile ducts
    - ☐ Cystic duct

45. After failure of stone removal by cholangioscopy:
    - ☐ A repeat ERCP with IPOC is scheduled
    - ☐ A percutaneous transhepatic drain is placed
    - ☐ Patient is scheduled for ESWL
    - ☐ Patient is referred to the surgeon
    - ☐ A percutaneous transhepatic drain is placed

Delineation of CCA

46. IPOC for delineation of CCA is part of the preoperative diagnostic work up protocol:
    - ☐ Yes, performed in all patients with CCA
    - ☐ Yes, performed in some patients with CCA
    - ☐ No (*go to question 51*)

47. Cholangioscopic delineation of CCA is performed:
    - ☐ Prior to surgery
    - ☐ During surgery

48. Cholangioscopic delineation of CCA is performed mainly for:
    - ☐ Distal CCA
    - ☐ Perihilar CCA
    - ☐ Intrahepatic CCA

49. Preoperative delineation of CCA is determined by:
    - ☐ Visual characteristics solely
    - ☐ Visual characteristics and mapping biopsies
    - ☐ Mapping biopsies solely

50. In my experience, preoperative delineation of CCA with IPOC results in an altered surgical approach in:
    - ☐ 0-20% of the patients
    - ☐ 21-40% of the patients
    - ☐ 41-60% of the patients
    - ☐ 61-80% of the patients
    - ☐ 81-100% of the patients

4. INDICATIONS FOR PANRCEATOSCOPY

51. I use IPOC for (*multiple options possible*):
    (please put between parentheses the percentage the indication accounts for in your daily clinical practice. The numbers need to add up to 100%)
    - ☐ Removal of pancreatic duct stones (… %).
    - ☐ Determination of indeterminate pancreatic strictures (… %).
    - ☐ Delineation of IPMN (… %).
    - ☐ Removal of foreign bodies within the pancreatic duct (… %).
    - ☐ Other (… %).

Removal of pancreatic duct stones

52. Is IPOC with lithotripsy used without prior ESWL performance?
    - ☐ Yes
    - ☐ No

53. Is IPOC with lithotripsy performed after a prior conventional ERCP with sphincterotomy (separately performed)?
    - ☐ Yes
    - ☐ No

54. Is IPOC usually performed after failed ESWL?
    - ☐ Yes
    - ☐ No

55. The type of lithotripsy procedure I use for removal of pancreatic duct stones is:
    - ☐ Electrohydraulic lithotripsy
    - ☐ Laser lithotripsy
    - ☐ Both

56. The type of lithotripsy I would prefer for removal of pancreatic duct stones is (not necessarily available in your hospital):
    - ☐ Electrohydraulic lithotripsy
    - ☐ Laser lithotripsy

57. IPOC-guided lithotripsy for stone removal is used for pancreatic stones located in the (*multiple options possible*):
    - ☐ Head
    - ☐ Neck
    - ☐ Body
    - ☐ Tail

58. The majority of stones can be removed in one IPOC session:
    - ☐ Yes (*go to question 62*)
    - ☐ No

59. If multiple IPOC sessions are necessary to obtain complete stone clearance, this is due to:
    - ☐ Size of the stone (*please answer question 60*)
    - ☐ Difficult stone location (*please answer question 61*)
    - ☐ Stricture distal to location of stones
    - ☐ Difficult stone fragmentation with EHL/ laser lithotripsy
    - ☐ Technical limitations or failure. If yes, specify .....

60. The size of the stone is:
    - ☐ 0-5 mm
    - ☐ 6-10 mm
    - ☐ >10 mm

61. In case of difficult stone location, the location is:
    - ☐ Head
    - ☐ Neck
    - ☐ Body
    - ☐ Tail

62. In all cases, a plastic stent is placed to provide drainage of pancreatic fluid:
    - ☐ Yes
    - ☐ No

Delineation of IPMN

63. IPOC for delineation of IPMN is part of the preoperative diagnostic work up protocol:
    - ☐ Yes, performed in all patients
    - ☐ Yes, performed in some patients
    - ☐ No

64. Pancreatoscopic delineation of IPMN is performed:
    - ☐ Prior to surgery
    - ☐ During surgery

65. Preoperative delineation of IPMN is determined by
    - ☐ Visual characteristics solely
    - ☐ Visual characteristics and mapping biopsies :
    - ☐ Mapping biopsies solely

66. In my experience, preoperative delineation of IPMN with IPOC results in an altered surgical approach in:
    - ☐ 0-20% of the patients
    - ☐ 21-40% of the patients
    - ☐ 41-60% of the patients
    - ☐ 61-80% of the patients
    - ☐ 81-100% of the patients

Chapter 3

Diagnostic accuracy and interobserver agreement of digital single-operator cholangioscopy for indeterminate biliary strictures

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Gastrointestinal Endoscopy, 2021

ABSTRACT

Background and aim: Digital single-operator cholangioscopy (d-SOC) with cholangioscopic biopsy sampling has shown promise in the evaluation of indeterminate biliary strictures. Some studies have suggested higher sensitivity for visual impression compared with biopsy sampling, although assessors were not blinded to previous investigations. We aimed to investigate the diagnostic accuracy and interobserver agreement (IOA) of d-SOC in the visual appraisal of biliary strictures when blinded to additional information.

Methods: A multicenter, international cohort study was performed. Cholangioscopic videos in patients with a known final diagnosis were systematically scored. Pseudonymized videos were reviewed by 19 experts in 2 steps: blinded for patient history and investigations and unblinded.

Results: Forty-four high-quality videos were reviewed of 19 benign and 25 malignant strictures. The sensitivity and specificity for the diagnosis of malignancy was 74.2% and 46.9% (blinded) and 72.7% and 62.5% (unblinded). Cholangioscopic certainty of a malignant diagnosis led to overdiagnosis (sensitivity, 90.6%; specificity, 33%), especially if no additional information was provided. The IOA for the presence of malignancy was fair for both assessments (Fleiss' $\kappa = .245$ [blinded] and $\kappa = .321$ [unblinded]). For individual visual features, the IOA ranged from slight to moderate for both assessments ($\kappa = .059$-$.400$ vs $\kappa = .031$-$.452$).

Conclusion: This study showed low sensitivity and specificity for blinded and unblinded d-SOC video appraisal of indeterminate biliary strictures, with considerable interobserver variation. Although reaching a consensus on the optical features of biliary strictures remains important, optimizing visually directed biopsy sampling may be the most important role of cholangioscopy in biliary stricture assessment.

INTRODUCTION

Indeterminate biliary strictures remain a major diagnostic challenge. A biliary stricture is classified as indeterminate when laboratory workup, abdominal imaging (eg, magnetic resonance imaging, CT, and EUS), and ERCP with tissue sampling are inconclusive as to the nature of the stricture (1). Although most indeterminate biliary strictures prove to be malignant (2), benign conditions, such as primary sclerosing cholangitis (PSC) and IgG4-related sclerosing cholangitis, may mimic malignancy, presenting diagnostic difficulty and subjecting patients to potentially unnecessary surgery. Traditional diagnostic methods such as ERCP with biliary cytology provide high specificity, but low sensitivity, for malignant strictures. A meta-analysis on the comparative effectiveness of biliary brush cytology and fluoroscopically guided intraductal biopsy sampling found the sensitivity to be 45% and 48%, respectively. Combining the 2 resulted in a modest improvement to 59% (3).

The use of digital single-operator cholangioscopy (d-SOC) may improve the detection of cholangiocarcinoma through direct stricture visualization and the ability to obtain targeted biopsy specimens. Several cholangioscopic features of malignant biliary strictures have been described in the literature, such as irregular, dilated, and tortuous vessels; polypoid masses; easy oozing; and an irregular mucosal surface (4-6). A recent systematic review reported sensitivity and specificity rates between 88.9% and 97% and 94.5% to 97.6%, respectively, for the visual diagnosis of malignant strictures. For the histologic diagnosis by intraductal biopsy sampling, sensitivity and specificity rates varied between 57.7% and 100% and 88.9% and 100%, respectively (7). This would suggest that a visual diagnosis may provide greater diagnostic accuracy than any form of pathological sampling.

However, a number of considerations require these results to be interpreted with some caution. First, most studies included only a few patients with a background of PSC (in which differentiating benign from malignant strictures may be particularly difficult) (4,8). Second, patients who were diagnosed with post–liver transplant anastomotic strictures were included, which is a group with a very low pretest probability of cholangiocarcinoma. Therefore, the study population may not be representative of patients undergoing d-SOC for the evaluation of indeterminate biliary strictures with suspected malignancy. A further limitation of previous studies examining the utility of visual inspection criteria is that endoscopists were not blinded to the clinical history and results of previous investigations, allowing the possibility of bias. Therefore, in this study we aimed to assess diagnostic accuracy and interobserver agreement (IOA) for the diagnosis of malignant biliary strictures by d-SOC in a representative study population with a high pretest probability of malignancy, while blinding the reviewing endoscopists to all clinical information except cholangioscopic appearances.

METHODS AND MATERIALS

Study design and study population

An international, multicenter, retrospective cohort study was performed in patients who underwent d-SOC for the evaluation of indeterminate biliary strictures in 14 European tertiary referral centers. All participants are members of the European Cholangioscopy Group, with significant personal experience in d-SOC.

Pseudonymized cholangioscopy videos of patients who underwent d-SOC for indeterminate biliary strictures were included for video assessment. Indeterminate biliary strictures were defined as (1) a bile duct stricture or filling defect of indeterminate nature after previous laboratory workup, abdominal imaging (magnetic resonance imaging, CT, and EUS), or ERCP with or without (2) negative or inconclusive cytology or histology after ERCP with brush cytology and/or intraductal biopsy sampling but with a persistent clinical suspicion of malignancy. Videos without a known final diagnosis based on histopathology reports and follow-up and of insufficient visual quality were excluded. This study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of each participating center.

d-SOC performance and video case selection

ERCP and d-SOC procedures were performed by an endoscopist experienced in SOC, having performed more than 30 cholangioscopies before this study. d-SOC was performed using the digital single-operator cholangiopancreatoscopy system (SpyGlass DS Direct Visualization System or SpyGlass DS II Direct Visualization System; Boston Scientific, Natick, Mass, USA). Depending on the institution, the procedure was performed with the patient under conscious sedation, propofol sedation, or general anesthesia. In all patients, prophylactic antibiotics were administered according to institutional protocol. During d-SOC, videos of the lesions were recorded, highlighting the area of interest and demonstrating both the abnormal mucosa and the surrounding (normal) mucosa. A malignant biliary stricture was defined as positive histopathology obtained via d-SOC or other sampling means (endoscopic, radiologic, or surgical), as confirmed by an experienced GI pathologist. Benign disease was defined as negative histopathology confirmed by an experienced GI pathologist and no clinical progression or obvious malignant disease over 12 months of follow-up.

Before submitting the videos to the coordinating investigator (P.M.C.S.), all videos were pseudonymized by participating endoscopists (ie, no cholangiography or any other patient-specific or clinical data). Videos had a duration of approximately 120 seconds. Before sending the entire set of videos to all endoscopists for video assessment, the study coordinator (P.M.C.S.) recoded the videos into new study identification numbers to prevent bias of recognition of videos.

Study assessment

Video assessment was done using a case record form. Before video assessment we did not define the appearance of the cholangioscopic features. In addition, all participating

endoscopists were experts with significant personal experience, and therefore there was no training before video assessment. For each video a final visual diagnosis of malignant or benign was required, with a level of certainty. A grading scale (1-4) was used to define the level of diagnostic certainty with 1 being absolutely uncertain and 4 being absolutely certain. Furthermore, a range of cholangioscopic features reported to be associated with either benign or malignant strictures was tabulated (5,9-13). Endoscopists were asked to record the presence of each feature (ie, yes or no). The set of videos was reviewed twice. In the first step, endoscopists were fully blinded to all patient details. When the endoscopist had completed and submitted the case record forms of all videos, including final prediction of diagnosis, to the coordinating investigator (P.M.C.S.), patient information, including demographics, clinical history, imaging, and blood results (including tumor markers), was sent to complete the second, unblinded assessment using an identical case record form.

Study outcomes

The primary outcome of the study was to evaluate the diagnostic accuracy and IOA for the diagnosis of malignant biliary strictures by visual appraisal with d-SOC for the blinded and unblinded video assessment. Secondary outcomes were the diagnostic accuracy rates when excluding patients with recognized increased diagnostic challenges (PSC, those with stents in situ before d-SOC, and hilar strictures), rates stratified for the level of certainty, and the intraobserver agreement. An additional outcome was the presence of individual cholangioscopic findings in malignant and benign strictures.

Statistical analysis

Statistical analysis contained descriptive statistics for general patient characteristics, tumor markers, previous clinical investigations, and stricture-related data using frequencies (%) for categorical variables, mean (standard deviation) for normally distributed continuous variables, or median (interquartile range) for non-normally distributed continuous variables. Estimates of sensitivity and specificity were obtained from logistic mixed models to take into account that measurements were not independent. Specifically, sensitivity was estimated from a model on videos of malignant cases with the reviewer's diagnosis (malignant vs benign) as the outcome. The model included as a fixed effect whether the reviewer was blinded to additional clinical information, enabling us to estimate differences in sensitivity between blinded and unblinded review. Estimates of the sensitivity under either scenario and corresponding 95% confidence intervals (CIs) were obtained from the marginalized fitted values and their standard errors. Estimates for specificity were obtained analogously from the subset of videos showing benign cases and using the reviewer's diagnosis (benign vs malignant) as the outcome. Investigation of sensitivity and specificity with regard to the level of certainty the reviewer had about the diagnosis was done using models that additionally included the level of certainty as a categorical covariate. Moreover, we performed sensitivity analyses for sensitivity and specificity (irrespective of the level of certainty) in the subset of cases without PSC, the subset of cases in which no plastic stent was placed before cholangioscopy, and in the subset of patients with nonhilar strictures (ie, strictures located in the distal common bile duct, proximal common bile duct, and cystic duct).

The IOA was measured using the Fleiss' κ statistic along with 95% CIs. Intraobserver agreement was measured using Cohen's κ statistics along with 95% CIs. Kappa statistics were interpreted based on the Landis and Koch convention: poor agreement, ≤.00; slight agreement, .01 to .20; fair agreement, .21 to .40; moderate agreement, .41 to .60; substantial agreement, .61 to .80; almost perfect agreement, .81 to 1.00. All calculations were performed in R version 4.0.2 (2020-06-22) (14) and using the package GLMMadaptive (0.7.15) (15).

RESULTS

Baseline characteristics

Forty-seven videos were submitted by 19 endoscopists from 14 different hospitals. The number of videos submitted per hospital ranged from 2 to 5. Forty-four videos were deemed eligible for video assessment by the coordinating investigators (P.M.C.S. and G.G.). Three videos were excluded because of insufficient visual quality. The median time between blinded and unblinded video assessment varied between participants and was 29 days (range, 1-65).

Twenty-five patients (56.8%) were diagnosed with malignant disease and 19 patients (43.2%) were diagnosed with benign disease. Twenty-six patients (59%) were men, and the mean patient age of 63 years. Baseline characteristics of the included patients are summarized in **Table 1**.

Diagnostic accuracy

Four observations had missing mucosal diagnoses. These were excluded from all sensitivity and specificity calculations. The sensitivity and specificity for the diagnosis of malignant biliary strictures, based on visual appraisal alone (blinded video assessment), were 74.2% (95% CI, 69-78.8) and 46.9% (95% CI, 37.8-56.1), respectively. For the unblinded video assessment, sensitivity and specificity were 72.7% (95% CI, 67.6-77.3) and 62.5% (95% CI, 53.4-70.8), respectively. Estimated sensitivity and specificity rates are shown in **Figure 1**. There was no statistically significant difference in sensitivity between blinded and unblinded review. **Table 2** shows the odds ratio for a positive diagnosis of a malignant sample in the unblinded setting versus the blinded setting. The odds ratio was .93, with a 95% CI ranging from .69 to 1.24 (P = .602), meaning there was no evidence for a difference in sensitivity in both scenarios. Specificity differed under both scenarios, and the odds ratio for a negative diagnosis in a benign sample in the unblinded versus blinded review was 2.08 with a 95% CI ranging from 1.51 to 2.86 (P = .001), confirming a higher specificity in the unblinded review than in the blinded review.

Table 1. Baseline characteristics of all 44 included patients

	Definite malignant diagnosis (n=25)	Definite benign diagnosis (n=19)
Sex, male	11 (44)	15 (78.9)
Age, mean (± SD), years	68 (± 9.8)	55.9 (±15.3)
Medical history		
• PSC	3 (12)	8 (42.1)
• Chronic pancreatitis	1 (4)	1 (5.3)
• Gallstone disease	1 (4)	4 (21.1)
• Malignancy	0 (0)	1 (5.3)
• HPB surgery	0 (0)	3 (15.8)
• Placement of biliary stents	13 (52)	10 (52.6)
• Bile duct stone removal	1 (4)	3 (15.8)
Stricture location		
• Distal CBD	4 (16)	3 (15.8)
• Proximal CBD	7 (28)	3 (15.8)
• Hilar	9 (36)	5 (26.3)
• Intrahepatic left	1 (4)	1 (5.3)
• Intrahepatic right	0 (0)	4 (21.1)
• Cystic duct junction	4 (16)	2 (10.5)
• Multiple locations	0 (0)	1 (5.3)
Previous diagnostic work-up		
• CA19.9	14 (56)	9 (47.4)
• Level CA19.9, median (IQR)	72.5 (2 – 17752)	24 (5 – 127)
• MRI	21 (84)	13 (68.4)
• CT	22 (88)	15 (78.9)
• EUS alone	7 (28)	3 (15.8)
• EUS with FNA/FNB	7 (28)	4 (21.1)
• ERCP with intraductal biopsies	3 (12)	2 (10.5)
• ERCP with brush cytology	15 (60)	11 (57.9)
• ERCP with intraductal biopsies and brush cytology	2 (8)	3 (15.8)

Values are n (%) unless otherwise defined.
CA19.9, Cancer antigen 19.9

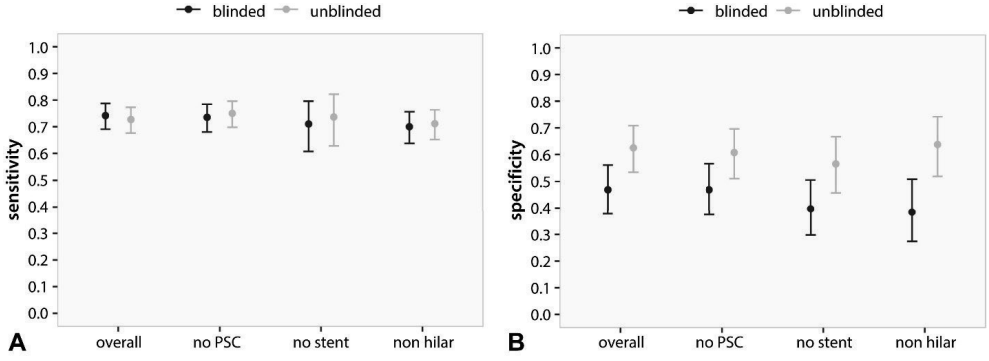

Figure 1. Diagnostic accuracy of digital single-operator cholangioscopy (d-SOC) in the diagnosis of biliary strictures; overall, excluding patients with PSC, excluding patients with a stent in situ before d-SOC, and excluding patients with hilar strictures. **A**, Sensitivity. **B**, Specificity. PSC, Primary sclerosing cholangitis.

Table 2. Comparison of sensitivity and specificity between blinded versus unblinded review

	OR unblinded / blinded	2.5%	97.5%	p-value
Overall				
Sensitivity	0.925	0.691	1.239	0.602
Specificity	2.078	1.511	2.859	0.001
Without PSC				
Sensitivity	1.080	0.789	1.479	0.630
Specificity	1.883	1.245	2.850	0.003
Without plastic stent				
Sensitivity	1.141	0.756	1.721	0.530
Specificity	2.225	1.392	3.559	0.001
Non-hilar strictures				
Sensitivity	1.053	0.732	1.515	0.781
Specificity	3.760	2.263	6.247	0.001

OR, Odds ratio

Figure 1 also shows sensitivity and specificity rates when excluding patients with PSC, a stent in situ before cholangioscopy, and/or hilar strictures. In all scenarios, the specificity increased after unblinding the reviewers for additional clinical information. The odds ratios for a negative diagnosis in a benign sample in the unblinded versus blinded review were 1.88 (95% CI, 1.24-2.85; P = .003), 2.25 (95% CI, 1.39-3.56; P = .001), and 3.760 (95% CI, 2.263-6.247; P = .001), respectively. Again, this provides strong evidence that specificity was higher in the unblinded video review. This is shown in **Table 2**.

An additional 20 observations had a missing level of certainty regarding the visual mucosal diagnosis, resulting in 24 missing observations in total (ie, 4 missing visual mucosal diagnosis and 20 missing level of certainty regarding visual mucosal diagnosis). They were excluded from the sensitivity and specificity calculations per level of certainty. The diagnostic accuracy rates are summarized in **Figure 2**. Accordingly, when stratified for the reported level of certainty, the sensitivity increased from 47.8% to 90.6% (blinded) and from 39.9% to 91% (unblinded) and the specificity decreased from 49% to 33.1% (blinded) and from 67.9% to 61.7% (unblinded).

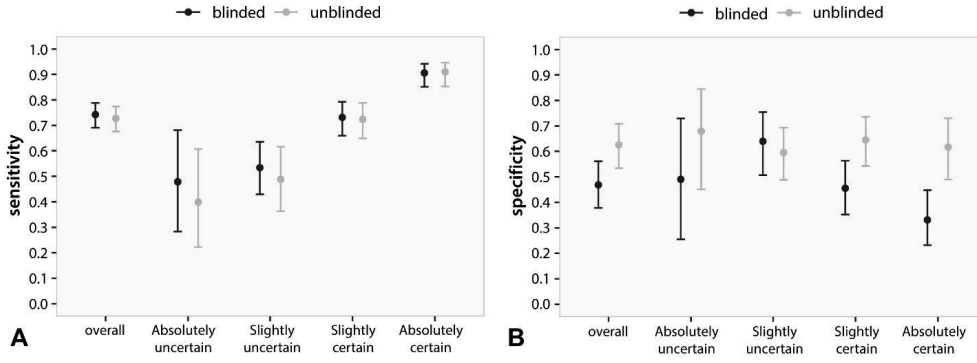

Figure 2. Diagnostic accuracy of digital single-operator cholangioscopy for the diagnosis of biliary strictures, stratified to the level of certainty. **A**, Sensitivity. **B**, Specificity.

Cholangioscopic features

Figure 3 shows the proportion of the videos of benign and malignant strictures in which the cholangioscopic features were identified as present by the reviewing endoscopists for both assessments. Certain cholangioscopic features, such as focal lesion, raised lesion, irregular nodularity, easy oozing, and dilated tortuous vessels, were more frequently identified in videos of malignant strictures as compared with videos of benign strictures.

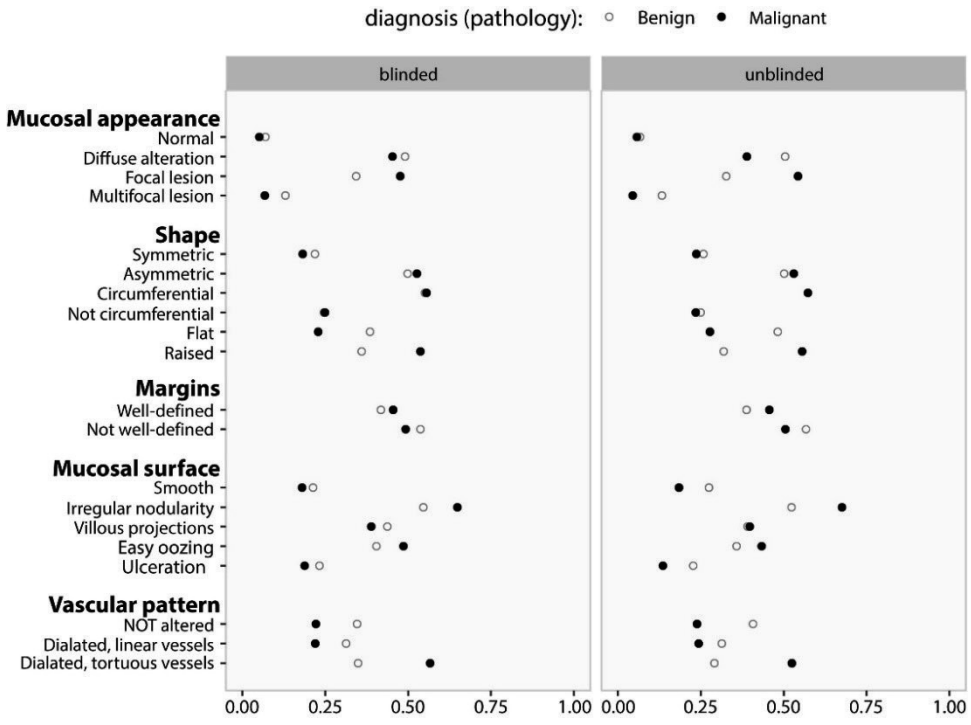

Figure 3. Cholangioscopic findings in benign and malignant strictures, for both blinded and unblinded video assessments.

IOA and intraobserver agreement

The IOA for the visual diagnosis of a malignant biliary stricture was fair for both assessments (κ = .245 [blinded] and κ = .321 [unblinded]). The IOA for the individual cholangioscopic features ranged from slight to moderate (κ = .059-.400 [blinded] and κ = .031-.452 [unblinded]). There was moderate agreement for circumferential lesions (κ = .400) in the blinded assessment and for villous projections (κ = .452) in the unblinded assessment.

The intraobserver agreement for the visual diagnosis of malignant biliary strictures was moderate (κ = .454). For cholangioscopic features this ranged between moderate and substantial (κ = .464-.700). **Figures 4** and **5** show the IOA and intraobserver agreement for the visual diagnosis and cholangioscopic features.

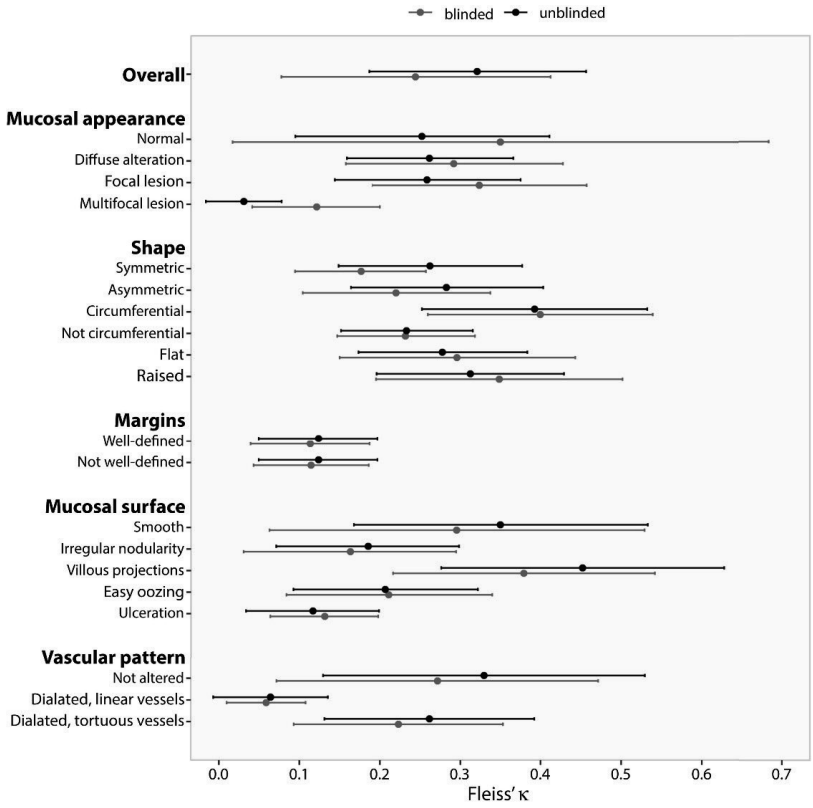

Figure 4. Interobserver agreement on the diagnosis of malignant strictures and the cholangioscopic features (Fleiss' κ and corresponding 95% confidence intervals). A κ < .20 slight agreement, .21-.40 fair agreement, .41-.60 moderate agreement, .61-.80 substantial agreement, and >.81 almost perfect agreement.

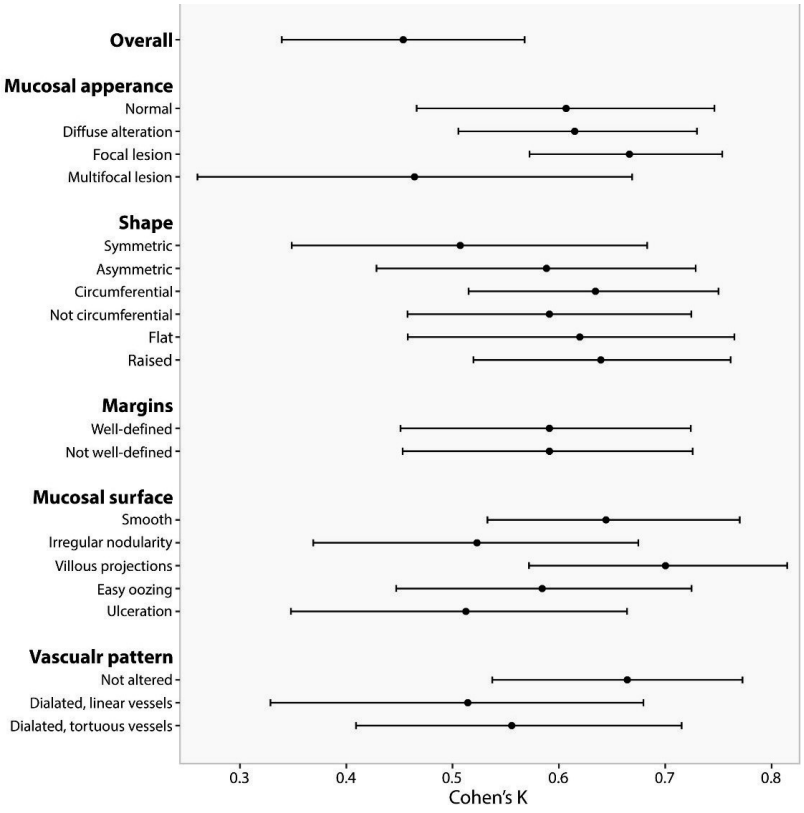

Figure 5. Intraobserver agreement on the diagnosis of malignant strictures and the cholangioscopic features (Cohen's κ and corresponding 95% confidence intervals). A κ < .20 slight agreement, .21-.40 fair agreement, .41-.60 moderate agreement, .61-.80 substantial agreement, and >.81 almost perfect agreement.

DISCUSSION

Studies investigating the diagnostic value of d-SOC in diagnosing indeterminate biliary strictures have shown promising result (7,16) However, in most of these studies the investigators were not blinded to patient history and previous results, and study populations were not always representative. This could have resulted in overly optimistic results when transferred to clinical practice. The aim of this study was to investigate the diagnostic accuracy and IOA of d-SOC imaging features alone while blinding the endoscopists using a clinically representative study population.

In our study, we found a sensitivity and specificity of 74.2% and 46.9%, respectively, where cholangioscopy videos were assessed without any clinical information (blinded) and of 72.7% and 62.5%, respectively, where this information was available (unblinded). These rates are lower than those published recently (7). In addition, a large prospective registry study by Almadi et al. (17), which was not included in this systematic review, of >250

patients with indeterminate biliary strictures reported a sensitivity of 87% and specificity of 71% for diagnosing malignancy based on visual impression. Although these were very promising results, this study did not describe the IOA, and again in this study endoscopists were not blinded to patient details, which might have biased the results. Our study shows that when absolutely no information is given and the cholangioscopic video is the only tool to diagnose an indeterminate stricture, it is difficult to diagnose malignant biliary strictures correctly based on visual appraisal, even for endoscopists who are experienced in cholangioscopy. After unblinding the endoscopists to patients' medical history and outcome of previous investigations, only the specificity increased. Thus, even when all patient information is available, it still proved difficult to definitively distinguish benign from malignant strictures. This may be in part because in PSC, for example, the history and additional information provide little supplementary means to guide a differentiation between benign and malignant stricturing, particularly where prior investigation has failed to make a distinction. An exception includes patients with a clear benign history and a low pretest probability of cholangiocarcinoma who become easier to identify and diagnose as having a benign stricture, which is demonstrated by an increased specificity after unblinding the endoscopists and an odds ratio of 2.08.

Reflecting real-life clinical scenarios, endoscopists were asked not only to make a binary decision as to whether a stricture was benign or malignant, but also to indicate their level of certainty. Of interest, absolute certainty as to the diagnosis of malignancy was associated with a high sensitivity (>90%) but poor specificity (33.1%) when blinded. If extended to clinical practice this may represent an incorrect "overdiagnosis" of malignancy based on visual assessment alone. Some improvement in specificity was made with "absolute certainty" when endoscopists were unblinded (61.7%) compared with blinded (33.1%), perhaps reflecting an overinterpretation of cholangioscopic features being tempered by additional information.

Why might this overdiagnosis occur? Whether benign or malignant disease was diagnosed in this study, there was a high frequency of identifying features often associated with malignancy. It may be that endoscopists, despite their experience, were not good at identifying these features. An important alternative explanation is that cholangioscopic features previously deemed characteristic of malignancy may occur in both benign and malignant biliary strictures (**Figure 3**). In this study endoscopists were required to identify cholangioscopic features that had previously been described in the literature as distinguishing benign from malignant biliary strictures (eg, a focal lesion, raised lesions, irregular nodularity, easy oozing, and dilated tortuous vessels (18)). Dilated, tortuous vessels, so-called tumor vessels, have been most strongly linked to malignancy. In a prospective study, Kim et al. (9) found a positive predictive value of 100% and discovered that, importantly, these abnormal blood vessels were not found in benign strictures. In contrast, but in accordance with de Vries et al. (19), we also found dilated, tortuous vessels to be identified in benign strictures (in 33%).

This is not the first study to report low sensitivity and specificity rates for d-SOC. Recently, de Vries et al. (19) demonstrated a sensitivity and specificity of 64% and 62%, respectively, even though endoscopists were not blinded to additional clinical information. Similar to

our study, a significant proportion of patients included had a diagnosis of PSC or had a stent in situ at the time of d-SOC. Both scenarios may be associated with localized or more diffuse mucosal change that may be difficult visually to differentiate from malignancy. To evaluate the influence of PSC and stents in situ before cholangioscopy on the diagnostic value of d-SOC in our cohort, we excluded patients with PSC and with stents in situ before cholangioscopy from the analysis, which in our study showed no significant difference in diagnostic accuracy between the 2 groups. This may be because our study was not powered to find a difference in diagnostic accuracy between patients with and without PSC or stents in situ before cholangioscopy. However, previous studies have shown that the presence of PSC or prior stent placement adds to the diagnostic difficulty based on cholangioscopy. A previous prospective study showed that d-SOC was unable to reliably distinguish benign from malignant lesions in PSC patients (20). This challenge was also addressed by de Vries et al. (19), who included a similar proportion of patients with stents in situ before d-SOC to our study. They found that 71% of patients with neovascularization had a stent in situ before d-SOC, a characteristic previously reported to be consistent with malignancy (9).

An important outcome of this study is the low IOA. Before video assessment we did not define the appearance of the cholangioscopic features, and no training sessions were organized to help interpret cholangioscopic images, because all participating endoscopists were considered to be experts in the field with significant personal experience in d-SOC performance for indeterminate biliary strictures. For both the blinded and unblinded video assessment, the IOA was slight to fair for most features. This shows that when not predefined, there is no consensus on the actual appearance of cholangioscopic features, even among endoscopists who perform d-SOC for this indication on a regular basis. This was also reported by Sethi et al. (21,22), who found only slight to fair agreement for different cholangioscopic features and for the visual diagnosis in 2 studies in which the investigators were also blinded to patients' clinical history and final diagnosis, as in this current study. We do not believe that the poor IOA or overall disappointing sensitivity and specificity of this study can be attributed to suboptimal visualization or to inexperience of the endoscopists, because significant improvement in visual acuity has been seen with cholangioscope development and the submitted videos were specifically selected for the quality of imaging. In addition, the relatively high intraobserver agreement suggests that endoscopists were consistent in their assessments with regard to identification of cholangioscopic features, which may in turn represent their experience in performance of d-SOC for indeterminate biliary strictures.

Our results suggest the need to further define cholangioscopic features that are associated with malignant biliary strictures. We have shown that we cannot rely on a visual impression alone to make a confident diagnosis and that the widely used phrase "tissue is the issue" remains central. Advances in visually targeted biopsy sampling may represent a crucial step in improving the diagnostic role of cholangioscopy.

Strengths of our study are the use of blinded videos, providing assessors with no information beyond the cholangioscopy itself, and the use of a representative study population, including patients with indeterminate strictures in whom distinguishing

benign from malignant is notoriously difficult, such as PSC (23). However, selecting patients with indeterminate strictures who by definition had disease that was difficult to define (even with prior ERCP and cytology) may have inadvertently selected a study group with inherently challenging strictures in which to make a cholangioscopic diagnosis. In addition, although this study did not prove a difference in d-SOC performance when patients with PSC were excluded from the analysis, previous studies did (24). Therefore, in daily practice it should be taken into account that it can be challenging to diagnose a stricture as benign or malignant, especially in patients with PSC. Considering this, achieving a 74% sensitivity in this highly selective group of patients may be seen as clinically useful. This study could not address the question as to whether cholangioscopy performed at the time of index ERCP would lead to improved diagnostic yield, avoiding the potential confounding factor of an effect of stenting on cholangioscopic appearance. Nevertheless, these clinical scenarios reflect clinical practice. The international, multicenter study design, involving only reviewing endoscopists with significant experience, suggests that the results for IOA are robust and not because of variable experience. In fact, the selection of experienced endoscopists from tertiary referral centers suggests that diagnostic rates in nonspecialist settings might be lower than the results found in this study.

In conclusion, we found low diagnostic accuracy rates for mere visual assessment at cholangioscopy in patients with indeterminate biliary strictures, with considerable interobserver variation. Malignancy was overdiagnosed, with cholangioscopic features characterized as being linked to malignancy frequently identified in both benign and malignant strictures. This indicates that the morphologic features of inflammatory and malignant disease may significantly overlap and not be exclusive or clearly discriminative, even for experienced endoscopists. These findings suggest that although reaching a consensus on visual characteristics remains important and urgently needed, optimizing visually directed pathologic sampling may be the most important role of cholangioscopy in the assessment of indeterminate strictures.

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Chapter 4

Endoscopic treatment of pain in chronic pancreatitis; Indications, optimal timing and technical aspects

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ABSTRACT

Endoscopic treatment of pain in chronic pancreatitis is aimed at decompression of the pancreatic duct (PD) or blocking of the afferent pancreatic pain signals. First-line treatment for PD stones is extracorporeal shockwave lithotripsy (ESWL) or, more recently, peroral pancreatoscopy with electrohydraulic or laser lithotripsy. For PD strictures, insertion of a single plastic stent is recommended. Alternatively, progressive plastic stenting protocol or a temporary fully covered metal stent may be used. In case of an inaccessible PD via endoscopic retrograde pancreatography (ERP) due to strictures, stones or previous surgery, endoscopic ultrasound (EUS)-guided pancreaticogastrostomy can be considered. Although challenging, this technique offers reasonably good clinical success. Finally, EUS-guided coeliac plexus block can be performed, but its effects are generally short lived. The choice of an optimal treatment strategy and its timing is challenging and should be decided based on multidisciplinary team discussion.

INTRODUCTION

Chronic pancreatitis (CP) is characterized by progressive inflammation leading to permanent fibrotic changes and subsequent loss of endocrine and exocrine function. The predominant symptom of CP is severe abdominal pain, which can seriously impair quality of life, work productivity, and social functioning (1,2). The nature and pathogenesis of pain in CP is complex and includes inflammation, changes in the peripheral and central nervous system, and cognitive and psychological aspects. Another important etiological factor is an increased pancreatic ductal pressure, resulting from ductal obstruction due to fibrosis or stones (3,4).

Achieving adequate pain relief is difficult and more than half of the patients continue to suffer from pain ten years after the onset of symptoms (5). Pain often leads to chronic use of opiates, which is associated with significant side effects and dependence. Along with medical treatment, ductal decompression is employed to alleviate pain in CP. Usually, a step-up approach is applied, with lifestyle changes and analgesics as first step, endoscopic therapy as second step and surgical intervention as last resort. In this chapter, a detailed overview is provided with regard to indications, optimal timing, technical aspects and outcome of endoscopic therapy for CP-associated pain.

SELECTING THE RIGHT PATIENT FOR ENDOSCOPIC THERAPY: WHO AND WHEN?

Endoscopic therapy (ET) for CP-associated pain generally aims at either decompression of the pancreatic duct (PD) or inhibition of the afferent pancreatic pain signals. PD drainage can be achieved through sphincterotomy, lithotripsy and stone extraction, and/or dilation or stenting of strictures. However, technically successful ductal decompression does not always translate to clinical improvement, which implies the involvement of other pathogenic factors of CP-associated pain, and underscores the complex nature of the pain syndrome in these patients. A careful selection of patients that qualify for ET is therefore of major importance.

Factors predictive of clinical success

Patients with CP who are most likely to benefit from endoscopic drainage have an obstructive stone in the head of the pancreas in the absence of a main pancreatic duct (MPD) stricture. Additional factors predictive of clinical success are short disease duration, non-severe pain, and absence or cessation of cigarette smoking and alcohol use (6). Imaging modalities such as high-resolution computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasonography (EUS) can be used to establish the presence and extent of MPD dilation and obstructive stones. These techniques provide a detailed image of the ductal system, with important information on the location and extension of stricture(s), location and size of stones, and anatomical variations such as pancreas divisum. Secretin is used in secretin-enhanced MRCP (s-MRCP) or EUS (s-EUS) to stimulate the pancreas to exert its exocrine function, thereby increasing fluid secretion and causing transient ductal dilation. This technique can delineate the

upstream anatomy of the MPD and the length of the strictures more clearly, and may help to identify strictures or obstructions that would have been missed without secretin stimulation. In patients with pancreas divisum, a dilated MPD after secretin administration is predictive of a beneficial effect from endoscopic therapy (7), but no such relation has been established for other CP patients. In severe CP the MPD becomes rigid rendering its response to secretin is less pronounced as compared to patients without CP (8,9).

Optimal timing and treatment choice

The management of pain in CP patients starts with lifestyle education. Patients should be counseled to quit drinking alcohol and stop smoking. Opioids are frequently used in the treatment of painful CP, but caution is advised since long-term use can be harmful and counterproductive as it may induce hypersensitivity to pain stimuli (10). Also, patients are at risk for developing opioid dependency. Estimating the optimal timing for an intervention in CP, either endoscopically or surgically, is challenging. The guideline of the European Society of Gastrointestinal Endoscopy (ESGE) recommends to perform ET and/or extracorporeal shock-wave lithotripsy (ESWL) as first-line therapy for patients with uncomplicated painful CP with an obstructed stone in the head or body of the pancreas. When ET and/or ESWL fails to improve pain, medical treatment with analgesics is recommended. Surgery should be considered in patients who fail to improve six to eight weeks after ET or in case of technical failure (11). In contrast to the ESGE guideline, in the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU), the timing of ET is positioned after failure of analgesics (6).

With regard to the choice between endoscopic and surgical drainage, data from retrospective studies suggest that surgery results in better outcomes of pain relief and endocrine pancreatic function. Furthermore, improved pain relief can be achieved in patients who do not use opioids prior to surgery and had less than five endoscopic treatment procedures preoperatively (12). In a prospective randomized controlled trial, comparing endoscopic and surgical PD drainage in patients with severe CP, surgical treatment was associated with higher rates of complete or partial pain relief, as compared to ET (75% versus 32%) (13). The long-term outcome after 7 years showed persistent superiority of surgery with regard to pain relief (80% versus 38%), and the need of additional drainage procedures after initial PD decompression. Nine patients (47%) who initially underwent endoscopic drainage had to undergo surgery due failure of endoscopic drainage (14). Although this study evidently showed that endoscopic drainage is inferior to surgery these results cannot be extrapolated to all CP patients, as only those with advanced disease were included (with a combination of large/multiple stones and strictures), most of them being opioid-dependent.

There is evidence that ductal decompression in an early disease-stage may prevent pancreatic function loss and irreversible damage. Studies have shown that a short disease duration prior to ET is a predictive factor for long-term pain relief (15-17). Besides, there is evidence that pancreatic insufficiency develops early in the disease course of obstructive pancreatitis with permanent insufficiency developing after several weeks (18). Therefore the Dutch Pancreatitis Study Group has conducted the ESCAPE-trial, a randomized

controlled trial comparing early surgery to a step-up approach in patients with non-opioid-dependent CP, with the Izbicki pain score as primary outcome. It revealed that early surgery resulted in a larger decrease in the Izbicki pain score (-26 vs -16, p=0.04). However, in a substantial number of endoscopically treated patients, there were protocol deviations rendering endotherapy not up to current standard. Furthermore, at the time of the trial direct pancreatoscopy with electrohydraulic lithotripsy (EHL) was not part of the treatment armentarium (19). Overall, it is still conceivable that ET is particularly beneficial for early CP with less complex pathology, but this needs further investigation.

It is important to note that ET and surgery should be seen as complimentary rather than competing treatments. Some patients, for example those with an enlarged pancreatic head, are better candidates for surgery, requiring a head resection rather than ductal drainage only. If pain relief after ET is not satisfactory, surgery should be considered as a next treatment step in order to prevent disease progression and improve long-term quality of life, and possibly better preservation of pancreatic function (20).

TREATMENT OF PANCREATIC DUCT STONES

Obstruction of the PD can be caused by strictures, intraductal stones or, in the majority of cases, by a combination of both. As pancreatic stones are usually hard and impacted in the PD, ET is often challenging, especially when combined with ductal strictures.

Extracorporeal Shock-wave Lithotripsy

Technical aspects

ESWL is the current cornerstone of treatment of stone-predominant symptomatic CP. Although small stones (<5 mm) can usually be extracted during endoscopic retrograde cholangiopancreatography (ERCP) with a basket or balloon after pancreatic sphincterotomy, the majority of the stones are large, hard, and impacted, requiring fragmentation prior to endoscopic removal (21). The clinical guideline of the ESGE recommends ESWL as first step, immediately followed by endoscopic extraction of stone fragments, as treatment for patients with uncomplicated painful CP and stones of 5 mm or larger obstructing the PD (11).

ESWL of pancreatic stones requires careful targeting of the stone with specialized equipment that consists of a strong electromagnetic lithotripter and a fluoroscopic targeting system. Therefore, the procedure is often only executed in expert centers. The procedure is usually performed under general anesthesia or deep conscious sedation as treatment is lengthy (on average one to two hours) and can be painful. Multiple sessions are often required to complete fragmentation and are usually carried out within a few days, during which time the patient remains admitted to the hospital.

After ESWL, ET is performed to extract fragmented stones and to evaluate the presence of MPD strictures (21). ESWL without subsequent ERCP may be indicated in patients with small radiopaque stones located in the head of the pancreas, and absence of MPD strictures (6,11). In case a pancreatic stone is not clearly visible on X-ray, endoscopic pancreatic

sphincterotomy may be required prior to ESWL for deployment of an endoprosthesis to facilitate targeting during ESWL. Other indications for endoprosthesis placement prior to or between ESWL treatment sessions are to facilitate pancreatic drainage and to prevent impaction of fragmented stones. ESWL is contraindicated in patients with coagulation disorders or pacemakers or defibrillators, pregnant women, and when calcified aneurysms are in the shock-wave path.

Effectiveness and safety

Two large meta-analyses showed that ESWL is an effective technique for clearance of the MPD and to decrease CP-related abdominal pain (22,23). Successful fragmentation of pancreatic stones is reported in 37.5-100% and generally requires one to four sessions (22,23). Successful fragmentation is more often achieved in case of a solitary stone in the absence of MPD stricture (24-26). According to the most recent meta-analysis, complete ductal clearance is achieved in 71% of patients, and partial clearance in 22% (23). Pain relapse occurs more frequently in patients without complete stone removal and/or with a MPD stricture (26,27). Furthermore, in patients with a pain relapse, approximately 40% has stone recurrence (28).

ESWL is a relatively safe procedure, with pancreatitis being the most common complication, occurring in 4% (23).

Pancreatoscopy-guided lithotripsy

Technical aspects

Peroral pancreatoscopy (POP) with lithotripsy of PD stones is a relatively new technique in which calculi are fragmented under direct endoscopic visualization. The first therapeutic POP was described by Howell in 1999, who performed EHL under direct vision using the mother–baby technique (29). However, wide clinical acceptance was not achieved, as the technique was hampered by the need for two operators to control the two scopes simultaneously, and cumbersome fragility of the baby scope with high repair costs and poor maneuverability. The introduction of a digital single-operator cholangiopancreatoscope in 2007 (SpyGlass Legacy, Boston Scientific, Natick, MA, USA) has overcome these limitations. Although the image quality of the first system with a fiberoptic probe was moderate, its upgrade to a single-operator video cholangioscope (SpyGlass DS, Boston Scientific) in 2015 resulted in higher resolution imaging with a wider view. The current system consists of a disposable 10-Fr delivery catheter with fourway deflection capabilities, and dedicated separate irrigation and succinate channels. The scope has a large accessory channel (1.2 mm) through which a guidewire, biopsy forceps, or electrohydraulic or laser lithotripsy device can be introduced.

Intraductal lithotripsy can be achieved by EHL or laser lithotripsy (LL). With EHL, shock-wave pulses are generated via a bipolar probe in aqueous medium. Fragmentation of nearby stones is achieved by absorption of these high-frequency hydraulic shock waves. To prevent damage to the ductal wall or perforation, direct visualization is necessary to position the probe close to the stone and away from the wall (**Figure 1**).

In LL, laser light at a particular wavelength is aimed directly at the stone to induce fragmentation. There are currently two systems available. First, the neodymium:yttrium–aluminum–garnet (Nd:YAG) laser system fragments stones by formation of plasma on the surface of the stone. The infrared light energy is then absorbed, which produces a forceful shock wave. The holmium:YAG laser system directly transmits light energy from the laser to the stone and surrounding fluids. With its longer wavelength, a direct flash on the surface of the stone results in fragmentation. Fragments are then removed by a vapor bubble that is created by water absorption of the laser energy.

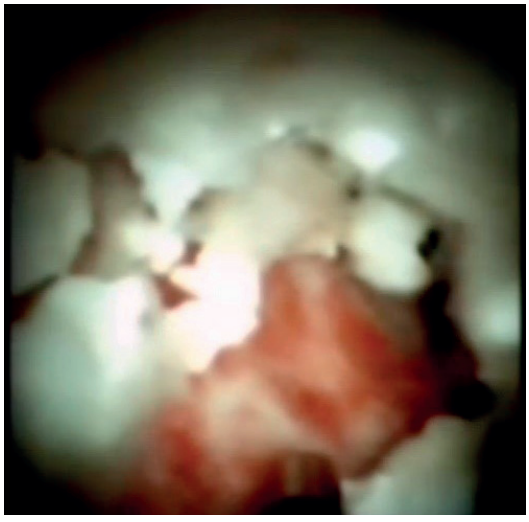

Figure 1. Fragmentation of an intraductal stone in the PD

Effectiveness and safety

Pancreatoscopy with intraductal lithotripsy is currently considered second-line therapy for MPD stones, after unsuccessful ESWL and ERCP. Although mainly from retrospective data, the literature shows promising results for stone removal in patients with calcified CP. Success rates for ductal clearance range between 43 and 100%, which is comparable to ESWL (30-32). Higher success rates seem to be obtained for stones located in the head or the neck of the pancreas (31,33). Also clinical success, defined as pain reduction, less opiate usage and/or reduced hospitalizations, is achieved in 74-95% of patients (31-34). To date, there is no prospective study has evaluated the differences in efficiency or safety of EHL and LL.

Adverse event rates for pancreatoscopy vary between 0-13,5% (30), again with pancreatitis as most common complication (32,33).

TREATMENT OF PANCREATIC DUCT STRICTURES

PD strictures can be single or multiple and are classified as dominant or nondominant. The definition of a dominant PD stricture, as defined by the HaPanEU Guideline, is a stricture in the head of the pancreas with an upstream MPD dilatation of 6 mm or more in diameter or a stricture that prevents outflow of contrast into the duodenum (**Figure 2**). Treatment of a dominant stricture, usually consisting of both stricture dilation and stenting, should be considered if it is located in the head and associated with pain (6).

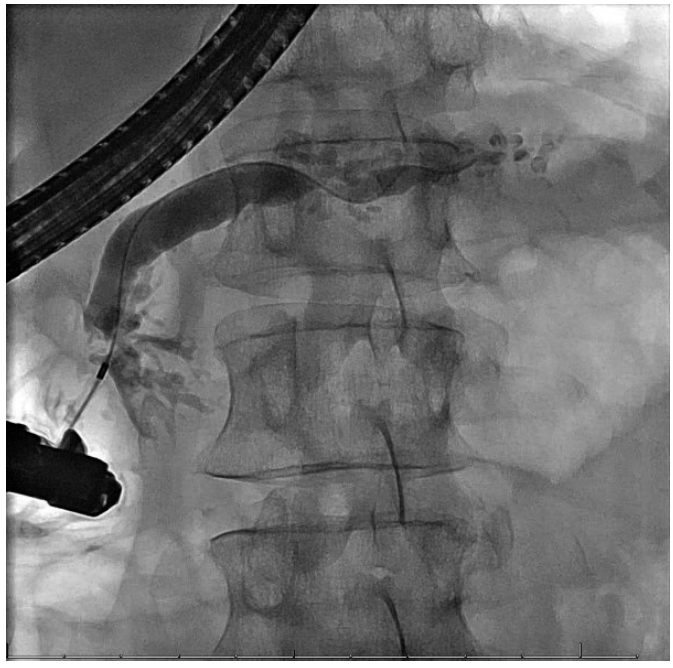

Figure 2. Pancreatic stricture in the head of the pancreas without outflow of contrast medium into the duodenum

Technical aspects

To provide good access to the PD, a selective pancreatic sphincterotomy should be performed. A sphincterotomy can be performed using the pull-sphincterotomy or needle-knife technique over a stent that was placed at a previous occasion. It is important to note that the sphincterotomy should be large enough to allow insertion of instruments and to prevent post-sphincterotomy stenosis. In patients with CP, cannulation of the PD can be difficult due to active inflammation and accompanying edema of the papilla. The majority of the strictures can be passed with a regular guidewire, but sometimes a thinner guidewire may be required to enable dilation with a balloon or graduated dilating catheter. For very tight strictures that cannot be passed with a dilation balloon catheter, a Soehendra dilating catheter can be advanced (screwed) through the stricture over a nonmetallic guidewire.

After cannulation and, if needed dilation, a stent can be placed. For pancreatic drainage, different stents are available. The choice of stent depends on the stricture diameter and location and shape and diameter of the MPD. The diameter of plastic stents ranges from 3 to 11.5 Fr. Small-diameter stents are associated with risk of occlusion and pain relapse. Therefore, the stent diameter should be as large as possible, or multiple smaller-sized stents may be inserted side by side. The ESGE guideline recommends inserting a single 10-Fr plastic stent (11). In the pancreas, straight polyethylene stents are most widely used, with S-shaped or wing-shaped stents as alternative, as they have a lower migration risk (35-37).

Also, fully-covered self-expandable metal stents (FC-SEMS) have been successfully deployed across pancreatic strictures, in particular in patients with a refractory MPD stricture (38). Compared to plastic stents, they provide a larger maximum radial force and have a longer patency, which may result in more effective stricture dilation. A drawback is the risk of migration, in particular proximal into the MPD (39). The use of biodegradable self-expandable stents has been reported to overcome this issue, but they are not yet routinely used in clinical practice (40).

The optimal duration of stent therapy remains a matter of debate. Some studies have suggested that prolonged stent therapy leads to intraductal damage and tailoring and limiting the duration of stent therapy could overcome this (41-44). On the other hand, prolonged stent therapy might have the advantage of improving stricture dilation and thereby reduce the risk of pain recurrence.

Stent exchanges may be performed in case of symptoms ("on demand") or at regular intervals. The HaPanEu guideline recommends that stent exchange should be performed within one year for single plastic stents, even if the patient is asymptomatic. For refractory strictures (i.e. persistent symptomatic strictures after one year of stenting), they recommend placement of multiple stents (6). A more aggressive approach is also being used, with stent exchanges every few months, to increase the number of stents up to the limit the PD can accommodate. The advantage of stent exchanges on a regular basis is prevention of pain relapse due to stent clogging (45,46). and frequent evaluation of stricture resolution. Thereby, treatment duration may be shortened when stenting is terminated as soon as the stricture has resolved, but this protocol has not been proven to be as effective as a fixed one-year stenting protocol. Criteria used during ERCP for stent removal are adequate outflow of contrast medium one to two minutes after ductal filling upstream from stricture, and easy passage of a 6-Fr catheter (6).

In our practice, we favor exchanging stents on a regular basis (i.e. every three months), and insert an increasing number of stents with each consecutive procedure to further dilate the stricture, analogous to the treatment of benign biliary strictures.

Effectiveness and safety

Long-term clinical results after insertion of a single PD stent have been reported by several retrospective studies. Pain improvement was reportedly achieved in 52%-94% of the patients after a mean follow-up ranging from 12 to 60 months (47-52). One study observed

excellent outcomes of multiple plastic stent insertion, with persistent pain relief in 84% after a mean follow-up of 38 months and only approximately 10% stricture recurrence (53). After placement of a FC-SEMS, the clinical success rate, defined as more than 50% pain resolution, was reported to be 83%. Stricture resolution rates ranged between 83 and 93%, a median of seven months after stent removal (54,55). Unfortunately, longer-term follow-up data are not available.

Complications associated with PD stenting include stent occlusion and migration, post-procedural abdominal pain, acute pancreatitis, and cholangitis (48,55).

EUS-GUIDED PANCREATICOGASTROSTOMY

Technical aspects

In cases where the PD is inaccessible through the major or minor papilla due to obstruction or rupture of the PD or surgically altered anatomy, access can be obtained by puncturing the PD under EUS guidance. First, the optimal access site is selected, with the smallest distance between the stomach and the PD, and without interposed vessels, taking into account the direction of the PD and fluoroscopic view. A fine-needle aspiration (FNA) needle is then used to access the PD, through which a guidewire is advanced (**Figure 3**).

Fluoroscopic imaging is used to ensure maintenance of access and an adequate scope position. Subsequently, two drainage techniques are available. First, the rendezvous (retrograde) technique, in which the PD is punctured using a curvilinear array echoendoscope and a guidewire is maneuvered past the stricture and/or stone deep into the duodenum. The echoendoscope is changed for a duodenoscope whilst leaving the guidewire in place. Using the duodenoscope, the wire in the duodenum can be retrieved for a rendezvous procedure and a plastic stent is placed into the PD, in retrograde, via the papilla. With the antegrade technique (direct drainage), scopes are not exchanged and the echoendoscope is used to place a plastic stent in the PD through the gastrointestinal tract wall, either across the obstruction or not (**Figure 4**). For this technique it is obligatory to dilate the tract in order to pass the stent (56).

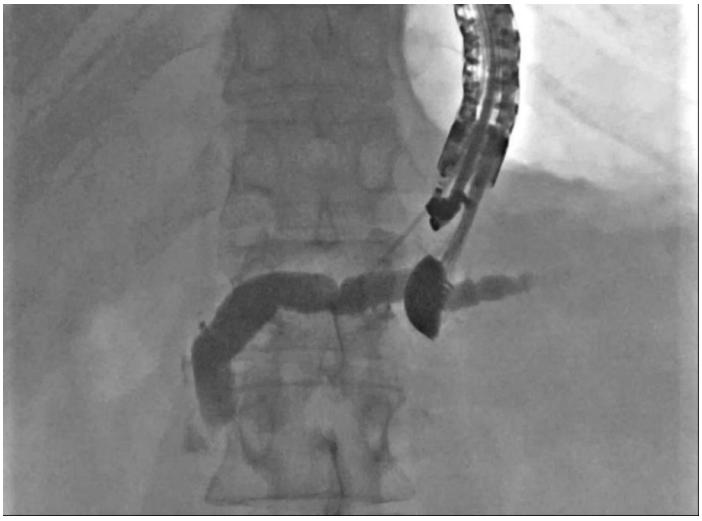

Figure 3. EUS-guided pancreaticogastrostomy – FNA needle puncturing the dilated PD

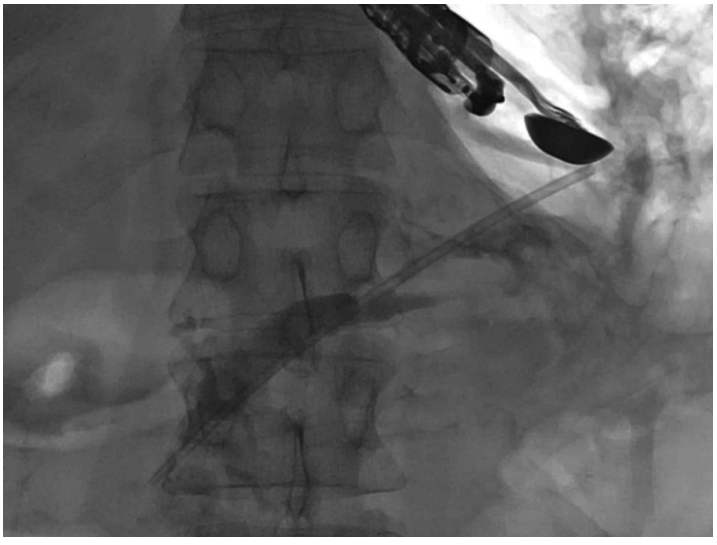

Figure 4. Antegrade technique – plastic stent placement in the PD through the gastrointestinal tract wall

Effectiveness and safety

A recent meta-analysis reported a technical success rate of 77%, amongst 222 reported patients (57). In the largest retrospective series to date, clinical success was achieved in 23 of 32 patients (72%) in whom a stent was successfully placed, 16 complete and seven partial (58). A similar clinical success rate was found in an earlier retrospective study, where

13 of 18 patients in whom successful PD drainage was achieved had long-term symptom relief after a median follow-up of 37 months (59). It is important to note that most studies were not confined to CP patients, but also included patients with anastomotic strictures, malignant strictures, or a disconnected PD for example. However, some studies did report an improved pain score specific for CP-patients (60,61).

Complications associated with this technique occurred in 19% of the patients according to the same meta-analysis and included abdominal pain, pancreatitis, bleeding, perforation and peripancreatic abscess (57).

CELIAC PLEXUS BLOCK

EUS-guided celiac plexus block (CPB) should be saved for patients who do not respond to other forms of treatment for CP-related pain. It is aimed at inhibition of the afferent neurotransmission of pancreatic pain-signals.

Technical aspects
Using EUS, the celiac plexus can be easily identified and accessed. Local anesthetics (bupivacaine) are injected into the celiac plexus, together with a corticosteroid (triamcinolone). In contrast, celiac plexus neurolysis for pain resolution in pancreatic cancer involves injection of ethanol, and should not be used for benign pancreatic disease since neurolysis can cause adhesions and thereby make surgery difficult or even impossible. Direct injection of bupivacaine and triamcinolone results in enlargement of the ganglia and is typically associated with an immediate (but shortlived) onset of pain, which can manifest itself as an abrupt increase in patient movement, attempted verbalization, or an altered pulse and/or respiration rate, even in patients under general anesthesia, which resolves within seconds.

Effectiveness and safety
Clinical success of CPB is less than other types of pain treatment in CP. A meta-analysis found a pooled success-rate of pain relief in 60% of the patients, with a median follow-up ranging from seven days to 15 weeks (62). Unfortunately, pain relief and decreased use of opioids are short-lived. Santosh et al. reported that only 10% of patients had pain relief for more than 24 weeks (63). Adverse events related to CPB are transient worsening of abdominal pain, diarrhea and hypotension. This is mainly due to parasympathic activation and occurs in approximately 40% of the patients (64).

SUMMARY

Endoscopic treatment of pain in patients with CP is aimed at either decompression of the PD, by means of stone removal or stricture dilation, or at blocking the afferent pancreatic pain signals by EUS-guided CPB. First-line treatment for obstructing PD stones of more than 5 mm is ESWL. More recently, POP with EHL or LL has been introduced as an alternative endoscopic technique to fragment PD stones. For PD strictures, insertion of a single plastic

stent is recommended. The optimal duration of stent therapy is unclear and should be based on clinical effect and the occurrence of complications. Alternatives for placement of a single plastic stent, in an attempt to improve stricture dilation, is employment of a progressive plastic stenting protocol or placement of a temporary FC-SEMS. EUS-guided pancreaticogastrostomy or rendezvous techniques provide an alternative technique for obtaining access to the PD in case of inaccessibility via ERCP. However, these are challenging procedures but with reasonably good clinical success rates when technically successful. Finally, EUS-guided CPB is a last resort option, but its effects are short-lived. The decision for and timing of ET in relation to surgical treatment options is challenging and should be reached by multidisciplinary team discussion.

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Chapter 5

Pancreatoscopy-guided electrohydraulic lithotripsy for the treatment of obstructive pancreatic duct stones: a prospective consecutive case series

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ABSTRACT

Background and aim: Pancreatoscopy-guided electrohydraulic lithotripsy (EHL) has shown potential in the treatment of patients with obstructive chronic calcifying pancreatitis (CCP). We aimed to prospectively investigate the efficacy and safety of EHL as first-line therapy in patients with CCP of the pancreatic duct (PD).

Methods: A prospective single-center consecutive case series was performed including symptomatic CCP patients with obstructing stones >5 mm in the head or neck of the pancreas. Stone fragmentation was performed using EHL. Primary study outcome was technical success. Secondary outcomes were clinical success, adverse events, and number of interventions.

Results: Thirty-four consecutive patients were included. Complete or partial stone clearance after EHL was achieved in 24 patients (70.6%). Pancreatoscopy was not performed because of failure to cannulate the PD (n=5) or resolution of stones after stent placement at the index endoscopic retrograde pancreaticography (ERP) procedure (n=3). After successful PD cannulation, pancreatoscopy was technically successful in 24 of 26 patients (92.3%). In 1 patient, the stone could not be visualized because of a resilient stricture. Complete stone clearance was achieved in 20 patients (80%) and partial clearance in 5 patients (20%), after a median of 2 ERP procedures (interquartile range, 2) and 1 EHL procedure (interquartile range, 1). In patients who underwent pancreatoscopy with EHL, mean Izbicki pain score at baseline was 62.3 ± 23.1 (25/25) and dropped significantly to 27.5 ± 35.0 (22/25) at the 6-month follow-up ($P < 0.001$). The most common adverse event was acute pancreatitis, all mild and treated conservatively (n=7).

Conclusion: Pancreatoscopy-guided EHL is a promising treatment for symptomatic CCP patients with obstructive PD stones. (Clinical trial registration number: NTR6853.)

INTRODUCTION

Chronic pancreatitis is a debilitating condition. In many cases, imaging investigations show an obstructive stone in the pancreatic duct (PD) in the head and neck of the pancreas. This may lead to an increased intraductal and parenchymal pressure and to ischemia, causing severe pain with or without flares. In current clinical practice, patients with symptomatic chronic pancreatitis are often treated following a step-up approach. First, medical therapy is applied using analgesics and pancreatic enzyme replacement therapy. If this fails, the next step is endoscopic treatment.

Endoscopic treatment in patients with symptomatic chronic pancreatitis aims at relieving pain, primarily by restoring outflow of the main PD (MPD) in the case of an obstruction (1). In a large multicenter study regarding endoscopic therapy in chronic pancreatitis patients, MPD obstruction was caused by either strictures (47%), stones (18%), or a combination of both (32%) (2). Endoscopic management of obstructing stones can be challenging because stones are often large, hard, or impacted above a stricture. Stones <5 mm can usually be extracted during endoscopic retrograde pancreaticography (ERP) using conventional techniques with a basket or a balloon, but success rates are low (3). Extracorporeal shock wave lithotripsy (ESWL) followed by endoscopic extraction of stone fragments is recommended for stones >5 mm, with reported success rates of up to 93% (4). However, drawbacks of this technique are limited availability and costs. In addition, ESWL alone does not address the issue of concurrent MPD strictures, which have been associated with high stone recurrence rates (5).

Pancreatoscopy-guided intraductal lithotripsy has been suggested as an alternative to treat obstructive MPD stones. Because this technique requires nonstandard equipment and materials, it is currently regarded as a second-line intervention after failed ESWL. Data on pancreatic intraductal lithotripsy are limited and come from retrospective, nonconsecutive series, with discordant success rates for stone fragmentation in small case series (47%-83%) and technical success rates varying between 79% and 91% (6-9). Pancreatoscopy-guided electrohydraulic lithotripsy (EHL) as a first-line treatment for obstructive MPD stones might have the advantages of permitting both stone fragmentation and removal and stricture treatment during the same procedure. The primary aim of this study was to prospectively assess the technical success of pancreatoscopy-guided EHL as a first-line treatment in a consecutive series of patients with chronic calcifying pancreatitis. Secondary aims were assessment of clinical success, safety, patient burden, and quality of life.

METHODS

Study design and population

A prospective single-center consecutive case series was conducted at the Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands, an academic tertiary referral center for hepatopancreaticobiliary diseases. Procedures and follow-up were performed in consecutive patients between December 2017 and July 2020.

All adult patients referred to our medical center for the treatment of chronic pancreatitis–related pain were discussed in a multidisciplinary hepatopancreaticobiliary meeting. Patients eligible for the study were consented at the index visit. Patients included in this study needed to have an established diagnosis of chronic pancreatitis according to the M-ANNHEIM criteria (10) and 1 or more PD stones ≥5 mm in the head or the neck of the pancreas as shown on cross-sectional imaging (ie, CT, MRCP) or EUS.

Exclusion criteria were age <18 years, asymptomatic patients, patients with chronic pancreatitis with stones located in the body or tail of the pancreas, previous treatment of PD stones using ESWL, history of surgical treatment of chronic pancreatitis, and pregnancy. In addition, patients were not eligible for study inclusion if endoscopic treatment was not deemed to be possible or successful because of, for example, a nondilated PD or a completely calcified pancreas. A history of pancreatic sphincterotomy and/or single stent placement in the MPD were considered first-line treatments and not considered to be an exclusion criterion (1,11).

Written informed consent was obtained from each participant. This study was conducted according to the guidelines in the Declaration of Helsinki and was approved by the local ethics committee.

Study protocol

At the start of the study, we aimed to perform pancreatoscopy with subsequent EHL at the index procedure. However, during the first few cases it became apparent that in some patients with a native papilla, cannulation of the PD was quite challenging and prolonged the procedure time considerably. This interfered with the logistics of our busy daily ERCP practice in such a way that it was decided to amend the treatment strategy. For difficult and prolonged PD cannulation, a PD stent was placed, and pancreatoscopy and EHL were performed in a subsequent procedure 4 to 6 weeks later. There were no strict rules (eg, time definition) as to when to place a stent, and this was done at the endoscopists' discretion. All patients who first received a stent were evaluated for the effect of the stent on clinical symptoms. All patients reported relief of pain symptoms after stent placement, and therefore we continued with pancreatoscopy and EHL performance.

Study endpoints

The primary study endpoint was technical success, defined as complete or partial clearance of MPD stones based on pancreatoscopic imaging and fluoroscopic pancreatogram after EHL. Complete and partial stone clearance were defined as 100% and 50% to 99% stone clearance, respectively. Failed stone clearance was defined as <50% stone clearance. Multiple procedures necessary to ensure technical success were allowed per protocol. In patients in whom pancreatoscopy and EHL were performed, the secondary study endpoints were clinical success, adverse event rate within 30 days of treatment, total number of ERPs performed, and quality of life based on the 12-Item Short-Form Health Survey (SF-12). Clinical success was defined as a ≥50% reduction in Izbicki pain scores or reduced opiate usage at the 6-month follow-up, based on previous studies (12). The Izbicki pain score consists of 4 items: frequency of pain, intensity of pain, use of pain medication, and disease-related inability to work (**Supplementary Table 1**).

The SF-12 is a validated questionnaire of 12 questions to measure both physical and mental quality of life (**Appendix 1**). Post-ERP pancreatitis (PEP) was classified according to the consensus criteria for PEP, defined as the development of new or worsening abdominal pain consistent with acute pancreatitis and elevation of pancreatic enzymes to more than 3 times the upper limit of normal, requiring new or continued hospitalization (13).

Procedure

All patients underwent ERP under propofol sedation. Prophylactic rectal nonsteroidal anti-inflammatory drugs were administered to prevent PEP. No prophylactic antibiotics were used, unless there was an established indication as per standard clinical practice guidelines. Anticoagulation medication was temporarily discontinued (international normalized ratio ≤1.5) or "bridged" by low-molecular-weight heparin as per standard clinical practice guidelines.

Interventions were carried out by 2 expert therapeutic endoscopists having performed at least 25 cholangioscopy-guided EHL procedures and 15 pancreatoscopy-guided EHL procedures (M.J.B., J.-W.P.). Each procedure was performed with a video duodenoscope (ED34-i10T2; Pentax Medical, Tokyo, Japan). Pancreatoscopy was performed with a digital single-operator cholangiopancreatoscopy system (SpyGlass DS Direct Visualization System; Boston Scientific Corp, Natick, Mass, USA), which was advanced either over a .035-inch guidewire or freehand into the MPD up to the level of the target stone.

In all patients pancreatic sphincterotomy was performed to facilitate introduction of the pancreatoscope, or, if needed, a pre-existing sphincterotomy was extended. If a stricture was present that precluded the passage of the pancreatoscope, a balloon dilatation was attempted. Pretreatment stone size was measured on fluoroscopic pancreatogram, before contrast injection into the PD, by comparing the stone size to the diameter of the duodenoscope. When the stone was visualized with the pancreatoscope a 1.9F EHL probe (Nortech AUTOLITH system; Northgate Technologies, Inc, Elgin, Ill, USA) was introduced, and EHL was performed. Depending on the characteristics of the stone (ie, size and hardness), generator settings of the AUTOLITH system were adjusted. Adjustments could be made in power settings varying from low to high and number of shots given per second (ie, 5, 10, or 15 shots). Usually, when starting EHL, the generator settings were at medium power and 10 shots per second. These settings were increased pending unresponsiveness of the stone to fragment at the discretion of the endoscopist.

After lithotripsy was performed, stone fragments were extracted using retrieval balloons, baskets, or both. PD stent placement was not standardized after sphincterotomy in case of a residual stricture indicated by the inability to traverse a standard extraction balloon. In this case a pancreatic stent(s) was placed, and a progressive stent placement protocol was initiated (ie, during successive ERCP procedures the number of stents was increased up to a maximum that was allowed by the diameter of the PD and left in situ for 1 year). Stone clearance was based on direct pancreatoscopic visual assessment and on fluoroscopy images. All patients were clinically observed for 24 hours after EHL performance and received instructions at discharge to contact in case of adverse events.

Data collection and follow-up

Data were collected by the coordinating investigators (S.E.V., P.M.C.S., D.M.D.). At baseline, demographic details, including age, sex, and medical history, were collected for each patient. Additionally, all patients were asked to complete the SF-12 and the Izbicki pain score. The baseline Izbicki pain scores represent the pain score before either stent placement or direct EHL performance. After successful ERP with EHL, patients were observed for 24 hours, and routine follow-up at the outpatient clinic was conducted after 4 to 6 weeks. In addition to routine clinical follow-up, the coordinating investigators contacted patients by phone at the 3- and 6-month follow-up, and patients were asked to complete both the SF-12 and Izbicki pain score. No routine follow-up imaging was performed during the 6-month study period, and imaging was only conducted when clinically indicated. Finally, all adverse events that occurred within 30 days after EHL were recorded.

Statistics

Statistical analyses were performed using SPSS 25.0 software (IBM Corp, Armonk, NY, USA). The primary study endpoint was analyzed as intention to treat, including all patients eligible for pancreatoscopy-guided EHL, and per protocol, including all patients with successful introduction of the pancreatoscope. All secondary outcomes were analyzed in patients with technical success (ie, complete or partial stone clearance after pancreatoscopy-guided EHL). Baseline characteristics and secondary outcomes are presented either as numbers and percentages for dichotomous variables or as means and standard deviations or medians and interquartile ranges for continuous variables. To compute the physical and mental component summaries (Physical Component Summary [PCS] and Mental Component Summary [MCS]) of the SF-12, regression weights were used that were derived from normative data of the Dutch general population, using the orthogonal rotation method (14). The scores range from 0 to 100, with higher scores indicating a better quality of life. A score of 50 represents the mean in the general population (15). For each follow-up time point, the mean Izbicki pain score, PCS, and MCS were calculated. Linear mixed models were fitted to investigate changes in the Izbicki pain score, PCS, and MCS over time. A patient-specific (random) intercept was used to take into account that repeated measurements of the same patient are not independent. A $P < 0.05$ was considered statistically significant.

RESULTS

Between December 2017 and August 2019, 148 chronic pancreatitis patients were referred for endoscopic treatment. One hundred fourteen patients did not meet the inclusion criteria (**Figure 1**), and therefore 34 consecutive patients were included for treatment of PD stones in the head and/or neck of the pancreas with pancreatoscopy-guided EHL. Patient demographics at baseline are presented in **Table 1**. At baseline, 18 patients (53%) used daily opiate medication.

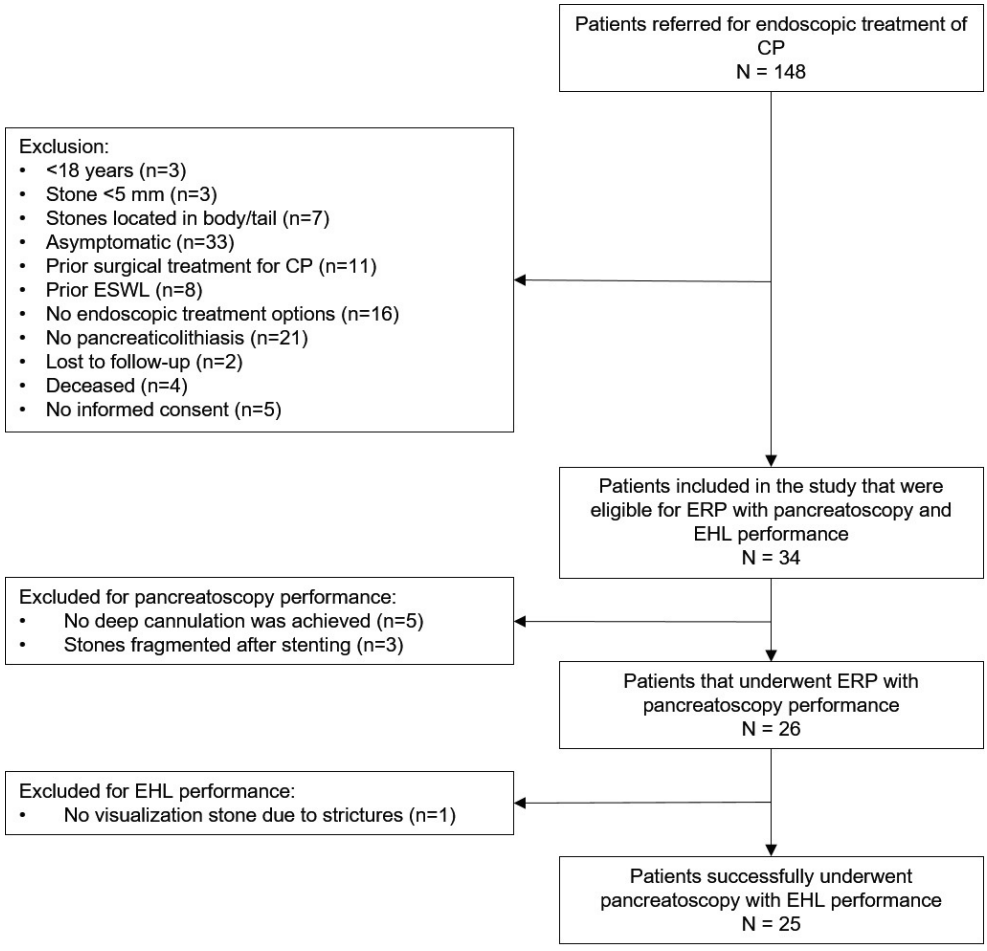

Figure 1. Flowchart of patient inclusion process. CP, Chronic pancreatitis; ESWL, extracorporeal shock wave lithotripsy; ERP, endoscopic retrograde pancreatography; EHL, electrohydraulic lithotripsy.

Table 1. Baseline characteristics of all patients eligible for pancreatoscopy-guided electrohydraulic lithotripsy (n = 34)

Characteristic	Value
Mean age, years (standard deviation)	56.7 (13.5)
Male gender	21 (62)
Mean body mass index, kg/m^2 (standard deviation)	23.5 (± 4.4)
ASA Classification	
• 2	23 (68)
• 3	11 (32)
Smoking	
• Yes	17 (50)
• No	4 (12)
• Quitted	11 (33)
• Unknown	2 (6)
Alcohol	
• Yes	9 (27)
• No	11 (33)
• Quitted	14 (41)
Etiology	
• Alcohol abuse	20 (59)
• Idiopathic	10 (30)
• Hypercalciemia	2 (6)
• Pancreas divisum and alcohol abuse	2 (6)
Symptoms at baseline	
• Abdominal pain	34 (100)
• Weight loss	17 (50)
• Nausea	11 (32)
• Vomiting	4 (12)
• Diarrhea or steatorrhoea	6 (18)
• Fever	3 (9)
• Back pain	1 (3)
• Fatigue	2 (6)
Opiate usage	18 (53)

Values are n (%) unless otherwise defined.

Technical success rate

From an intention-to-treat perspective, ERCP with subsequent EHL was technically successful in 24 of 34 patients (70.6%) with >5-mm PD stones. In 5 of 34 patients (14.7%) no deep cannulation of the PD could be achieved because of a stricture or obstructing stones in the head and/or neck of the pancreas. These patients received the following treatment for symptomatic chronic calcifying pancreatitis: Frey procedure (n=2), Whipple procedure (n=1), and ESWL (n=1). For the remaining patient, initially symptoms resolved without treatment but returned 2 years later with recurrent complaints of abdominal pain that could then be successfully treated endoscopically.

Successful PD cannulation was achieved in 29 of 34 patients (85.3%). In 3 of these 29 patients (11%) a stent was placed at the index procedure resulting in stone fragmentation without the need for subsequent EHL. In another patient a resilient stricture precluded passage of the pancreatoscope and EHL was not possible. Finally, 1 patient who underwent 2 EHL procedures resulting in partial stone clearance underwent additional ESWL after EHL. In this patient the stone was of very hard consistency, and therefore it

was difficult to fragment the stone using EHL, even at the highest EHL settings. Additional ESWL treatment was deemed necessary to remove the residual stone fragment. Therefore, in this patient EHL was considered unsuccessful, even though already >50% of the stones were fragmented using EHL. Clinical success was not assessed because this patient underwent additional treatment after EHL. In summary, the proportion of patients in whom duct clearance was achieved without additional ESWL or surgical interventions was 82.4% (28/34).

From a per-protocol perspective, EHL was technically successful in 24 of 26 patients (92.3%) in whom pancreatoscopy was attempted after successful deep cannulation of the PD. A flowchart is shown in **Figure 2**.

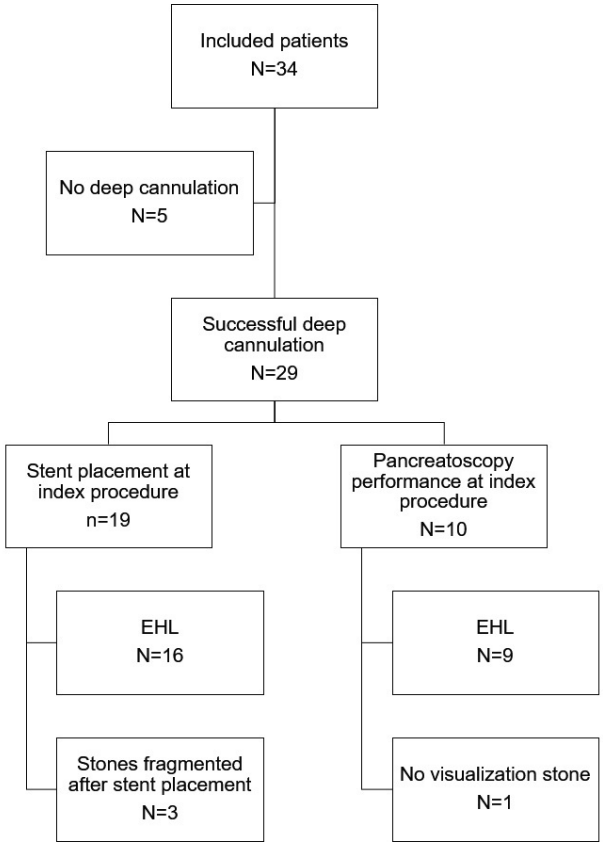

Figure 2. Flowchart of study procedures for all included patients (n = 34). EHL, Electrohydraulic lithotripsy.

ERP procedure and stone clearance

Table 2 summarizes the procedural findings of the 25 patients who underwent pancreatoscopy-guided EHL. To achieve stone clearance, a median number of 2 ERPs

(range, 1-3) and a median number of 1 EHL procedure (range, 1-2) were required. Complete stone clearance was achieved in 20 of 25 patients. Partial stone clearance occurred in 5 patients, of whom 1 patient underwent additional ESWL. Two of the remaining 4 patients were treated successfully according to the study criteria. In 1 patient follow-up data were missing. The final patient had no clinical success according to the study criteria but reported to have no symptoms of abdominal pain at routine clinical follow-up and therefore did not undergo any additional interventions. However, it should be noted that without a control group it can be difficult to tell whether the intervention (ie, EHL with stone removal) actually made a clinical difference in the subgroup of patients with partial stone clearance. Six patients underwent a single ERP procedure with immediate EHL (24%). Of the 16 patients who received a stent before EHL performance, 14 (87.5%) had complete stone clearance and 2 (12.5%) had partial clearance. Of the 9 patients who did not receive a stent before EHL, 6 (66.7%) had complete stone clearance and 3 (33.3%) had partial clearance.

Table 2. Procedure characteristics of patients who underwent pancreatoscopy-guided EHL (n = 25)

Characteristic	Value
Technical success	
• Intention-to-treat, %	70.6
• Per protocol, %	92.3
Pre-EHL	
Sphincterotomy	
• Pancreatic	25 (100)
• Biliary	8 (32)
Anatomy of the PD	
• Normal	22 (88)
• Pancreas divisum	3 (12)
Stricture	14 (56)
Stent placement prior to EHL performance	16 (64)
Balloon dilatation of stricture prior to pancreatoscopy	11 (44)
Dilated pancreatic duct	25 (100)
Pancreatic duct diameter, mm	8 (6 – 12)
Location of the stones based on the pancreatogram	
• Head	23 (92)
• Neck	2 (8)
Number of stones present based on the pancreatogram	1 (1 – 3)
Size of the stones based on pancreatogram, mm	8.6 (± 3.3)
EHL	
Number of ERP procedures	2 (1 – 3)
Number of EHL procedures	1 (1 – 2)
Stone clearance	
• Complete	20 (80)
• Partial	5 (20)
Total procedure time, min	63.8 (± 4.8)
EHL time, min	16.5 (± 2.1)
Number of shots required to fragment the stones	1197 (± 1422)

Characteristic	Value
Stone removal after fragmentation by EHL (n=28)	
• Balloon extraction	3 (10.7)
• Basket extraction	6 (21.4)
• Plastic stent placement	11 (39.3)
• Spontaneous	8 (28.6)
Initiation of progressive stenting protocol after EHL	4 (16)
Stent in situ at the end of follow-up	4 (16)
Adverse events	
Post-ERP pancreatitis	7 (28)
• Mild	6 (24)
• Moderate	1 (4)
Post-procedural pain	2 (8)
Cholangitis	1 (4)
NSAID prophylaxis	25 (100)
Time to onset, days	0.5 (0-5)

Values are n (%), median (range), or mean ± standard deviation unless otherwise defined.
EHL, Electrohydraulic lithotripsy; ERP, endoscopic retrograde pancreatography.

Adverse events

Adverse events occurred in 10 of 25 patients (40%) in whom pancreatoscopy with EHL was attempted after successful deep cannulation of the PD. The most frequent adverse event was PEP in 7 patients (28%). Two patients (8%) had postprocedural abdominal pain without elevated lipase or amylase. In 1 of these patients a CT showed a fluid collection with a maximum transverse diameter of 82 mm that was managed conservatively with antibiotics and no additional drainage. A follow-up CT showed resolution of the fluid collection. All adverse events ran a mild course and were treated in the hospital conservatively for a maximum of 5 days (range, 2-5).

Clinical success

Table 3 shows the Izbicki pain scores and the number of patients who used opioids at baseline, the 3-month follow-up, and the 6-month follow-up for the 25 patients who underwent pancreatoscopy with EHL performance. The linear mixed model showed that the observed differences were statistically significant (F-test: $P < .001$).

At the 6-month follow-up, data were missing in 3 of 25 patients. With regard to the individual Izbicki pain scores at the 6-month follow-up as compared with baseline, 14 of 22 patients showed >50% reduction in total Izbicki pain score, of which 7 of 14 had 100% pain reduction. In summary, clinical success was achieved in 16 of 22 patients (72%) according to the primary outcome measure definition (ie, >50% pain reduction or reduction in opioid usage): 2 with partial stone clearance and 14 with complete stone clearance. According to the study definition, clinical success was not achieved in 6 of 22 patients (27%), of which 3 still had a PD stent in situ in the context of a progressive stent placement protocol. With regard to stent placement before EHL, 12 of 16 patients (75%) with a stent in situ before EHL had clinical success and 4 of 16 (25%) did not. Four of 6 patients (66.7%) who did not receive a stent had clinical success and 2 (33.3%) did not.

Quality of life

The mean PCS and MCS were derived from the SF-12 and are shown in **Table 3** for the 25 patients who underwent pancreatoscopy with EHL. The mean scores at baseline and the 6-month follow-up were lower compared with the normative data from the Dutch general population. The mean scores at the 3-month follow-up were comparable with the normative data from the Dutch general population (14). The linear mixed model showed that these observed differenced were not statistically different for both the PCS (F-test: P = .080) and MCS (F-test: P = .164).

Table 3. Izbicki pain scores, opioid use, and quality of life at baseline and follow-up of the 25 patients who underwent pancreatoscopy and electrohydraulic lithotripsy

	Baseline	3 months	6 months
Clinical success			
Izbicki pain score*	62.3 ± 23.1 (25/25)	16.5 ± 17.7 (22/25)[†]	27.5 ± 35 (22/25)[†]
Opioid usage	13 (52) (25/25)	2 (8) (22/25) [†]	4 (16) (22/25) [†]
Quality of life (SF-12)			
Physical component summary[‡]	40.1 ± 11.1 (25/25)	47.2 ± 10.1 (21/25)[§]	43.2 ± 10.3 (21/25)[§]
Mental component summary[‡]	43.9 ± 13.1 (25/25)	50.1 ± 9.6 (21/25)[§]	45.9 ± 12.3 (21/25)[§]

Values are mean ± standard deviation (n/N) or n (%) (n/N).
* Scale ranges from 0 to 100 points (increasing scores indicating more pain severity). Questions consist of 4 items: frequency of pain, intensity of pain, use of pain medication, and disease-related inability to work.
[†] Data were missing for 3 patients
[‡] Scores ranges from 0 to 100 with higher scores indicating better quality of life.
[§] Data were missing for 4 patients

DISCUSSION

This is the first prospective consecutive case series study on the technical and clinical success of peroral pancreatoscopy-guided EHL as a first-line treatment in patients with symptomatic chronic pancreatitis with an obstructing stone in the head or neck of the PD. We reported a technical success rate of 70.6% that was mainly limited by the inability in certain patients to achieve deep cannulation of the PD. When ductal access could be secured, a technical success rate of 92.3% was achieved with complete stone removal in 80% of patients in a median of 1 EHL procedure. Clinical success was achieved in most patients after EHL (72%), with >50% decrease in pain scores or reduction in opioid usage at 6 months of follow-up. In addition to being the first prospective study, in contrast to previous studies, this study only included patients without previous treatment, such as ESWL, and only included patients with stones located in the head or neck of the PD. In addition, this study included a more extensive follow-up, including technical and clinical success and quality of life, in a patient population that is known to be difficult to follow. Therefore, this study is relevant to clinicians regarding what to expect from first-line treatment with EHL in chronic pancreatitis patients with a stone in the head or neck of the PD.

In recent years multiple studies have been performed on the technical and clinical success of pancreatoscopy with intraductal lithotripsy. Most studies are retrospective, do not include consecutive patients, and use pancreatoscopy with EHL or laser lithotripsy as second-line therapy after failure of ESWL (6,7,9,16-21). McCarty et al. (22) recently published a systematic review and meta-analysis to evaluate the treatment of difficult PD stones by peroral pancreatoscopy with either EHL or laser lithotripsy, with difficult PD stones defined as prior failure of conventional endoscopic treatment. A pooled technical success rate of 91% was found in 302 patients. Technical successes for EHL and laser lithotripsy were not significantly different (86% and 98%, respectively). Previous studies have shown the need for 1 to 4 ERP procedures of which 1 to 2 included EHL. From an intention-to-treat perspective, in our current study we found a technical success rate of 70.6%. This success rate may seem modest when compared with these previous studies; however, because we performed a prospective study we believe our results show a more accurate likelihood of clinically relevant performance compared with those from retrospective studies.

An advantage of using pancreatoscopy with intraductal lithotripsy as first-line treatment is that the endoscopist is in full control of all aspects of the treatment, including stone fragmentation, without depending on an ESWL facility. There are very few GI centers with a dedicated ESWL facility, and most services are provided by the urology department with no to little experience with pancreatic stone fragmentation. Another potential advantage of pancreatoscopy with intraductal lithotripsy is the possibility to fragment and remove stones and to treat concomitant strictures in a single procedure. However, during our study we experienced that for logistical reasons it was preferable to divide the procedure into first achieving deep cannulation of the PD and then to plan pancreatoscopy with EHL. The strategy for this may differ from institution to institution depending on the case load for ERCP. Of note, with this change in the protocol, the stone was already fragmented in 3 patients by stents alone and could be easily removed without the need for pancreatoscopy and EHL. By placing a stent before EHL, the clinical success of ductal decompression might be evaluated before proceeding with pancreatoscopy-guided EHL. Whether this is indicative for the future clinical success of stone fragmentation remains to be investigated.

An important finding of our study is the relatively high adverse event rate of 40%, of which 70% constituted PEP. McCarty et al. (22) described a pooled adverse event rate of 14.1%, varying from 0% to 30.4%, of which PEP occurred with a pooled rate of 8.7%. The severity of PEP in our cohort, however, was mild with conservative treatment and short-term hospital admission. A possible explanation for the high incidence of PEP could be because of the prospective design of our study, with active standardized follow-up of all included patients. Prospective studies usually show higher but a more accurate estimation of adverse events compared with retrospective studies. All patients were admitted for observation at least 1 night after the procedure, and for postprocedural abdominal pain there was a low threshold for measuring serum lipase concentration. On the other hand, pancreatoscopy with EHL is an invasive procedure encompassing a significant amount of intraductal device instrumentation and saline solution irrigation. Causing high pressure in the PD by irrigation should be avoided to minimize the risk of PEP. PD stent placement

after EHL may be considered to reduce the risk of PEP. When compared with ESWL, the rate of PEP after pancreatoscopy-guided lithotripsy seems to be higher, with an average of 4% reported for ESWL (23).

To the best of our knowledge, this is the first prospective consecutive case series and the first study to report on pancreatoscopy with EHL as the first-line treatment in patients with obstructive chronic calcifying pancreatitis CCP. However, some limitations need to be considered. First, the sample size of our study was small, which could be seen as a limitation. However, this was a single-center study that included a selective study population, and therefore including a large sample size was relatively difficult. During the study we adapted the treatment strategy. The ability and duration of achieving deep cannulation of the PD had such an impact on the logistics of our ERCP practice that for difficult and time-consuming cannulation, pancreatoscopy and EHL were done in a separate session. In fact, in this series the inability to achieve deep cannulation of the PD was the most important limiting factor for the technical success of pancreatoscopy and EHL. It needs to be mentioned that here lies a potential advantage of ESWL. It has been reported that ESWL in up to 38% of cases is the sole treatment, obviating the need for PD cannulation and stone fragment removal (24). Another limitation of the current study is that endoscopic therapy in some patients was ongoing at the end of the 6-month study follow-up because of a resilient PD stricture for which a progressive stent placement protocol was initiated. Of note, all procedures in this series were carried out by 2 highly skilled endoscopists in ERCP, and therefore results cannot easily be extrapolated to general practice. In any case, we believe these complex procedures are best carried out in high-volume expert centers. Larger series by other centers need to be performed to confirm or contradict our results. Comparative studies rather than consecutive case series, for example with primary ESWL treatment or surgery, would be of great interest. Because chronic pancreatitis is a benign disease, such studies would require a longer clinical follow-up (2 years and beyond), which is illustrated by an observation in the current study of an insignificant trend toward higher pain scores and the need for opiate use with a decrease in quality of life between 3 and 6 months of follow-up.

In conclusion, from this prospective consecutive case series we believe that pancreatoscopy with EHL holds promise as a first-line treatment for chronic pancreatitis patients with obstructing stones in the head or neck of the PD and deserves further exploration and evaluation.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Izbicki pain score system

Items	Score
Frequency of pain attacks	
• Daily	100
• Several times a week	75
• Several times a month	50
• Several times a year	25
• None	0
Visual analogue scale	
• Imaginative maximum of pain	100
• No pain	0
Analgetic medication	
• Morphine	100
• Buprenorphine	80
• Pethidine	20
• Tramadol	15
• Metamizol	3
• Acetylsalicylacid	1
Time of disease-related inability to work	
• Permanent	100
• ≤ 1 year	75
• ≤ 1 month	50
• ≤ 1 week	25
• None	0

Pain score = Sum of the values of the four aspects divided by four.

APPENDIX

12-Item Short-Form Health Survey

Your health and well-being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer each question by choosing just one answer. If you are unsure how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

Excellent	Very Good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
Accomplished less than you would like?	☐	☐
Were limited in the kind of work or other activities.	☐	☐

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
Accomplished less than you would like?	☐	☐
Were limited in the kind of work or other activities.	☐	☐

5. During the past 4 weeks, how much did pain interfere with your normal work (including work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

6. These questions are about how you have been feeling during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
Have you felt down-hearted and blue?	☐	☐	☐	☐	☐	☐

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
☐	☐	☐	☐	☐

Chapter 6

The role of pancreatoscopy in the diagnostic work-up of intraductal papillary mucinous neoplasms: a systematic review and meta-analysis

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ABSTRACT

Background and aim: Confirming the diagnosis, invasiveness, and disease extent of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas is challenging. The aim of this study was to summarize the literature on the efficacy and safety of peroral pancreatoscopy (POP) in the diagnosis of IPMN, including the impact of pre- and intraoperative POP on the management of IPMN.

Methods: The EMBASE, Medline Ovid, Web of Science, Cochrane CENTRAL, and Google Scholar databases were systematically searched for articles. Eligible articles investigated cohorts of patients who underwent POP for (suspected) IPMN.

Results: 25 articles were identified and included in this review; with 22 of these reporting on the diagnostic yield of POP in IPMN and 11 reporting on the effect of pre- or intraoperative POP on clinical decision-making. Cannulation and observation rates, and overall diagnostic accuracy were high across all studies. Frequently reported visual characteristics of IPMN were intraductal fish-egg-like lesions, hypervascularity, and granular mucosa. Overall, the adverse event rate was 12%, primarily consisting of post-endoscopic retrograde cholangiopancreatography pancreatitis, with a pooled rate of 10%, mostly of mild severity. Regarding the impact of POP on clinical decision-making, POP findings altered the surgical approach in 13%–62% of patients.

Conclusion: POP is technically successful in the vast majority of patients with (suspected) IPMN, has a consistently high diagnostic accuracy, but an adverse event rate of 12%. Data on intraoperative pancreatoscopy are scarce, but small studies suggest its use can alter surgical management. Future studies are needed to better define the role of POP in the diagnostic work-up of IPMN.

INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) is a common precancerous lesion of the pancreas, characterized by intraductal papillary proliferation of mucin-producing cells, resulting in cystic dilatation of the pancreatic duct (PD) (1,2). IPMN may progress from adenomatous lesions to high grade dysplasia (HGD) and finally to invasive carcinoma. Branch-duct IPMN (BD-IPMN) is the most prevalent subtype. Main-duct IPMN (MD-IPMN) is however associated with the highest risk of progression to malignancy and is considered an indication for surgery if the main PD (MPD) diameter is>10mm, or if there is evidence of jaundice or mural nodules (3,4). Early identification of MD-IPMN is important to allow surgery to be performed before the development of cancer.

Currently, imaging modalities used for the diagnosis of IPMN include computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). Even with the addition of endoscopic retrograde cholangiopancreatography (ERCP) and ERCP-guided brushing, the diagnosis of MD-IPMN and BD-IPMN can be challenging, as is determining the presence of HGD or invasive carcinoma. As a result, some patients undergo unnecessary pancreatic surgery for IPMN with low grade dysplasia (LGD) or benign cystic lesions (5). In addition, when surgery is indicated, preoperative determination of the extent of MD-IPMN using these techniques can be difficult. This could result in either unnecessary loss of pancreatic tissue in the case of an overly extensive resection, or progression of disease in the case of an incomplete resection. Although intraoperative frozen section analysis of the resection margin is routinely performed during pancreatic surgery, this strategy does not account for discontinuous "skip" lesions (6).

Over the past decades, peroral pancreatoscopy (POP) has been used more frequently in the diagnostic work-up of pancreaticobiliary disorders. It has potential additional value for the diagnosis of IPMN and in determining the intraductal extent of the lesion. Moreover, intraoperative pancreatoscopy (IOP) can assess residual skip lesions (7). However, the exact role of POP in the diagnosis and treatment of IPMN is unclear. Therefore, this systematic review and meta-analysis aimed to summarize the current literature on the technical success, safety, diagnostic yield, and clinical utility of POP in the management of IPMN.

METHODS

Eligibility criteria

Studies eligible for inclusion were randomized controlled trials, prospective and retrospective cohort studies, and case series. Case reports, reviews, poster abstracts, and studies in a language other than English were excluded. Studies examining adults with a (suspected) diagnosis of IPMN, undergoing POP, either performed during diagnostic work-up for IPMN or perioperatively, were deemed eligible.

Search strategy and study selection

On 11 February 2022, according to the PRISMA guidelines (**Table 1 s**), a systematic literature search was performed in EMBASE, Medline Ovid, Web of Science, Cochrane CENTRAL,

and Google Scholar. Predefined keywords used in this search were "pancreatoscopy" and "IPMN" to identify relevant articles. The full search strategy is presented in **Table2s**.

After duplicates of the retrieved articles had been removed, the titles and abstracts were independently screened for eligibility by two authors (D.d.J. and P.S.). The full text of potentially relevant articles was retrieved and independently assessed. Disagreement was resolved by consensus after discussion with a third author (P.J.d.J.). The references listed within the selected articles were screened to identify additional studies relevant for inclusion in this literature review.

Data extraction

Data were systematically extracted from all included studies using a predefined standardized form. Data extracted included study design, patient characteristics, and intervention-related characteristics (e.g. successful cannulation and the ability to visualize the target area). In addition, any pancreatoscopic visual characteristics of IPMN that were reported in the articles, the use and diagnostic value of adjunctive modalities such as NBI, and the effect of POP findings on clinical management were noted.

The evaluated outcomes were: (i) technical success, defined as the ability to advance the pancreatoscope to the target area/lesion within the MPD, and safety, including adverse events (AEs) such as post-ERCP pancreatitis (PEP), perforation, and bleeding; (ii) diagnostic pancreatoscopic features and accuracy, defined as the rate of agreement between these features and pathological examination of the surgical or autopsy specimens, for both POP visualization alone and for POP-guided biopsy or cytology; and (iii) the effect on clinical decision-making, defined as the surgical approach being altered on the basis of the pre- or intraoperative pancreatoscopic findings.

Statistical analysis

Statistical analyses were mostly limited to descriptive statistics using frequencies and percentages. For the pooled AE rate, meta-analysis was performed using R version 4.0.1 with the "meta" package. Random-effects meta-analysis was used, regardless of the results of heterogeneity testing. The effect size can vary per study because of differences in cohorts and the included patients, therefore random-effect meta-analysis is more suitable than fixed-effects meta-analysis. Data are presented as means with 95% CIs. Sensitivity analysis was performed for studies that reported the AEs on patients with IPMN only and for all patients, also including patients who underwent POP for indications other than IPMN.

RESULTS

A total of 25 articles met the inclusion criteria (8-32). The process of article selection and reasons for exclusion are summarized in (**Figure1**). The data extracted from the included studies are summarized in (**Table1**) and (**Table2**). There were 22 studies that primarily reported on the diagnostic yield of POP for all IPMN types (8–19,21,22,24–30,32) and 11 articles that reported on the effect of the POP findings, in the preoperative and/or

intraoperative setting, on clinical decision-making (i.e. choice to proceed to surgery and extent of surgery) (10,13,14,19,21–24,28,29,31).

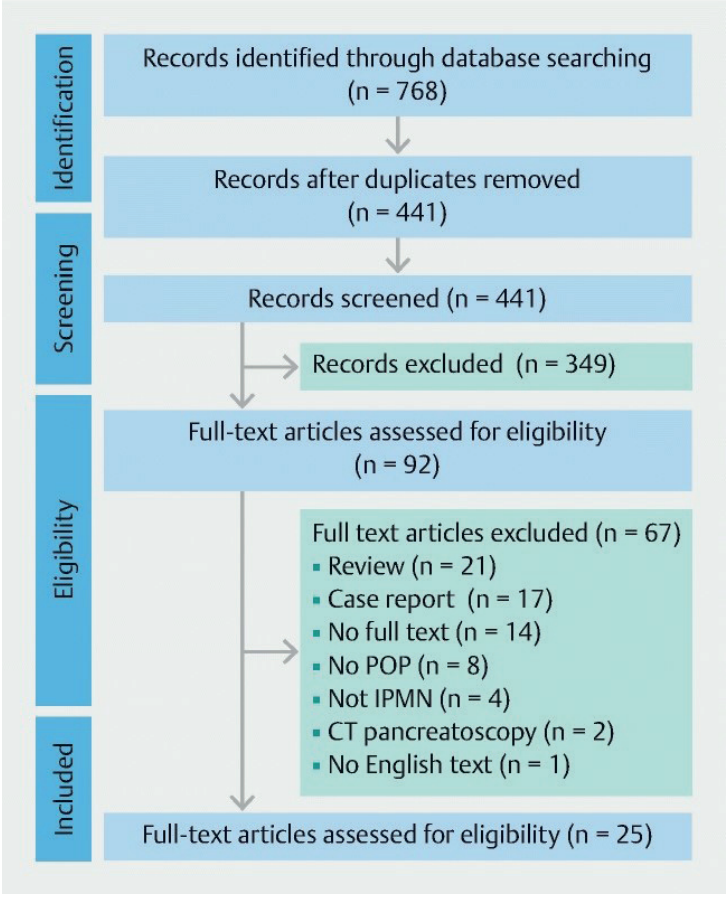

Figure1. Flowchart showing the selection and exclusion of articles. POP, peroral pancreatoscopy; IPMN, intraductal papillary mucinous neoplasm; CT computed tomography.

Table1. Studies investigating the role of peroral pancreatoscopy in the diagnosis and treatment of intraductal papillary mucinous neoplasm (IPMN).

Author (year)	Design (n)	Cannulations/ target area observed, %	Pancreatoscopy type	Key findings	Adjunct modalities	AE, %
Fujita et al. (1990) (8)	Retro (8)	86/ 100	Mother–baby: PF24, XCPF 3.3, BF-3C10, CHF-P10	IOP is useful for determination of lesion extent	NA	NA
Özkan et al. (1995) (9)	Retro (9)	89/ 100	Mother–baby: CFS-B20SL	IPMN is characterized by villous-like mucosal growths and clear jelly-like mucin substances	NA	0
Kaneko et al. (1998) (10)	Prosp (24)	100/ 100	Ultrathin pancreatoscope	IOP is able to detect lesions not detected by preoperative ERCP or EUS	NA	NA
Mukai et al. (1998) (11)	Retro (25)	100/ 60	Mother–baby: CHF-B20, CHF-B200, CHF-BP30, XCHF-B27	Papillary lesions >3 mm have a higher chance of malignancy	Biopsy: sensitivity 57%, specificity 100%, accuracy 75% Irrigation fluid cytology: sensitivity 63%, specificity 100%, accuracy 89%	4
Yamaguchi et al. (2000) (12)	Retro (41)	100/ 73	Mother–baby: XCHF-B27, CHF-B20, CHF-BP30	Severe atypical adenoma and carcinoma are associated with multiple morphologic features (i.e. frequently villous or vegetative elevations and red colored markings)	NA	NA
Atia et al. (2002) (13)	Retro (5)	100/ 100	FCP-9P	100% correct diagnosis of IPMN by POP	NA	20
Hara et al. (2002) (14)	Retro (60)	100/ 100	Mother–baby: CHF-BP30, OPTISCOPE	Combination of IDUS and POP improve differentiation between malignant and benign IPMN	Pancreatic juice cytology: sensitivity 13%, specificity 100%, accuracy 44% IDUS (MD): sensitivity 56%, specificity: 71%, accuracy 63% IDUS (BD): sensitivity: 77%, specificity: 100%, accuracy 88%	6.7
Yamao et al. (2003) (15)	Retro (60)	95/ 100	Mother–baby: CPF-PAB, PF8	Friability and protruding lesions more frequently seen in malignancy	NA	12[1]
Yamaguchi et al. (2005) (32)	Retro (103)	100/ 100	Mother–baby: CHF-BP30	Cytology has better diagnostic accuracy when collected by POP than when catheter-assisted	Pancreatic juice cytology: sensitivity 68%, specificity 100%	NA

Author (year)	Design (n)	Cannulations/ target area observed, %	Pancreatoscopy type	Key findings	Adjunct modalities	AE, %
Yasuda et al. (2005) (16)	Retro (26)	100/ 100	Mother–baby: NA	Detection of polypoid tumor >3 mm by POP 67% No adenocarcinoma in protrusions <3 mm	Biopsy: sensitivity 50%, specificity 100% Pancreatic juice cytology: sensitivity 50%, specificity 100%	0
Itoh et al. (2007) (17)	Prosp (5)	100/ 100	Mother–baby: CHF-BP260	NBI improves visualization of small vessels and superficial architecture	NBI	NA
Itoi et al. (2007) (18)	Retro (3)	100/ 100	Mother–baby: CHF-BP260	NBI is able to identify skip lesions otherwise not seen and shows capillary vessels more clearly	NBI	0
Miura et al. (2010) (19)	Prosp (21)	100/ 91	Mother–baby: CHF-BP260, CHF-B260	POP combined with NBI shows vascular patterns and protrusions more clearly and is useful for differentiation	NBI: correct excision line based on POP + NBI in 100% patients	0
Brauer et al. (2013) (20)	Retro (4)	100/ 100	Mother–baby: CHF-BP30 or Spyglass DVS	POP via dorsal duct is technically feasible	NA	0
Arnelo et al. (2014) (21)	Prosp (41)	93/ 100	SpyGlass DVS	Overall: sensitivity 84%, specificity 75% Accuracy: for MD-IPMN 76%, for BD-IPMN 78%	Biopsy in 17/41: benign 9, HGD 4, inadequate 4 Irrigation fluid cytology in 22/41: malignancy 5%	17
Nagayoshi et al. (2014) (22)	Retro (17)	77/ 100	SpyGlass DVS or ERCP catheter pancreatoscopy	100% sensitivity of irrigation fluid cytology for detecting malignancy	Biopsy: sensitivity 25%, specificity 100% Irrigation fluid cytology: sensitivity 100%, specificity 100%	35
Pucci et al. (2014) (23)	Retro (18)	100/ 100	Flexible choledochoscope	IOP is a valuable tool to determine the surgical resection margin	NA	NA
Navez et al. (2014) (24)	Retro (21)	100/ 100	NA	IOP is able to detect occult lesions and in combination with biopsies it could change the initial surgical plan	NA	NA
Kurihara et al. (2016) (25)	Prosp (17)	88/ 100	SpyGlass DVS	Visual diagnostic accuracy of POP in MD-IPMN was 87.5% (i.e. papillary stricture, fish-egg-like lesion)	Biopsy: 91% adequate samples	0
El Hajj et al. (2017) (26)	Retro (78)	100/ 97	Mother–baby: CHF-BP30, CHF-BP160, CHF-Y002 or SpyGlass DVS	POP-directed biopsies increased diagnostic accuracy of visual impression	Biopsy: sensitivity 87%, specificity 100%, PPV 100%, NPV 84%, accuracy 92% (in differentiating between neoplasia and non-neoplasia)	12[2]

Author (year)	Design (n)	Cannulations/ target area observed, %	Pancreatoscopy type	Key findings	Adjunct modalities	AE, %
Parbhu et al. (2017) (27)	Retro (16)	100/ 100	SpyGlass DVS and DS	Accuracy of biopsy alone (64%) increased to 100% in combination with visualization to correctly diagnose IPMN	Biopsy: sensitivity 64%, specificity 100% (in diagnosing IPMN)	6
Ohtsuka et al. (2018) (28)	Retro (7)	100/ 100	SpyGlass DS	Good visualization of the target area in all patients, with low diagnostic accuracy of targeted biopsies for detecting HGD	Biopsy: sensitivity 0% Irrigation fluid cytology: sensitivity 33%	14
Trindade et al. (2018) (29)	Retro (31)	100/ 100	SpyGlass DS	POP is of added value in patients with MD-IPMN and a diffusely dilated MPD, without focal lesions on cross-sectional imaging or EUS	Biopsy: in 28/31: LGD 79%, HGD 18%, adenocarcinoma 4%	29
Han et al. (2019) (30)	Retro (13)	100/ 100	Mother–baby: CHF-BP30 or SpyGlass DS	In patients with presumed idiopathic chronic pancreatitis, POP is able to identify MD-IPMN	NA	NA
Tyberg et al. (2019) (31)	Retro (13)	100/ 100	SpyGlass DS	POP can be effectively used as mapping tool preoperatively	NA	0

[1] Calculated over the total group of patients and not in patients with IPMN only.
[2] Calculated per pancreatoscopy procedure, not per patient.
AE, adverse events; BD, branch duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; HGD, high grade dysplasia; IDUS, intraductal ultrasonography; IOP, intraoperative pancreatoscopy; MD, main duct; MPD, main pancreatic duct; NBI, narrow-band imaging; NPV, negative predictive value; NA, not applicable; POP, peroral pancreatoscopy; PPV, positive predictive value; Prosp, prospective; Retro, retrospective.

Table2. Studies investigating the effect of preoperative or intraoperative pancreatoscopy on clinical management of intraductal papillary mucinous neoplasm (IPMN).

Author (year)	Design (n)	Timing	Gold standard	Adjunctive modality	Excision line based on pancreatoscopic findings	Altered surgical approach
Kaneko et al. (1998) (10)	Prosp (24)	IOP	Surgical specimen	NA	NA	13%: 10/24 extra lesions detected; 5/10 multifocal lesions; 3/5 more extensive resection
Atia et al. (2002) (13)	Retro (5)	Preop	Surgical specimen	NA	In 4/4 of patients with IPMN (100%); pancreatic cyst identified in fifth patient	NA
Hara et al. (2002) (14)	Retro (40)	Preop	Surgical specimen	IDUS	Continuous lesion in 35/40 (87.5%). Positive resection margin in one patient (2.5%)	NA
Miura et al. (2010) (19)	Retro (21)	Preop	Surgical specimen	NBI	In 7/7 patients, negative resection margins	
Arnelo et al. (2014) (21)	Prosp (44)	Preop	Surgical specimen, follow-up	NA	NA	95% additional information, in 76% affected clinical decision-making
Nagayoshi et al. (2014) (22)	Retro (17)	Preop	Radiology, surgical specimen	NA	In three patients (17.6%), excision line determined	
Pucci et al. (2014) (23)	Retro (18)	IOP	Surgical specimen	NA	NA	33%: 29% extended margins; 6% spared margins
Navez et al. (2015) (24)	Retro (21)	IOP	Radiology, surgical specimen	NA	NA	Additional lesions detected in 38%: 29% extended margins, 6% spared margins
Ohtsuka et al. (2018) (28)	Retro (7)	Preop	Surgical specimen	NA	NA	14% extended margins
Trindade et al. (2018) (29)	Retro (31)	Preop	Surgical specimen	NA	In 42% surgery dictated by POP on basis of additional findings. Significantly more often in patients with a diffusely dilated MPD (77% vs. 17%, $P = 0.001$)	NA
Tyberg et al. (2019) (31)	Retro (13)	Preop	Surgical specimen	NA	NA	62%: 31% extended margins, 31% spared margins Positive resection margins in 2/4 with spared margins (50%)

IDUS, intraductal ultrasonography; IOP, intraoperative pancreatoscopy; NA, not applicable; NBI, narrow-band imaging; Prosp, prospective; MPD, main pancreatic duct; Preop, preoperative; Retro, retrospective.

Technical success and adverse events

In all studies, technical success rates were reported, defined as the ability to advance the pancreatoscope into the MPD. This cannulation rate ranged from 86% to 100% (8–32). Pancreatoscopy was performed for diagnosis of a suspected MD-IPMN, BD-IPMN, or mixed-type IPMN (MT-IPMN). A dilated MPD was not required. Predictive factors reported for successful cannulation were a dilated MPD or a wide papillary orifice. It was not often reported how many patients underwent papillotomy prior to or during the POP procedure; however, where reported, it ranged from 0% to 92.7%. One study reported that POP was successfully performed via the minor papilla in four patients (20).

After successful cannulation, the rate of adequate visualization of the PD and region of interest ranged from 60% to 100%, but the specific location of the lesion in the PD was often not described. Of the 25 included studies, only six reported an observation rate lower than 100% (11,12,19,22,25,26), resulting in a combined observation rate of 95.6%. Reasons for the inability to visualize the target area were: inadequate clearance of mucus; a nondilated MPD; and concomitant anatomical features, such as a ductal stricture. Abundant mucus impaired visual characterization of the IPMN or wall of the MPD, despite flushing (12,25). Visualization of BD-IPMN was more difficult as compared with MD-IPMN, mainly owing to more difficult angulation of the pancreatoscope in reaching the area of interest and the smaller diameter of the MPD (11,12,22).

The occurrence of AEs was reported in 17 out of 25 studies (9,11,13–16,18–22,25–29,31). The overall pooled AE rate of these 17 studies was 12% (95% CI 9%–17%) (**Figure2**). PEP was the most common AE, with a pooled incidence rate of 10% (9% CI 7%–15%) (11,13–15,20–22,26–29) (**Figure1s**). The severity of PEP was mild in 24 patients (70.6%), moderate in seven (20.6%), severe in two (5.9%), and unknown in one (2.9%). One patient with severe PEP died (21).

In reporting AE rates, three studies did not make a difference between patients with and without (suspected) IPMN and therefore the reported overall AE rate and PEP rate might differ for patients with IPMN, albeit sensitivity analysis showed no significant difference between these (15,20,26). Most studies did not elaborate on the MPD diameter in relation to PEP. Trindade et al. reported that PEP occurred more frequently in patients with a focally dilated MPD (n=7/18; 39%) compared with patients with a diffusely dilated MPD (n=1/13; 8%; P=0.05) (29). In addition, Arnelo et al. reported that 6/7 patients diagnosed with PEP had a normal or only slightly dilated MPD (21). Other AEs included post-sphincterotomy bleeding (1.3%) (26), a mild sedation-related event (3.2%) (29), and cholangitis (8.3%) (22). The included articles did not clarify whether surgery was deferred or postponed because of these AEs.

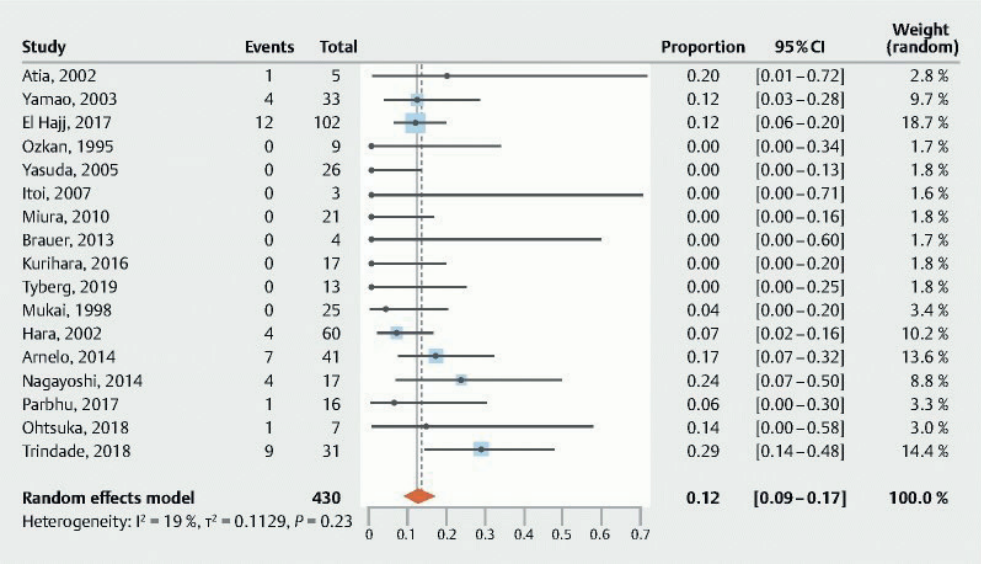

Figure 2. Pooled AE rate for all studies that reported adverse events

Visual diagnosis of IPMN and detection of high risk features by POP

Pancreatoscopic characteristic features of IPMN were intraductal papillary or villous projections, and the presence of mucus (33). Other features included: intraductal fish-egg-like lesions, that were sometimes seen on a protruding lesion, and granular mucosa (8,9,11–16,18,19,22,24–26,28–30). However, not all classical features are consistently seen. For example, in patients with a radiological diagnosis of MD-IPMN, the classical features of IPMN, such as a fish-eye papilla and oozing of mucus from the papilla, were detected in only 35% of patients in whom MD-IPMN was confirmed by histology (21). Examples of some of the visual characteristics of IPMN seen on POP can be found in (**Figure3**) and (**Video 1**) and (**Video 2**) (available online at www.endoscopy.thieme.com).

Seven studies reported on the sensitivity, specificity, and overall diagnostic accuracy rates of POP in the visual diagnosis of IPMN (10,13,16,21,25,27,30). In these studies, the results of POP were compared to pathology results after resection or from biopsies, or the absence of progression during long-term follow-up. Reported sensitivity rates ranged between 64% and 100% (10,13,16,21,27,30), specificity rates between 75% and 100% (13,21,27,30), and overall diagnostic accuracy between 87.5% and 100% (10,13,25).

The ability to differentiate noninvasive and malignant MD-IPMN with POP has been investigated in eight studies (8,10–12,14–16,26). The visual classification system proposed by Hara et al. allowed for discrimination of malignant IPMN from noninvasive IPMN with an accuracy of 88% for MD-IPMN and 67% for BD-IPM (14). Pancreatoscopic findings that were more frequently observed in patients diagnosed with malignancy were a coarse mucosa, friability, and tumor vessels (12,15,16). Another important finding by Trindade et al. was that 13 patients (42%) had additional high risk features on POP that were not seen

on imaging or EUS, for example papillary projections, nodules, and in one patient a frank mass (29).

Additional imaging modalities, such as narrow-band imaging (NBI) using the Olympus CHF-BP260, have been evaluated in three studies (17,18,19) and are described in **Appendix 1s**. The diagnostic value of targeted biopsies, cytology, and pancreatic juice collection are presented in (**Table1**) and **Appendix 2s**.

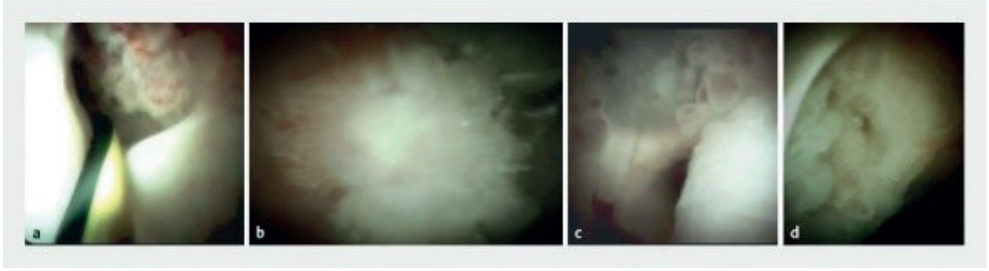

Figure3. Example images during peroral pancreatoscopy (POP) in four patients with intraductal papillary mucinous neoplasm (IPMN) showing: **a** a clear proximal margin of a main-duct IPMN (MD-IPMN) that was suspicious for malignancy, but was found to be a mixed-type IPMN without any malignancy on pancreatoduodenectomy (see also [Video 1)); **b** a clear image of a visible polypoid lcgesion in the setting of MD-IPMN, with biopsy revealing focal malignant transformation; **c** the clear fish-egg-like lesions in an MD-IPMN; **d** a very wide side branch in the body of the pancreas, with a nodular mass seen at the opening of the side branch, which showed mild dysplasia on POP-guided biopsy and later pancreatoduodenectomy.

Effect on clinical decision-making

Eleven articles reported on the pre- or intraoperative assessment of the intraductal extent of IPMN by pancreatoscopy and the effect of its findings on clinical management (10,13,14,19,21–24,28,29,31).

In four studies, the resection line was based on preoperative POP findings (13,14,19,29). Atia et al. reported that POP correctly identified and located IPMN in 4/4 patients with a final diagnosis of IPMN (100%) and correctly identified a pancreatic cyst in a further patient (13). In another study, the resection margin was based on preoperative POP and intraductal sonography, and comparison with postoperative surgical specimens revealed only one positive resection margin (2.5%) (14). Miura et al. used POP with NBI to determine the extent and resection line in seven patients, with postoperative examination showing no tumor in the excision stumps (19). In a study by Trindade et al., POP dictated the surgical plan determined prior to POP in 42% of patients with MD-IPMN (13/31) (29). This was more common in those with a diffusely dilated MPD >10mm (10/31; 77%) compared with those with a focally dilated MPD (3/18; 17%; P=0.001).

Five studies investigated whether pre- or intraoperative pancreatoscopy findings altered the intended surgical approach, which was based on cross-sectional imaging, ERCP, and/or EUS (10,23,24,28,31). After initial transection, IOP was performed to check the remaining PD for lesions. For POP, it was not clearly reported how the additional margin

was determined. Overall, determination of the extent of the lesion or identification of skip lesions by visualization or biopsy resulted in an altered surgical approach in 13%–62% of patients: in 13%–31% of patients, it resulted in a more extensive surgical resection (10,23,24,28,31); in 6%–31% of patients, it resulted in a less extensive surgical resection (23,24,31). Two studies reported that preoperative POP findings affected clinical decision-making or determination of the excision line, without reporting the initial surgical plan (21,22). The specifics of these studies can be found in (**Table2**) and **Appendix 3s**. Complications related to IOP were not reported.

DISCUSSION

The risk of malignancy in IPMN is highly variable as BD-IPMNs contain malignancy in a minority of patients, while MD-IPMNs have a higher reported incidence of malignancy (3,4). Although the general recommendation of the International Association of Pancreatology and others is that mucin-producing neoplasms with high risk features or MD-IPMN >10mm should undergo surgical resection, obtaining a definite diagnosis and assessing the possible intraductal extent can often be difficult. As such, the primary utility of POP in IPMN is considered threefold: (i) to confirm the diagnosis in equivocal cases based on imaging and history, especially when there is a question of chronic pancreatitis versus IPMN; (ii) to assess the presence of malignancy or high grade dysplasia; and (iii) to map the IPMN in order to guide resection margins. In current clinical practice, the exact role of POP remains to be determined. Its use remains limited to large volume referral centers, and available data regarding its efficacy and safety are limited and heterogeneous. In this meta-analysis, we summarize the available data on the use of POP in patients with (suspected) IPMN. Following a strict predefined search strategy, we identified 25 articles eligible for inclusion.

Overall, cannulation of the MPD with the pancreatoscope was successful in the vast majority of patients in whom standard MPD access had already been was achieved (86%–100%), and adequate visualization of the target area could be achieved in 60%–100% of patients, with the vast majority of studies reporting success rates of 100%. Predictive factors reported for failure to reach the target area were: impaired visibility due to an abundance of mucus; anatomical features such as strictures; or a nondilated MPD (11,12,22,25).

Despite these high technical success rates, AEs occurred in 12% of patients (11,13-15,20-22,26-29). Because the indication for pancreatoscopy is only diagnostic, the risk of complications may more readily outweigh the benefit of the procedure in comparison with therapeutic procedures. An acknowledgement of the high risk of pancreatitis is of clinical relevance because it may lead to postponement or even deferral of surgery. However, in the majority of the patients, PEP was treated conservatively and its severity was mild to moderate. The most important risk factor for PEP in the evaluated studies was the presence of a focally or mild-to-nondilated MPD, as compared with patients with a diffusely widened MPD, in whom the incidence of PEP was lower (21,29). All this should be interpreted in light of the observation that preoperative pancreatoscopy influenced the

type/extent of surgery in the vast majority of patients with a diffusely dilated MPD, but only in less than 20% of those with a focally dilated MPD (29).

Several studies have investigated the different pancreatoscopic features that are consistent with benign and malignant IPMN (8,10–12,14–16,26). Features that were more frequently identified in patients diagnosed with malignant IPMN were intraductal fish-egg lesions, prominent vascular changes, villous projections, and vegetative projections. Also, friability and a coarse mucosa were described as being related to malignancy. In addition, three studies investigated the additional value of NBI in the assessment of intraductal lesions and showed promising results, with improved visualization of the vasculature and flat lesions, along with identification of skip lesions that were otherwise not detected (17-19). Subsequently, identification of these areas could improve the yield of intraductal (targeted) biopsies.

Unfortunately, there are no studies available that have investigated the interobserver agreement of the different pancreatoscopic features and therefore their exact clinical value remains unclear. Sethi et al. previously showed that interobserver agreement of visual assessment of indeterminate biliary strictures is very low, even among experienced endoscopists (34). It is likely that this would be the case for IPMN as well.

Considering the moderate sensitivity and specificity rates reported in this review for a visual diagnosis of IPMN (64%–100%, and 75%–100%, respectively), histological confirmation remains important. The yield of POP-guided targeted biopsies and/or cytology was reported in eleven studies with widely varying results, with sensitivity rates ranging from 13% to 100% and specificity rates ranging from 53% to 100% (11,14,16,21,22,25–29,32). This variation can be explained by the small biopsies obtained via POP, owing to difficult maneuvering of the biopsy forceps, which make pathological diagnosis difficult. With regard to cytology examination, different sampling methods were used and different rates were reported for irrigation fluid compared with pancreatic juice obtained via POP. Interestingly, two studies showed that samples obtained by POP showed higher diagnostic accuracy rates than samples obtained by a catheter (22,32).

To improve the diagnostic yield of POP-guided targeted biopsies and cytology, future studies are needed to investigate the best collection method of fluid for cytology examinations and biopsy samples. To further optimize the yield of POP, there are some studies that have indicated that probe-based confocal laser endomicroscopy might be helpful in determining the nature of pancreatic lesions, such as IPMN, and its clinical management (35,36).

The most important question in the setting of pancreatoscopy as a complementary diagnostic tool in the work-up of IPMN is its actual impact on clinical (therapeutic) management and patient outcomes. Results varied greatly between the studies, from only 13% of patients having their surgical approach altered to almost all patients being impacted (10,13,14,19,21–24,28,29,31). In some studies, POP detected multifocal lesions that were otherwise not detected or could have been mistaken for chronic pancreatitis (10,20,–37). The nature of the included studies makes it difficult however to determine

the exact role of POP in the preoperative diagnostic work-up.Ideally, the primary utility of POP in IPMN would be to confirm the diagnosis of IPMN in persistent equivocal cases, or to map the extent of the IPMN where there is uncertainty regarding the extent of surgery. However, it should preferably only be performed after a diagnostic work-up including imaging (CT and/or MRI) and EUS with tissue acquisition, and following a multidisciplinary meeting. The Fukuoka guidelines advise performing EUS if there are worrisome features present on cross-sectional imaging (4). However, the yield is relatively low with a pooled sensitivity of 54% (95% CI 49%–59%) and specificity of 93% (95% CI 90%–95%) for EUS-guided fine-needle aspiration (38).

When determining the exact position of POP in the diagnostic work-up of IPMN, the risks and benefits should be weighed. As mentioned before, POP carries a considerable risk of PEP, although this is mainly mild. In addition, POP might be more costly compared with other diagnostic tools, such as CT or MRI. On the other hand, performing unnecessary or overly extensive surgery carries a risk of surgery-related AEs and is also costly. Currently, new studies on POP and IOP are underway that are also taking into account cost-effectiveness (NCT03062124 and NCT03729453), and results are eagerly awaited.

Some limitations need to be discussed. First, most studies were of a retrospective nature, did not involve a consecutive case series, and reported only descriptive data. Second, many different types of pancreatoscopes were used and, maybe more importantly, only five studies used the Spyglass DS, a digital pancreatoscope with an improved image quality compared with previous through-the-scope pancreatoscopes. In today's clinical practice the Spyglass DS and the Spyglass DS II are the most commonly used pancreatoscopes (39). These scopes have a wider range of view, with an enhanced image quality, which may increase the diagnostic yield of pancreatoscopy in the setting of the diagnostic work-up of IPMN. Third, as discussed in the previous paragraph, the included studies used different diagnostic work-up protocols and different outcome measurements, making it difficult to directly compare their outcomes in order to define the role of POP in the current diagnostic work-up.For all these reasons, a systematic quantitative data analysis was not possible for most outcome parameters, which prohibits the drawing of a definite conclusion regarding the role of POP in current clinical practice.

In conclusion, this is the first literature review to summarize the current knowledge on the role of POP in the diagnostic algorithm of IPMN. POP has a high technical success rate and seems to provide adequate visualization of the target area, in particular in patients with a dilated MPD. POP may be useful in the preoperative work-up for assessment of the extent and exact location of the lesion, as well as to identify the existence of skip lesions. However, despite the reasonably high diagnostic accuracy rates that have been reported, the exact role of POP in the diagnostic work-up still remains unclear, mostly because of methodological shortcomings and heterogeneity between studies. Large multicenter consecutive prospective studies performed according to a predefined protocol, including well-described procedural aspects, imaging documentation (preferably by video), and the application of intraductal pancreatoscopy-guided biopsies, are needed to better define the role of POP in the diagnostic algorithm of IPMN.

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SUPPLEMENTARY MATERIAL

Section and Topic	Item #	Checklist item	Page number where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3-4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3-4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3-4, Suppl
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	n.a.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4

Section and Topic	Item #	Checklist item	Page number where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	n.a.
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	n.a.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	n.a.
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5, Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	n.a.
Study characteristics	17	Cite each included study and present its characteristics.	5, Fig 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	n.a.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	5-8, Fig 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	n.a.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	5, Fig 2 & 4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n.a.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n.a.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n.a.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n.a.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9-11
	23b	Discuss any limitations of the evidence included in the review.	9-11
	23c	Discuss any limitations of the review processes used.	9-11
	23d	Discuss implications of the results for practice, policy, and future research.	9-11

Section and Topic	Item #	Checklist item	Page number where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	n.a.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	n.a.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n.a.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	12
Competing interests	26	Declare any competing interests of review authors.	12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	n.a.

Table 2s. Full search strategy and results on 11th of February 2022

Database	Search strategy	N
EMBASE (via Pubmed)	('intraductal papillary mucinous tumor'/de OR 'pancreas intraductal papillary mucinous tumor'/de OR (((intraductal* OR intra-ductal*) NEAR/10 (papill* OR pancrea*) NEAR/10 (tumo* OR neopla* OR carcinoma* OR adenocarcinoma* OR adenoma* OR cystadeno* OR lesion*)) OR ((pancrea*) NEAR/10 (intrapapill* OR intra-papill*) NEAR/10 (tumo* OR neopla* OR carcinoma* OR adenocarcinoma* OR adenoma* OR cystadeno* OR lesion*)) OR ipmn OR ipmt OR ipmc OR ipma OR ipmns OR ipmts OR ipmcs OR ipmas):ab,ti) AND ('cholangiopancreatoscopy'/de OR 'pancreatoscopy'/de OR 'pancreatoscope'/de OR 'peroral pancreatoscopy'/de OR pancreatography/de OR 'single operator peroral pancreatoscope'/de OR 'single operator peroral pancreatoscopy'/de OR 'intraoperative pancreatoscopy'/de OR (cholangiopancreatoscop* OR pancreatoscop* OR spyglass* OR spy OR Pancreaticocholangioscop* OR pancreatograph*):ab,ti) NOT ([Conference Abstract]/lim)	322
Medline Ovid	(Pancreatic Intraductal Neoplasms/ OR (((intraductal* OR intra-ductal*) ADJ10 (papill* OR pancrea*) ADJ10 (tumo* OR neopla* OR carcinoma* OR adenocarcinoma* OR adenoma* OR cystadeno* OR lesion*)) OR ((pancrea*) ADJ10 (intrapapill* OR intra-papill*) ADJ10 (tumo* OR neopla* OR carcinoma* OR adenocarcinoma* OR adenoma* OR cystadeno* OR lesion*)) OR ipmn OR ipmt OR ipmc OR ipma OR ipmns OR ipmts OR ipmcs OR ipmas).ab,ti.) AND ((cholangiopancreatoscop* OR pancreatoscop* OR spyglass* OR spy OR Pancreaticocholangioscop* OR pancreatograph*).ab,ti.) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt.	185
Web of science	TS=(((((intraductal* OR intra-ductal*) NEAR/10 (papill* OR pancrea*) NEAR/10 (tumo* OR neopla* OR carcinoma* OR adenocarcinoma* OR adenoma* OR cystadeno* OR lesion*)) OR ((pancrea*) NEAR/10 (intrapapill* OR intra-papill*) NEAR/10 (tumo* OR neopla* OR carcinoma* OR adenocarcinoma* OR adenoma* OR cystadeno* OR lesion*)) OR ipmn OR ipmt OR ipmc OR ipma OR ipmns OR ipmts OR ipmcs OR ipmas)) AND ((cholangiopancreatoscop* OR pancreatoscop* OR spyglass* OR spy OR Pancreaticocholangioscop* OR pancreatograph*))) AND DT=(article)	158
Cochrane CENTRAL	((((intraductal* OR intra next ductal*) NEAR/10 (papill* OR pancrea*) NEAR/10 (tumo* OR neopla* OR carcinoma* OR adenocarcinoma* OR adenoma* OR cystadeno* OR lesion*)) OR ((pancrea*) NEAR/10 (intrapapill* OR intra next papill*) NEAR/10 (tumo* OR neopla* OR carcinoma* OR adenocarcinoma* OR adenoma* OR cystadeno* OR lesion*)) OR ipmn OR ipmt OR ipmc OR ipma OR ipmns OR ipmts OR ipmcs OR ipmas):ab,ti) AND ((cholangiopancreatoscop* OR pancreatoscop* OR spyglass* OR spy OR Pancreaticocholangioscop* OR pancreatograph*):ab,ti)	3
Google scholar	"intraductal|ductal papillary|pancreas|pancreatic tumor|neoplasm|tumors|neoplasms" cholangiopancreatoscopy|pancreatoscopy|spyglass|Pancreaticocholangioscopy	100

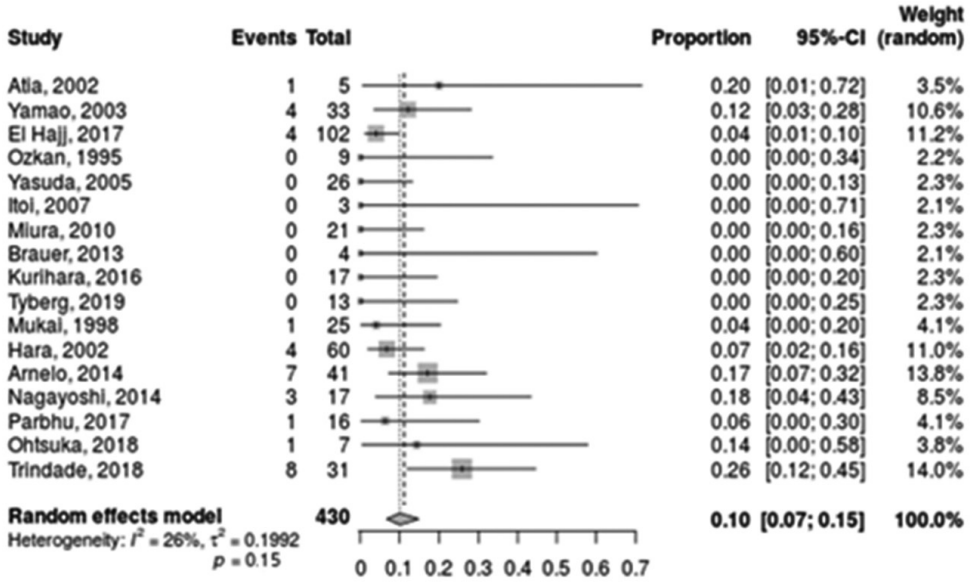

Figure 1s. Pooled post-ERCP pancreatitis rate: all studies that reported post-ERCP pancreatitis

APPENDIX

Appendix 1s Narrow-band imaging

Miura et al. assessed POP-guided NBI in 21 patients (1). Vascular patterns and protrusions were detected more clearly as compared to white light. Similar to this, Itoh et al. also described that in all five patients (100%) NBI was able to visualize small vessels and the superficial architecture, providing good delineation of IPMN (2). Finally, in a study by Itoi et al., including three patients, NBI showed fine capillary vessels in all three patients, that were otherwise not detected by using white light only, resulting in detection of skip tumor lesions in the tail of the pancreas in one patient and detection of a tumor at the transition site of head to body in another (3).

Appendix 2s Diagnostic value

A Targeted biopsies and cytology obtained using POP

Six studies investigated the diagnostic accuracy of targeted biopsies taken under direct pancreatoscopic visualization, for differentiation between malignant and non-invasive disease in patients with IPMN (4-9). Results are shown in Table 1. Kurihara et al. reported that adequate tissue samples could be obtained in 10/11 patients (91%) with suspicion of MD-IPMN (10). Ohtsuka et al. found a sensitivity of 0% for detecting HGD (8). During the preoperative work-up targeted biopsies were taken from the lesion of interest, but showed no HGD contrary to the surgical specimens of three patients. El Hajj et al. found that POP-guided biopsies in addition to visualization alone improved the sensitivity (87% to 91%), specificity (86% to 95%), positive predictive value (83% to 94%), negative predictive value (91% to 93%), and accuracy (87% to 94%) (11), in detecting pancreatic duct neoplasia, both in patients with and without IPMN. Parbhu et al. reported a 64% sensitivity and 100% specificity of POP-guided biopsies in correctly diagnosing IPMN (12). Results regarding pancreatic juice collection by POP are presented in **Table 1**.

B Pancreatic juice collection by POP

Seven studies investigated the diagnostic characteristics of pancreatic fluid cytology directly obtained via pancreatoscopy. Presence of malignancy or high suspicion of malignancy were indicative of malignant IPMN. Sensitivity rates ranged between 13-100% and specificity rates were 100% (4-8,13,14). Two studies reported on molecular markers. No studies reported on the use of secretin. Of note, different rates are reported for cytology on pancreatic juice and on irrigation fluid analysis. Four studies reported on the use of cytological analysis on irrigation fluid, with sensitivity rates between 33-100% (4 7,8), specificity of 100% (47), and accuracy of 89% (4). In addition, Arnelo et al. reported that cytology results showed malignancy in one of the 22 (out of 41) patients in whom irrigation fluid cytology was performed (6). Important to note is that in situ hybridization (FISH) was used in 3/41 patients and DNA flow cytometry in 27/41. Finally, three studies reported on diagnostic characteristics of pancreatic juice cytology (5,13,14). According to these studies sensitivity ranged from 15-67% (5, 13, 14) and specificity was 100% (5,13,14), with an overall diagnostic accuracy of 44% (13). Hara et al. determined the presence of the K-ras point mutation in the pancreatic juice. Yamaguchi et al. compared the diagnostic accuracy of pancreatic juice cytology collected by POP or by catheter and found a higher

sensitivity, but not statistically significant, for pancreatic juice cytology collected by POP as compared to catheter-assisted aspiration (68% versus 38%, respectively, p=0.055) (14).

A study by Uehara et al. who investigated the diagnostic value of pancreatic cytology in diagnosing carcinoma in situ, showed that in all eleven patients cancerous cells were found on examination of pancreatic fluid aspirated through the pancreatoscope (15). These findings suggest that pancreatic juice sampling via POP should be considered for cytopathological examination, particularly in cases in which the EUS-fine needle aspiration was inconclusive or not possible. Because pancreatic juice cytology collection is time consuming, preselection of patients with high suspicion of malignancy can be considered.

Appendix 3s Determination of the extent of IPMN by pancreatoscopy

In a retrospective study from Ohtsuka et al. pancreatoscopy changed the surgical management only in 1/7 patients (14%) and failed to detect 1 concomitant ductal adenocarcinoma (8). Kaneko et al. found that IOP detected 10 cases of IPMN that were not detected by EUS or ERCP. Half of them (5/10) were intraductal multicentric lesions. Finally, in 3/5 patients (60%) an additional pancreatic resection was performed, resulting in an altered surgical plan in 13% of patients overall (16). Pucci et al. reported that in 8/23 patients (35%) final resection margins were influenced by pancreatoscopic findings. With regards to patients with suspected IPMN (n=18), pancreatoscopy identified six additional lesions in 6 patients, after which in five patients (29%) the resection margin was extended and in one patient (6%) margin was spared (17). In two patients adenocarcinoma was removed with the extended margin, in one patient with HGD, in one patient with moderate dysplasia and in one patient with a BD-IPMN with LGD. In the patient with less extensive margin LGD was found in the neck. Navez et al. reported that IOP and intraductal biopsies modified initial planned surgical resection in 23.8% of the 21 patients (18). POP-guided biopsies may also be helpful in determining the resection margins intraoperatively. Tyberg et al. reported that in 7 of the 8 patients in whom the surgical plan was changed, this was based on visual findings in combination with results from targeted biopsies (19). In 2/8 patients in whom the surgical plan was altered on POP findings, from total pancreatectomy to pancreatoduodenectomy, post-operative resection margins were positive.

Regarding the two studies not reporting prior surgical plan, Arnelo et al. reported that additional information was provided by POP in 39 out of 41 patients (95%) with suspected IPMN while affecting clinical decision making in 76% (6). According to Nagayoshi et al., in 3/17 patients (18%) POP was useful in determining the excision line. In the three patients in whom POP contributed to determination of the excision line, a transition of fish-egg like lesions to normal mucosa could be clearly identified (7).

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Part III

Treatment optimization of EUS and ERCP in biliary and pancreatic diseases

Chapter 7

Urgent endoscopic ultrasound-guided endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis (APEC-2): a multicentre prospective study

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ABSTRACT

Background and aim: Routine urgent endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy (ES) does not improve outcome in patients with predicted severe acute biliary pancreatitis. Improved selection of patients may challenge these findings. Endoscopic ultrasonography (EUS) can detect bile duct stones and sludge and identify patients who may benefit from ERCP with ES.

Methods: A multicentre, prospective cohort study (APEC-2) included patients with a predicted severe biliary pancreatitis without cholangitis and compared outcomes with the conservative treatment group (n=113) of the APEC trial (Lancet 2020). Patients underwent urgent EUS, followed by ERCP with ES in case of common bile duct stones or sludge, within 24 hours after hospital presentation and within 72 hours after symptom onset. The primary endpoint was a composite of major complications or mortality within 6 months after inclusion.

Results: Overall, 83 patients underwent urgent EUS at a median of 21 hours (IQR 17-23) after hospital presentation and at a median of 29 hours (IQR 23-42) after start of symptoms. Gallstones or sludge in the bile ducts were detected by EUS in 48/83 patients (58%), all of whom underwent immediate ERCP with ES. The primary endpoint occurred in 34/83 patients (41%) in the urgent EUS-guided ERCP group as compared to 50/113 patients (44%) in the conservative treatment group (risk ratio [RR] 0.93, 95% CI 0.67–1.29; p=0.65).

Conclusion: In patients with predicted severe acute biliary pancreatitis without cholangitis, urgent EUS-guided ERCP with ES did not reduce the composite endpoint of major complications or mortality, as compared with conservative treatment.

INTRODUCTION

Acute pancreatitis is one of the most common gastrointestinal diseases requiring acute hospital admission and its incidence has been increasing throughout the years (1,2). Acute biliary pancreatitis is caused by gallstones and sludge obstructing the ampulla of Vater, creating a transient impediment of the flow of secretion from the pancreatic duct (3,4). The duration of the pancreatic duct obstruction appears related to the severity of inflammation of the pancreas (5). Consequently, in an attempt to ameliorate the disease course it seems attractive to decompress the pancreatic duct by removing bile duct stones or sludge with endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) as early as possible. Recent guidelines state that urgent ERCP with ES is warranted in patients with acute biliary pancreatitis and concomitant cholangitis, and not recommended in patients with a predicted mild disease course, but provide limited guidance on the indication of urgent ERCP with ES in patients with a predicted severe disease course (6,7,8).

The recently published APEC trial investigated whether urgent biliary decompression using ERCP with ES is beneficial in patients with predicted severe acute biliary pancreatitis without cholangitis (9). In this trial, 232 patients were randomized between conservative treatment and urgent ERCP with ES. 'Urgent' was defined as within 24 hours after hospital presentation and within 72 hours after symptom onset. Urgent biliary decompression with ERCP with ES did not reduce the composite endpoint of major complications or mortality as compared to conservative treatment (9). In the APEC trial however, the probability for a biliary origin and the indication for ERCP was based on common bile duct (CBD) dilation, an increase in serum alanine-aminotransferase (ALT) or sludge or stones on imaging (located in the gallbladder or CBD). Studies have shown that elevated liver enzymes and radiological signs of CBD stones are poorly correlated to the actual presence of CBD stones or sludge during ERCP (10,11). This was confirmed in the APEC trial, where 55% of the patients in the urgent ERCP group did not show CBD stones or sludge during ERCP. After spontaneous stone passage into the duodenum, biliary decompression is no longer necessary and ERCP with ES may even be harmful (e.g. haemorrhage and aggravation of pancreatitis) (12). The most sensitive modality for diagnosing CBD stones or sludge is endoscopic ultrasonography (EUS) (13,14) When EUS is performed immediately before an intended ERCP with ES, it allows to perform ERCP exclusively in patients with confirmed stones or sludge in the CBD who are most likely to benefit.

The APEC trial showed that urgent ERCP with ES had no benefit over a conservative approach in predicted severe acute biliary pancreatitis without cholangitis when inclusion was based on biochemical tests and transabdominal ultrasound. This is supported by a recent meta-analyses that also included the APEC trial (15). Yet, it remains unclear whether urgent ERCP with ES is beneficial in the selected group of patients with confirmed bile duct stones or sludge on EUS. Therefore, in this prospective multicentre study we assessed whether urgent EUS-guided ERCP with ES reduces major complications or mortality in patients with predicted severe acute biliary pancreatitis and confirmed CBD stones or sludge (APEC-2).

METHODS

Study design and participants

This multicentre, prospective cohort study was performed in 15 Dutch hospitals. The outcomes of this prospective cohort were compared to the outcomes of the conservative treatment group of the original APEC trial. Details on the APEC trial (Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus conservative treatment) can be found both in the previously published trial protocol and main publication (9,16). In the APEC-2 study the 15 participating centres were selected based on their high inclusion rates during the APEC trial and their ability to organize EUS and consecutive ERCP with ES within 24 hours after hospital presentation. We adhered to protocol used in the APEC trial, except for the EUS procedure prior to ERCP in all included patients (16).

All patients presenting to the emergency department with acute pancreatitis were assessed for eligibility. Inclusion and exclusion criteria for this study were identical to those in the original APEC trial (9). Acute pancreatitis was defined according to the revised Atlanta criteria, as the presence of at least two out of the following criteria: 1) upper abdominal pain, 2) serum amylase or lipase concentration more than three times the upper limit of normal, or 3) features of acute pancreatitis on imaging (17). A predicted severe disease course was defined as an Acute Physiology and Chronic Health Evaluation (APACHE II) score of eight or more, an Imrie score of three or more, or if the C-reactive protein serum level was higher than 150 mg/L within 24 hours of presentation at the emergency department (18-22).

Biliary pancreatitis was defined by either biliary sludge or gallstones on imaging, a dilated CBD on imaging (>8 mm in patients ≤75 years of age, or >10 mm in patients >75 years of age) or a serum alanine aminotransferase (ALT) level of more than twice the upper limit of normal (7,23,24).

Exclusion criteria included pancreatitis due to other causes than biliary, a previous sphincterotomy or needle knife pre-cut, suspected bacterial cholangitis or a history of chronic pancreatitis. Cholangitis was defined as fever in combination with either proven CBD stones, a dilated CBD or (progressive) cholestasis (detailed definitions and an overview of all inclusion and exclusion criteria can be found in **Supplementary Table S1**). Written informed consent was obtained from each participant. This study was performed in accordance with the Dutch law regarding research involving human subjects and the Declaration of Helsinki. The ethical committee of the Erasmus MC University Medical Centre in Rotterdam, the Netherlands, approved both the trial protocol of the APEC trial and the current APEC-2 study protocol. The study protocol was registered with the ISRCTN registry (ISRCTN15545919). This study was reported in accordance with the STROBE guidelines (25).

Investigational treatment

For the current study, EUS needed to be performed within 72 hours after symptom onset and within 24 hours after presentation at the emergency department. If gallstones or sludge in the CBD were detected during EUS, ERCP with ES was performed subsequently.

EUS was considered positive for gallstones or sludge when a persistent echogenic intraluminal material was seen in the CBD or common hepatic duct, with or without posterior acoustic shadow. If no gallstones or sludge were detected during EUS or when the bile ducts could not be visualized during EUS, the patient was treated conservatively.

EUS and ERCP were both carried out by, or under the direct supervision of, an experienced endosonographist and interventional endoscopist. This was defined as a lifetime experience of more than 400 EUS/ERCPs performed for choledocholithiasis as a primary responsible investigator and more than 50 EUS/ ERCPs annually on average in the previous three years. Biliary sphincterotomy was mandated in all patients undergoing ERCP. When biliary cannulation was not successful, even after pre-cut sphincterotomy, the procedure was abandoned and the patient was treated conservatively, with re-ERCP in case of persistent cholestasis or cholangitis.

Management of the conservative treatment group was described in the original APEC trial (9). In this group, ERCP with sphincterotomy was performed only if a patient developed cholangitis after inclusion, or in case of persistent cholestasis or retained bile duct stones after recovery from the initial acute pancreatitis episode.

Standardized case record forms were used by local clinicians to collect data and patients underwent a CT scan 5 to 7 days after hospital presentation to assess the presence of pancreatic (parenchymal) necrosis. All scans were re-assessed by an experienced radiologist (TLB). Use of both in-hospital and out-of-hospital utilization of healthcare was registered, either as part of data collection or by self-administered questionnaires. An independent monitor compared the study documents with source data to ensure proper data collection.

Outcomes

The primary endpoint was a composite endpoint of major complications or mortality occurring within 6 months after inclusion. Major complications included: bacteraemia, cholangitis, new onset persistent organ failure (>48 hours or <48 hours and leading to death), pancreatic parenchymal necrosis, pneumonia, and pancreatic endocrine or exocrine insufficiency (definitions can be found in **Supplementary Table S2**). Secondary endpoints included: the incidence of the individual components of the primary endpoint, occurrence of new onset transient (<48 hours) and persistent multiorgan failure and single organ failure, ERCP-related complications (definitions in **Supplementary Table S3**), length of hospital stay, intensive care unit (ICU) admission, length of ICU stay, number of interventions (i.e. endoscopic, radiological, or surgical), readmission for biliary events (i.e. recurrent biliary pancreatitis, cholecystitis, biliary colic, cholangitis, and choledocholithiasis), and quality of life. Quality of Life was measured using the SF-36 questionnaire.

An adjudication committee consisting of two surgeons and three gastroenterologists assessed all potential endpoints individually. Disagreements were resolved during a consensus meeting.

During the original APEC trial, an independent Data Safety Monitoring Committee (DSMC) assessed protocol adherence, patient recruitment, and patient safety. Adverse events were reported by treating clinicians to the coordinating investigators, who reported the events to the Dutch Central Committee for Research involving human subjects. All events were reported to the DSMC per consecutive group of 60 patients (9).

Patient and Public Involvement

The Dutch Pancreatitis Study Group (DPSG) has close ties with the Dutch Patient Association for Pancreatic Diseases. This association was actively involved in the design of the APEC trial and also partially funded the trial. This APEC-2 study was an additional part of the trial and as such the design was discussed during DPSG meetings that included representation of the patient association. Once the trial has been published, participants will be informed of the results through the DPSG website.

Statistical analyses

The sample size calculation of this prospective comparative study was based on data from the interim analysis of the APEC trial since full trial results were not yet available. Cholestasis or bile duct stones on transabdominal ultrasound in the conservative group were used as a proxy for bile duct obstruction. In the APEC trial, the prevalence of the composite endpoint in the patients in the conservative study group with cholestasis or bile duct stones was 45%. In the ERCP with ES group the composed endpoint was seen in 29% of patients that had CBD stones during ERCP that were successfully removed. As a result, in case of bile duct obstruction, a reduction of 16 percentage points in the composite endpoint was achieved after ERCP with ES. To account for the possibility of missed small stones in the conservative group and intention bias (i.e. actors perceive a greater motivation to complete a task when the underlying indication to perform the procedure is supposedly more scientifically based), an additional 5 percentage points reduction of the primary endpoint was expected in the group that would be treated with urgent EUS-guided ERCP with ES. Using a Chi-square test without continuity correction we established that with an expected reduction of 21 percentage points in the composite endpoint, a 2-sided significance level of 5 and a 1% dropout rate, a total of 78 patients needed to be included to have a power of 80%. Patients in whom the composed primary endpoint could not be assessed due to withdrawal of informed consent were replaced. Furthermore, to provide a total of 78 *evaluable* patients for the per-protocol analysis, additional patients were added to replace patients that did not undergo EUS or in whom EUS was incomplete, and patients in whom ERCP was not successful. The adjudication committee was only allowed to exclude patients before the statistical analyses were performed, these patients were not replaced but were excluded from the analyses. The composite primary endpoint and the individual components of the primary endpoint were analyzed according to the intention-to-treat principle. A per-protocol analysis was also performed. All other secondary endpoints were analyzed according to the intention-to-treat principle.

Continuous data were compared with the Mann-Whitney U test, dichotomous data with the Pearson's χ^2 test or Fisher's exact test. A two-sided p value of <0.05 was considered statistically significant. Results are presented as risk ratios (RRs) with their corresponding

95% confidence interval (CI). Missing data for the primary and other secondary endpoints were classified as no event for both the intention-to-treat analysis and the per-protocol analysis. Data on mortality was acquired for all patients. For other analyses, data were considered to be missing completely at random and a complete case analysis was performed. The analyses of the primary endpoint and the quality of life analyses were performed by an independent statistician (NE). Logistic regression models were used for sensitivity analyses to investigate the influence of baseline differences between the two groups on the primary outcome. For statistical analysis IBM SPSS Statistics version 25 and R version 4.1.3 (2022-03-10) were used.

RESULTS

Between the 15th of August 2017 and the 21st of August 2019, 522 patients with acute biliary pancreatitis were assessed for eligibility. **Figure 1** shows the inclusion flowchart. Most eligible patients did not meet the inclusion criteria due to a predicted mild disease course. Eighty-seven patients with a predicted severe disease course were treated with urgent EUS-guided ERCP with ES, of whom four were excluded due to either withdrawal of consent (n=2) or cholangitis at inclusion (n=2). Subsequently, 83 patients were included in the analyses. The patients from this prospective cohort were compared to a historic cohort, consisting of 113 patients with predicted severe acute biliary pancreatitis that were treated conservatively in the APEC randomized trial (9).

Baseline characteristics

Baseline characteristics are shown in **Table 1**. In the urgent EUS-guided ERCP group fewer patients were included with severe systemic disease and organ failure (according to the Modified Marshall Score of 2 or higher which could indicate either single or multi organ failure) at baseline (26). In this group baseline CRP levels were higher. Cholestasis was present in 53 out of 83 patients (64%) in the urgent EUS group and in 67 out of 113 patients (59%) in the conservative treatment group.

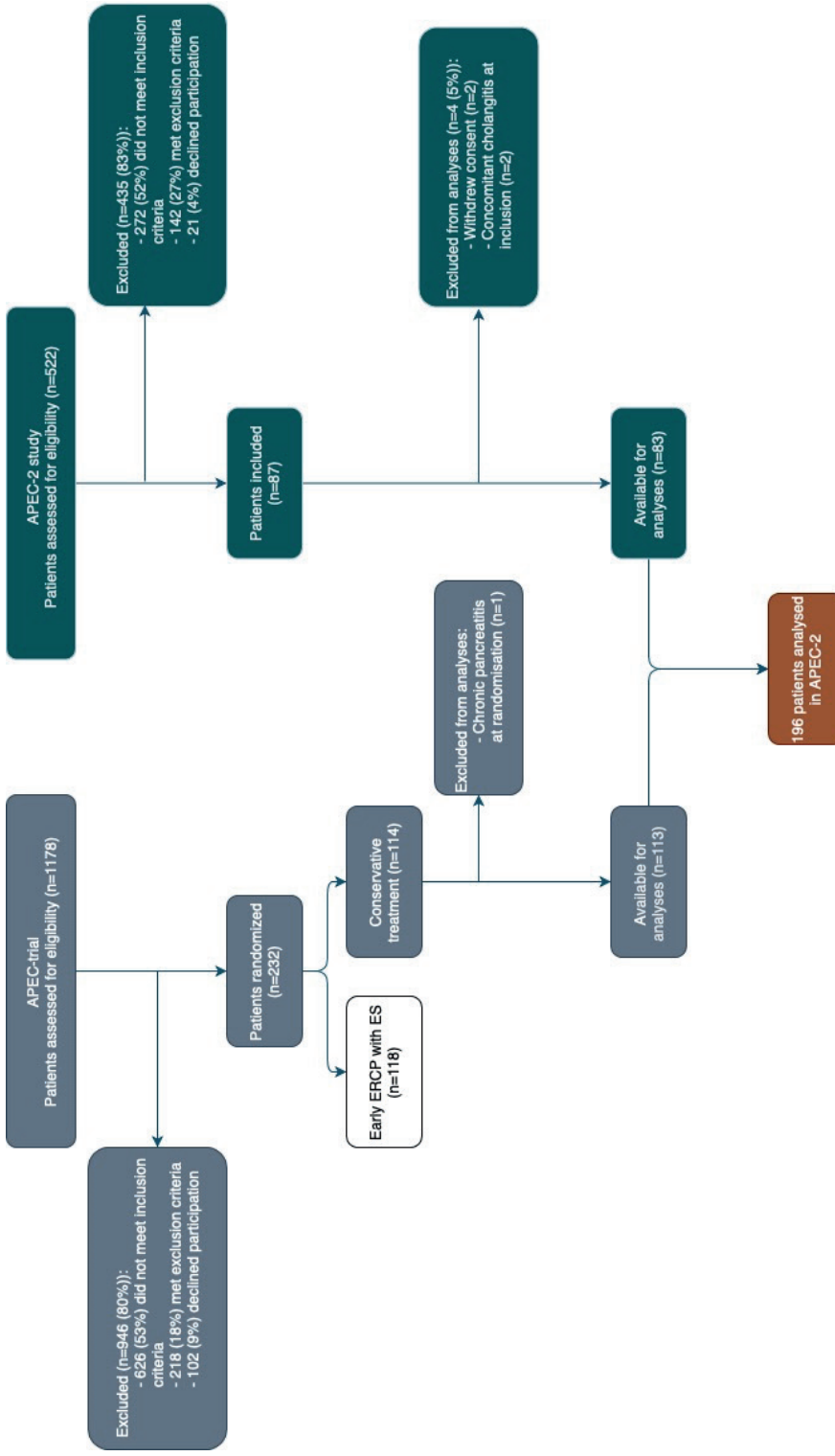

Figure 1. Combined inclusion flowchart of patients included in the APEC-trial and the current APEC-2 study

Table 1. Baseline characteristics

Characteristic	Urgent EUS ± ERCP with ES (n=83)	Conservative treatment (n=113)	p-value
Age in years, mean (SD)	70 (11)	71 (12)	0.65
Female sex	37 (45)	53 (47)	0.75
ASA score			*0.03*
• Healthy status	16 (19)	16 (14)	
• Mild systemic disease	52 (63)	57 (50)	
• Severe systematic disease	15 (18)	40 (35)	
BMI (kg/m^2), mean (SD)	29 (5)	29 (6)	0.58
Severity of disease on admission			
• APACHE-II score, median (IQR)	10 (9-13)	10 (8-13)	0.87
• Modified Glasgow score, median (IQR)	2 (2-3)	2 (1-3)	0.24
• CRP, median (IQR)	78 (28-164)	38 (11-104)	*0.003*
• SIRS	45 (54)	61 (54)	0.97
• Organ failure	7 (8)	25 (22)	*0.01*
Biliary aetiology			
• Gallstones on imaging	57 (69)	88 (78)	0.19
• Dilated CBD on imaging	18 (22)	32 (28)	0.32
• Serum ALT>2 times the upper limit of normal	77 (93)	93 (82)	*0.03*
• Serum ALT>2 times the upper limit of normal in absence of other biliary criteria	23 (28)	18 (16)	0.05
Cholestasis			
• Bilirubin (>40umol/L, >2.3mg/dL)	46 (55)	51 (45)	0.16
• Dilated common bile duct on imaging	18 (22)	31 (27)	0.36
Time from onset of symptoms to presentation at emergency department in hours – median (IQR)	11 (5-20)	9 (5-18)	0.38

Values are in n (%) unless otherwise defined.
ASA score = American Society of Anesthesia Physical status Classification System. BMI = Body Mass Index. CRP = C-reactive protein. SIRS = Systemic Inflammatory Respons Syndrome Score. ALT =Alanine aminotransferase.

Primary and secondary endpoints

The primary composite endpoint of major complications or mortality occurred in 34 out of 83 patients (41%) in the urgent EUS group compared to 50 out of 113 patients (44%) in the conservative treatment group (RR 0.93, 95%CI 0.67-1.29, p=0.65). Apart from a difference in the occurrence of pancreatic exocrine insufficiency, no other differences were found in the individual components of the primary endpoint. Pancreatic exocrine insufficiency was observed in 9 patients (11%) in the urgent EUS group and in 2 patients (2%) in the conservative group (RR 6.13, 95% CI 1.36-27.62, p=0.01). Exocrine insufficiency was defined by a low faecal elastase at three months after inclusion and the use of enzyme replacement therapy at six months after inclusion. By using a faecal elastase level of <200 mg/g, irrespective of replacement therapy, the difference remained significant between groups (23 patients (33%) versus 13 patients (18%), respectively (RR 1.82, 95%CI of RR 1.01-3.30, p=0.04)).

Five patients (6%) died in the in the urgent EUS group versus 10 patients (9%) in the conservative group (RR 0.68, 95%CI 0.24-1.91, p=0.46). An overview of the primary and secondary endpoints is presented in **Table 2**.

Sensitivity analyses were used to investigate the effect of the baseline differences between groups on the primary outcome. Logistic regression analysis showed no significant relation between ASA grade or organ failure at baseline and the effect of urgent EUS-guided ERCP on the primary endpoint (adjusted odds ratio 0.94, 95%CI 0.57-1.86, p=0.94). The ASA score did not have a significant effect (OR 0.99, 95%CI 0.40-2.46 and OR 0.82, 95%CI 0.42-1.62), neither did organ failure (OR 1.86, 95%CI 0.85-4.10), although in the latter case a possible effect could not be ruled out completely (full model can be found in **Supplementary Table S4**).

Hospital stay was shorter in the urgent EUS group versus the conservative treatment group, with a median of 11 days (IQR 6-22) and 14 days (IQR 10-26) respectively (p=0.03). ICU admission was required in 14 patients (17%) in the urgent EUS group compared to 13 (12%) the conservative group (RR 1.48, 95% CI 0.74-2.99, p=0.27).

Results from the per-protocol analysis, including 75 patients, did not differ meaningfully from the intention-to-treat analysis. Full results and the inclusion flowchart of the per-protocol analysis can be found in the **Supplementary Part 5; Figure S1** and **Table S5**.

Table 2. Primary and secondary endpoints – Intention-to-treat analysis

Outcome	Urgent EUS ± ERCP with ES (n=83)	Conservative Treatment (n=113)	Risk Ratio (95% CI)	p-value
Primary composite endpoint				
Major complications or mortality	34 (41)	50 (44)	0.93 (0.67-1.29)	0.65
Secondary endpoints				
Death	5 (6)	10 (9)	0.68 (0.24-1.91)	0.46
New-onset persistent organ failure	14 (17)	17 (15)	1.12 (0.59-2.14)	0.73
• Single organ failure (any duration)	12 (15)	18 (16)	0.91 (0.46-1.78)	0.78
• Persistent single organ failure	8 (10)	9 (8)	1.21 (0.49-3.00)	0.68
• Multiple organ failure (any duration)	7 (8)	13 (12)	0.73 (0.31-1.76)	0.48
• Persistent multiple organ failure	5 (6)	8 (7)	0.85 (0.29-2.51)	0.77
Cholangitis	6 (7)	11 (10)	0.74 (0.29-1.92)	0.54
Bacteraemia	13 (16)	25 (22)	0.71 (0.39-1.30)	0.26
Pneumonia	7 (8)	10 (9)	0.95 (38-2.40)	0.92
Pancreatic parenchymal necrosis	19 (23)	18 (16)	1.47 (0.81-2.56)	0.22
Pancreatic endocrine or exocrine insufficiency	9 (11)	3 (3)	4.08 (1.14-14-63)	*0.02*
• Endocrine insufficiency	3 (4)	2 (2)	2.04 (0.35-11.95)	0.42
• Exocrine insufficiency	9 (11)	2 (2)	6.13 (1.36-27.62)	*0.01*
Hospital stay in days	11 (6-22)	14 (10-26)	-	*0.03*
ICU admission	14 (17)	13 (12)	1.48 (0.74-2.99)	0.27
ICU stay in days	9 (5-21)	8 (4-35)	-	0.91
Readmission for biliary complication	6 (7)	24 (21)	0.34 (0.15-0.80)	*0.01*
• Recurrent biliary pancreatitis	2 (2)	10 (9)	0.27 (0.06-1.21)	0.06
• Cholangitis	1 (1)	3 (3)	0.46 (0.05-4.29)	0.48
• Cholecystitis	3 (4)	7 (6)	0.58 (0.16-2.19)	0.42
• Biliary colic	1 (1)	7 (6)	0.19 (0.02-1.56)	0.08
• Choledocholithiasis	0 (0)	7 (6)	-	*0.02*

Data are presented as no. (%) or median (IQR).

Biliary complications and adverse events

Biliary complications occurred less often in the urgent EUS group; 6 patients (7%) in the urgent EUS group versus 24 patients (21%) in the conservative treatment group (RR 0.34, 95% CI 0.15-0.80, p=0.01) including recurrent biliary pancreatitis (2% versus 9%, p=0.06) and choledocholithiasis (0% versus 6%, p=0.02) (**Table 2**). As previously reported, 10 patients (9%) in the conservative group were readmitted with recurrent biliary pancreatitis. Of these, four patients had a cholecystectomy prior to randomization, four patients had a mild disease course but did not undergo same-admission cholecystectomy, one patient had a severe disease course and did not undergo a cholecystectomy, and one patient had pancytopenia leading to delayed cholecystectomy (9). In the urgent EUS group two patients (2%) were readmitted for recurrent biliary pancreatitis, of whom one had a cholecystectomy prior to inclusion and one underwent cholecystectomy between the initial pancreatitis episode and the recurrent episode.

Adverse events occurred in 63 out of 83 patients (76%) in the EUS group versus 90 out of 113 patients (80%) in the conservative treatment group (RR 0.95, 95% CI 0.82-1.11, p=0.53). All adverse events are presented in **Supplementary Table S6**.

Procedural characteristics of EUS and ERCP

In the urgent EUS group, 81 patients (98%) underwent EUS at a median of 29 hours (IQR 23-42) after symptom onset and 21 hours (IQR 17-23) after presentation at the emergency department (**Table 3**). Median duration of EUS was 14 minutes (IQR 8-18). In two patients, EUS and ERCP were cancelled after inclusion by the treating physician, due to rapidly developing organ failure. Presence of gallstones or sludge in the biliary tract was confirmed by EUS in 48 patients (58%), all of whom underwent immediate ERCP. Median time between EUS and ERCP was 10 minutes (IQR 5-33).

Table 3. Characteristics of first EUS procedure

Study group*	Urgent EUS ± ERCP with ES (n=83)
EUS performed	81 (98)
Time from onset symptoms to first EUS (hours)	29 (23-42)
Time from presentation to first EUS (hours)	21 (17-23)
Duration of first EUS procedure (minutes)	14 (8-18)
First EUS performed by trainee under direct supervision	0 (0)
Papilla visualized • Gallstones or sludge in papilla (n=71)	71 (86) 17 (24)
Common bile duct visualized • Diameter of CBD (n=78) • Gallstones or sludge in common bile duct	80 (96) 7 (5-9) 47 (59)
Cystic duct visualized • Gallstones or sludge in cystic duct	35 (42) 5 (14)
Proximal biliary tract visualized • Gallstones or sludge in proximal biliary tract	59 (71) 1 (1)
Stones visualized on EUS	48 (58)

Data are presented as no. (%) or median (IQR).
*No EUS procedures were performed in the conservative group

In the urgent EUS group, 53 patients (64%) underwent ERCP with ES. In 48 patients, performance of ERCP was based on urgent EUS-findings. In five patients (6%) the initial EUS investigation during admission was negative, but these patients underwent ERCP at a later stage. Three patients had progressive cholestasis and CBD stones were found and removed during ERCP (9 days, 22 days and 2 months after the initial EUS, respectively). One patient had cholangitis due to a CBD stenosis due to pancreatitis. The fifth patient had intra-abdominal biliary leakage secondary to a liver abscess for which a biliary stent was placed. ERCP characteristics of all first ERCP procedures, including these five patients, are shown in **Table 4**.

In the conservative group, an indication to perform ERCP occurred in 35 of 113 (31%) patients a median of 8 days (IQR 3–34) after inclusion. Sphincterotomy was performed in 30 of 35 patients (86%). The indication for ERCP was persistent cholestasis in 21 patients (19%) and cholangitis in 13 patients (12%), in 25 patients (71%) stones were found and extracted. In each group one patient had a procedural complication, in the urgent EUS group a patient developed post sphincterotomy bleeding 9 days after the initial procedure and in the conservative group one patient had a cardiovascular complication.

Table 4. Characteristics of first ERCP procedure

Study group	Urgent EUS ± ERCP with ES (n=83)	Conservative treatment (n=113)
ERCP performed	53 (64)	35 (31)
Total number of ERCPs performed	65	44
ERCPs per patient	1 (1-1)	0 (0-1)
Total number of first ERCPs performed based on EUS results	48 (58)	0
Time from onset symptoms to first ERCP (h)	31 (24-48)	216 (99-832)
Time from presentation to first ERCP (h)	22 (19-24)	211 (75-815)
Time between EUS and ERCP (min)[&]	10 (5-33)	-
Duration of first ERCP procedure (min)[^]	24 (16-43)	25 (17-50)
Indication for first ERCP		
• Study-related	48	0
• Progressive cholestasis and/or suspicion of CBD stones	3	21
• Cholangitis according to treating physician	1	5
• Cholangitis according to study criteria	-	8
• Endoprosthesis placement	1	1
Main bile duct stones or sludge on cholangiography*	42 (79)	23 (66)
Common bile duct cannulation*	48 (91)	32 (91)
Pancreatic duct cannulation*	27 (51)	12 (34)
Pre-cut sphincterotomy*	16 (30)	6 (17)
Sphincterotomy*	48 (91)	30 (86)
Stone extraction*	45 (85)	25 (71)
• Incomplete*	1 (2)	1 (3)
ERCP-related complications[‡]	1 (2)	1 (3)

Data are n (%) or median (IQR), unless otherwise defined.
[&]Data on time between EUS and ERCP was missing in 1 patient. [^]Data on the duration of the ERCP procedure was missing in 4 patient in the urgent EUS group and in 13 patients in the conservative treatment group. *Denominators are the number of patients who had ERCP (ie, 53 in the urgent EUS group and 35 in the conservative treatment group). [‡]ERCP-related complications included bleeding, perforation, respiratory insufficiency, and cardiovascular complications.
Definitions are provided in the Supplementary appendix Table 3.

In patients in whom ERCP was performed based on EUS, biliary cannulation was achieved in 43 out of 48 patients (90%) (**Table 5**). Unintentional pancreatic duct cannulation was seen in 50% of patients. In five patients, biliary cannulation could not be achieved; in three patients there was an inflammatory stenosis of the duodenum which could either not be passed or prohibited adequate exposure of the papilla, and in two patients biliary cannulation failed. Complete stone extraction was achieved at the initial ERCP in 42 patients (88%). In one patient stone extraction was incomplete and a biliary stent was placed.

Quality of life analysis and costs

The association between treatment strategy and quality of life over time was investigated using linear mixed models. There was no significant difference in quality of life as measured with the SF-36 questionnaire, between study groups at 1 month, 3 months and 6 months after inclusion. The overview of scores, the analyses and details on missing data are provided in **Supplementary Part 7**. During the study period data on utilization of healthcare was registered. However, we have decided to omit the cost-effectiveness analysis as the health intervention in this study was not beneficial.

Table 5. Characteristics of ERCP procedures performed based on EUS results

Study group	Urgent EUS and ERCP with ES (n=48)
Total number of ERCPs performed – no. of procedures	56
ERCPs per patient	1 (1-1)
Time from onset symptoms to first ERCP (hours)	31 (24-48)
Time from presentation to first ERCP (hours)	22 (19-24)
Time from EUS to ERCP (minutes)	10 (5-33)
Duration of first ERCP procedure (minutes)	24 (15-45)
First ERCP performed by trainee under direct supervision	0
Common bile duct stones or sludge on cholangiography[$]	40 (83)
Common bile duct cannulation	43 (90)
Pancreatic duct cannulation	24 (50)
Pre-cut sphincterotomy	15 (33)
Sphincterotomy	43 (90)
Stone extraction • Incomplete	42 (88)* 1 (2)[&]
ERCP-related complications	1 (2)

Data are no. (%) or median (IQR), unless otherwise defined.
[$] Cholangiography data was not available in 5 patients. * In one patient stones had passed between EUS and ERCP.
[&] A pancreatic duct stent was placed

DISCUSSION

This prospective multicentre APEC-2 cohort study found that urgent EUS-guided ERCP with ES did not reduce the composite endpoint of major complications or mortality as compared to the conservative arm of the APEC randomized trial. In 58% of patients, bile

duct stones or sludge were found with urgent EUS within 24 hours after presentation at the emergency department and within 72 hours of start of symptoms. Immediate ERCP with ES was performed successfully in 90% of with a low complication rate (2%). Urgent EUS-guided ERCP showed favourable outcomes with regard to the readmission rate for biliary events, specifically recurrent biliary pancreatitis and symptomatic choledocholithiasis, and length of hospital stay.

Anderloni et al. performed a prospective study on early EUS-guided ERCP with ES (within 48 hours after admission) in 71 patients with acute biliary pancreatitis with a predominantly predicted mild disease course (11). CBD stones were found in 31 patients (44%), all of whom underwent ERCP. Clinical outcomes of the pancreatitis episode and rates of recurrent biliary events were not reported. In addition, De Lisi et al. performed a meta-analysis comparing EUS-guided ERCP with ERCP in acute biliary pancreatitis including 7 studies with a total of 545 patients of whom 188 had a severe acute biliary pancreatitis. An EUS-guided strategy prevented 57%-74% of ERCP procedures. However, clinical superiority could not be established (13). In contrast to our study, most patients included in this meta-analysis had a predicted mild disease course. Moreover, we identified more CBD stones (58% vs 29%), presumably because we included patients very early in their disease course, leaving less time for stones to pass into the duodenum spontaneously.

Pancreatic damage and start of the inflammatory reaction in acute pancreatitis develop instantly. This hypothesis is supported by animal models that have shown active trypsin in the pancreas within fifteen minutes after induction of acute pancreatitis (27). In the current study all procedures were performed urgently, EUS was performed at a median of 29 hours (IQR 23-42) after symptom onset and 21 hours (IQR 17-23) after presentation at the emergency department. In addition, adequate decompression of the CBD and pancreatic duct was achieved in the current study in almost all patients with a positive initial EUS. Combining the results of both the previously published APEC trial and the current APEC-2 study we conclude that urgent ERCP, with or without EUS, does not improve the outcome of patients with predicted severe acute biliary pancreatitis without cholangitis. Further shortening of the time window between start of complaints and EUS-guided ERCP in an attempt to improve outcomes of biliary pancreatitis patients does not seem feasible. Future research might therefore shift focus to medical interventions that curtail the early inflammatory response preventing the disease from worsening.

With regard to the individual components of the primary endpoint, we only found that pancreatic exocrine insufficiency (PEI) occurred more frequently in the intervention group. The occurrence of endocrine insufficiency did not differ between groups and patients in the urgent EUS-guided ERCP group had the same level of pancreatic parenchymal necrosis as the conservatively treated patients. We believe that this is not an actual effect but an incidental finding.

Readmission for recurrent biliary events, especially recurrent biliary pancreatitis, was more frequent in the conservative treatment group compared to the urgent EUS-guided ERCP group. Cholecystectomy is the most effective strategy to prevent recurrent biliary events after acute biliary pancreatitis, both in the case of a mild and a severe disease course

(28,29). In case of a mild disease course, cholecystectomy should be performed during the same admission. In the conservative treatment group however, four out of ten patients had a mild disease course, but did not undergo a same-admission cholecystectomy. In those patients, the chance of recurrent biliary pancreatitis might have been reduced by performance of early ERCP with ES or same-admission cholecystectomy. Therefore, we cannot recommend urgent EUS-guided ERCP in the acute phase of biliary pancreatitis to prevent recurrent biliary events.

There are some limitations of our study that need consideration. First, this study was not a randomized trial, but comprised of a prospective cohort series that was compared with the control group from a recently published randomized controlled trial, the APEC-trial (9). In the current APEC-2 study we used the exact same protocol (e.g. eligibility criteria, endpoints etc.) as in the original trial with an preprocedural EUS to the urgent ERCP with ES arm. Patients were included in the same group of hospitals and treated by experienced endoscopists with in a high success rate of both the EUS and ERCP with ES procedures comparable to the APEC-trial. Second, some differences in baseline characteristics were seen between the groups, such as fewer patients with organ failure at baseline in the urgent EUS-guided ERCP group, despite similar APACHE-II scores, modified Glasgow scores and SIRS scores. Sensitivity analyses confirmed that these differences did not impact on the primary outcome of this study.

In conclusion, the combined results of this current prospective APEC-2 study and the APEC-trial show that in patients with a predicted severe biliary pancreatitis without cholangitis, urgent ERCP with ES, even when guided by EUS, does not reduce severe complications or mortality. Therefore, we recommend a conservative treatment strategy in patients with a predicted severe acute biliary pancreatitis, with an ERCP only in case of concomitant cholangitis (urgent indication) and symptomatic and/or persistent choledocholithiasis (elective indication).

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Inclusion criteria and exclusion criteria

Inclusion criteria
1. Acute pancreatitis; defined as the presence of at least 2 out of the following 3 criteria: • Pain in the upper abdomen • Serum amylase and/or lipase concentration > 3 times the upper limit of normal • Signs of pancreatitis on CT or MRI/MRCP
2. Predicted severe course of the acute pancreatitis attack based on either one of the following positive scores within <24 hours after admission: • CRP >150 mg/L • Imrie score ≥ 3 (as per original APEC-trial protocol) • APACHE II score ≥ 8 (as per original APEC-trial protocol)
3. High probability ABP based on at least one of the following criteria: • Gallstones and/or biliary sludge on imaging (US, CT or MR) • Dilated common bile duct on imaging (US, CT or MR) defined as >8mm in patients ≤ 75 years or > 10mm in patients >75 years • ALAT > two times upper limit of normal (≈ 80 U/L, no absolute numerical value is chosen because of multicentric design with upper limits of normal varying between hospitals and differences in upper limit of normal values between men and women)
4. Ability to perform both EUS and ERCP within 24 hours after presentation at the ED department and within 72 hours after symptom onset
5. Age ≥18 year
6. Written informed consent
7. In case of a previous episode of necrotizing pancreatitis, patient should be fully recovered (confirmed on imaging)
Exclusion criteria
8. Cholangitis*
9. AP due to other causes such as alcohol abuse (either chronic >4 units/day or binge drinking), metabolic causes (hypertriglyceridemia, hypercalcemia), medication, trauma, etc.
10. Previous precut sphincterotomy and/ or sphincterotomy
11. Chronic pancreatitis
12. Anticoagulation that cannot be corrected with co-fact or fresh frozen plasma below an International Normalized Ratio below 1.5
13. Pregnancy

* Definition cholangitis:

- Body temperature
  - ◊ 38.5 degrees or higher with chills, without an obvious other cause or fever (e.g. cystitis, pneumonia, thrombophlebitis, etc), OR
  - ◊ 39 degrees or higher regardless of chills, without an obvious other cause for fever.

And either:

- Choledocholithiasis on US, CT, EUS or MRI/MRCP

Or

- In the absence of gallstones and/or sludge, a dilated common bile duct on imaging (US, CT or MR) defined as >8mm in patients ≤ 75 years or > 10mm in patients >75 years

Or

- Progressive cholestasis for at least two consecutive days AND a bilirubin 40 µmol/L [> 2.3 mg/dL].

*As per the APEC-trial (1)

Supplementary Table S2. Definitions of the composed primary endpoint

Event	Definition
New-onset organ failure	New-onset (i.e. not present at randomisation) and persistent (i.e. >48 hours) failure of organ(s) according to the modified Marshall score (2,3)
Pancreatic necrosis	Presence of diffuse or focal areas of pancreatic non-enhancement on contrast enhanced CT performed at 5-7 days after admission
Bacteremia	Demonstrated with positive blood cultures. For non-pathogens (e.g. Coagulase negative staphylococci) at least 2 samples have to be positive
Cholangitis	Highest in-hospital body temperature in previous 24 hours: ≥ 38.5ºC with chills, without an obvious other cause (e.g., cystitis, pneumonia, thrombophlebitis, etc), **or** 39ºC without chills, without an obvious cause for fever, **and either:** 1) Choledocholithiasis on abdominal US, CT, EUS or MRI, **or** in the absence of gallstones and/or sludge 2) A dilated common bile duct on imaging defined as >8mm in patients ≤75 years or >10mm in patients >75 years **or** 3) Progressive cholestasis for at least two consecutive days and a bilirubin >2.3 mg/dL (40 µmol/L)
Pneumonia	Coughing, dyspnoea, chest film showing infiltrative abnormalities, lowered arterial blood gas with positive sputum culture. If in intensive care, a positive endotracheal culture is mandatory.
Exocrine pancreatic insufficiency	Fecal elastase <200µg/g and the need for pancreatic enzyme supplementation at 3 months after discharge; this requirement was not present before onset of pancreatitis
Endocrine pancreatic insufficiency	The need for insulin or oral antidiabetic drugs at 3 months after discharge; this requirement was not present before onset of pancreatitis
Recurrent biliary event	Biliary events (recurrent acute gallstone pancreatitis, cholecystitis, biliary colics, or cholangitis)

As per the APEC-trial (1)

Supplementary Table S3. Definitions of ERCP-related complications

Event	Definition
Clinically relevant bleed	The presence of melena, hematochezia or hematemesis, in combination with a hemoglobin drop of 1.3 mmol/L or the need for blood transfusion (defined according to the American Society for Gastrointestinal Endoscopy ASGE) (4)
Perforation	New development of free gas on imaging with progressive complaints of abdominal discomfort and pain after ERCP, or perforation detected at surgery
Respiratory insufficiency	pO_2<60mmHg despite FiO_2 of 30% or requiring mechanical ventilation
Cardiovascular complications	
Acute myocardial infarction	(1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: (a) ischemic symptoms; (b) development of pathologic Q-waves on the ECG; (c) ECG changes indicative of ischemia (ST segment elevation or depression); or (d) coronary artery intervention (e.g., coronary angioplasty) (5)
Cerebrovascular accident	Defined by the clinical event and subsequent findings on cross-sectional imaging investigations
Shock	Systolic blood pressure below 90 mmHg despite adequate fluid resuscitation or need for inotropic catecholamine support

Supplementary Table S4. Sensitivity analysis. Logistic regression model of predicting factors for the primary endpoint (severe complications or death)

Variable	Odds ratio	95% CI for Odds ratio	Wald	p-value
Study arm	1.03	0.57-1.86	0.01	0.94
Organ failure at baseline	1.86	0.85-4.10	2.38	0.12
ASA classification			0.43	0.81
ASA classification (1)	0.99	0.40-2.46	0.00	0.40
ASA classification (2)	0.82	0.42-1.62	0.32	0.57
Constant	0.73		0.30	0.58

Supplementary Part 5. Per protocol analysis

Per protocol analysis

Figure S1 shows the inclusion flowchart for the per-protocol analysis. In 8 out of 83 patients either EUS or ERCP was not successful. Consequently, 75 patients that underwent urgent EUS and subsequent ERCP with ES in case of bile duct stones or sludge were included in the per-protocol analysis. To ensure sufficient statistical power for the per-protocol analysis, it was required to replace patients in whom either EUS or the subsequent ERCP were not successful, as defined in the study protocol. During the study period nine patients were replaced, two because of consent withdrawal, and seven because of an unsuccessful EUS or ERCP. One out of the eight patients in whom EUS or ERCP was not successful was erroneously not replaced during the study period. This resulted in one missing patient for the per-protocol analysis. In the per-protocol analysis, no significant difference was found in the primary endpoint between the conservative and urgent EUS group (**Table S5**). Simulation by adding one extra 'dummy patient' to replace the missing patient and compare the groups (n=76) with this patient having either achieved the primary endpoint or not, did not change results (p=0.31 and p=0.23, respectively).

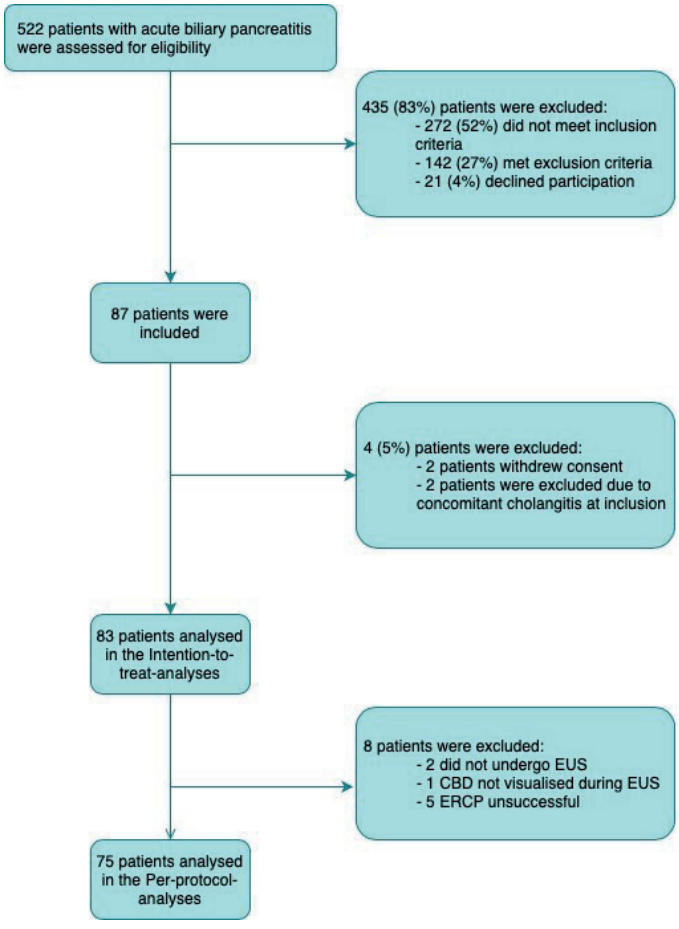

Figure S1. Inclusion flowchart of patients included in the per-protocol analysis

Supplementary Table S5. Primary endpoints - Per-protocol analysis

Outcome	Urgent EUS ± ERCP with ES (n=75)	Conservative Treatment (n=113)	Risk Ratio (95% CI)	p-value
Primary composite endpoint				
Major complications or mortality	27 (36)	50 (44)	0.81 (0.56-1.17)	0.26
Secondary endpoints				
Death	2 (3)	10 (9)	0.30 (0.07-1.34)	0.09
New-onset persistent organ failure	9 (12)	17 (15)	0.80 (0.38-1.70)	0.55
• Single organ failure (any duration)	9 (12)	18 (16)	0.75 (0.35-1.59)	0.45
• Persistent organ failure	6 (8)	9 (8)	1.00 (0.37-2.71)	0.99
Multiple organ failure (any duration)	5 (7)	13 (12)	0.58 (0.22-1.56)	0.27
Persistent multiple organ failure	3 (4)	8 (7)	0.56 (0.16-2.01)	0.38
Cholangitis	4 (5)	11 (10)	0.55 (0.18-1.66)	0.28
Bacteraemia	9 (12)	25 (22)	0.54 (0.27-1.10)	0.77
Pneumonia	4 (5)	10 (9)	0.60 (0.20-1.85)	0.37
Pancreatic parenchymal necrosis	15 (20)	18 (16)	1.26 (0.66-2.33)	0.47
Pancreatic endocrine or exocrine insufficiency	8 (11)	3 (3)	4 (1.10-14.66)	*0.02*
• Endocrine insufficiency	2 (3)	2 (2)	1.51 (0.22-10.47)	0.68
• Exocrine insufficiency	8 (11)	2 (2)	6.02 (1.32-27.60)	*0.01*

Supplementary Table S6. Overview of all adverse events in the urgent EUS-guided ERCP group

Patients in prospective cohort		232-262	263-319	N	%
(S)AE's					
Safety Parameters	Death	AP234, AP245, AP249	AP282, AP309	4	6%
	ICU admission	AP234, AP240, AP245, AP253	AP271, AP273, AP280, AP291, AP293, AP300, AP318	11	16%
Complications ERCP	Bleeding	AP240	AP267	2	3%
	Perforation			0	0%
	Respiratory insufficiency during EUS and/or ERCP	AP248		1	1%
Other complications	Intraabdominal abcess	AP253	AP286	2	3%
	(Re-)ERC	AP252	AP273	2	3%
	Acute myocardial infarction	AP238		1	1%
	Cardiac arrhythmia	AP234, AP240, AP247, AP259	AP263, AP276, AP280	7	10%
	Anemia treated with transfusion and/or medication	AP240, AP248, AP252, AP257, AP259,	AP263, AP267, AP309, AP318	9	13%
	Bacteremia	AP234, AP240, AP243, AP246, AP252	AP269, AP270, AP273, AP274, AP280, AP293, AP299, AP318	13	19%
	Cardiomyopathy, dilated apex of left ventricle		AP309	1	1%
	Cholangitis	AP234, AP240,	AP266, AP270, AP273, AP278, AP280, AP292	8	12%
	Cholecysitis treated operatively		AP267, AP287	2	3%
	Cholecystitis treated with percutaneous drainage	AP257	AP302	2	3%
	Cholecystoduodenal fistula		AP267	1	1%
	Clostridium infection	AP259	AP309	2	3%
	ICU aquiered weakness	AP240		1	1%
	Cerebrovascular accident	AP234		1	1%
	Bowel ischemia	AP245		1	1%
	Decompensatio cordis	AP242, AP259	AP286, AP302, AP303	4	6%
	Delerium	AP238, AP240, AP248, AP249, AP253	AP288, AP318	7	10%

Patients in prospective cohort		232-262	263-319	N	%
Other complications	Biloma treated with percutaneous drainage	AP253		1	1%
	Fistula (enteral/cutaneous or other)		AP310	1	1%
	Fracture	AP243	AP277, AP285	3	4%
	Cholangiocarcinoma of the gallbladder	AP257		1	1%
	Peritonitis		AP273	1	1%
	Bile duct injury	AP252	AP286, AP306	3	4%
	Gastroenteritis		AP267	1	1%
	Infected (peri)pancreatic fluid collection	AP234, AP246, AP248, AP249	AP263, AP273, AP289, AP318	8	12%
	Hypertension	AP242, AP246	AP269	3	4%
	Electrolyte disorder (other)	AP234, AP240, AP248	AP283, AP318, AP319	6	9%
	Hypokalemia or hyperkalemia	AP233, AP236, AP239, AP241, AP244, AP246, AP248, AP251, AP258, AP259,	AP264, AP266, AP267, AP278, AP283, AP303, AP313, AP318	18	26%
	Ileus/ gastroparesis	AP234, AP248	AP270, AP273, AP283, AP293	6	9%
	Gout		AP263, AP277	1	1%
	Liver abces treated with percuteneous drainage	AP252		1	1%
	Melaena		AP267	1	1%
	Morbus Kahler		AP282	1	1%
	Multiorgan failure	AP234, AP240, AP245, AP253		4	6%
	Necrotising pancreatitis treated with intervention		AP294	1	1%
	Renal insufficiency/renal failure		AP267, AP279, AP280, AP282, AP286, AP300	6	9%
	Oral candidiasis	AP242	AP286	2	3%
	Pencreatic insufficiency	AP241, AP246	AP281, AP311, AP317, AP318	6	9%
	Pancreatic parenchymal necrosis	AP241, AP249, AP261	AP262, AP266, AP267, AP273, AP280, AP282, AP293, AP317, AP318	12	17%
	peripancreatic fluid collection	AP233, AP238, AP247, AP261	AP267, AP283, AP309	7	10%
	Pleural effusion	AP253	AP280	2	3%
	Pneumonia	AP234, AP240, AP241, AP246, AP249	AP266, AP270, AP273, AP282, AP283, AP289	11	16%

Patients in prospective cohort		232-262	263-319	N	%
Other complications	Urinary tract infection	AP233, AP236, AP238, AP244, AP246, AP249, AP252	AP271, AP278, AP304, AP306, AP318	12	17%
	Pylorusstenosis		AP296	1	1%
	Recurent pancreatitis	AP252, AP258	AP273, AP290	4	6%
	Respiratoiry insufficiency	AP243, AP249	AP271, AP280, AP291, AP293, AP300	7	10%
	Retained CBD stone	AP254	AP290	1	1%
	Septic shock	AP253		1	1%
	Biliary colics		AP287	1	1%
	Jugular vein thrombosis			0	0%
	Splanchic thrombosis	AP233, AP240, AP249	AP294	4	6%
Total number of (S)AEs				221	
Number of patients with one or more (S) AEs in EUS-guided ERCP arm		AP233, AP234, AP236, AP238, AP239, AP240, AP241, AP242, AP243, AP244, AP245, AP246, AP247, AP248, AP249, AP251, AP252, AP253, AP254, AP257, AP258, AP259, AP261, AP262	AP263, AP264, AP266, AP267, AP270, AP271, AP273, AP274, AP276, AP277, AP278, AP279, AP280, AP281, AP282, AP283,AP285, AP288, AP289, AP290, AP291, AP292, AP293, AP294, AP296, AP299, AP300, AP302, AP303, AP304, AP306, AP309, AP310, AP311, AP313, AP317, AP318, AP319		62/82 (76%)

Supplementary Part 7. Quality of life analysis

The quality of life was measured using the 36-Item Short Form Survey at 1 month (0-59 days), 3 months (60-120 days) and 6 months (120-220 days) after inclusion. Data was missing for some patients at some time points. **Table S7.1** shows the number and proportion of missing values for each individual domain per period.

Supplementary appendix Table S7. Number and proportion of missing values

Variable	Month 1	Month 3	Month 6
General health	56 (29%)	51 (26%)	73 (37%)
Social functioning	52 (27%)	49 (25%)	72 (37%)
Health change	52 (27%)	49 (25%)	69 (35%)
Physical functioning	53 (27%)	50 (26%)	72 (37%)
Role physical health	58 (30%)	55 (28%)	77 (39%)
Role emotional health	60 (31%)	55 (28%)	75 (38%)
Bodily pain	54 (28%)	50 (26%)	71 (36%)
Vitality	52 (27%)	49 (25%)	73 (37%)
Mental health	53 (27%)	49 (25%)	73 (37%)

Following the SF36 manual the summary scores PCS and MCS were only calculated for patients who had at least 50% of the relevant items observed.

In the analysis missing values were handled in three different ways to explore the potential impact of the missing values:

1. When a patient had at least 50% of the items in a scale observed, the scores were calculated on the observed part of the items, otherwise the score was left missing and the observation was excluded from the analysis (i.e., following the instructions of the SF36 manual).
2. Best case scenario: missing values were replaced with the best possible value.
3. Worst case scenario: missing values were replaced with the worst possible value.

In all three scenarios, the score was set to 0 for patients that had died.

An overview of the distribution of the data for each of the components in both arms under scenario 1 is shown in **Figure S7.2**. In **Figure S7.3** the distribution of the data across all time-points (1, 3 and 6 months) is shown.

Figure S7.2 Health related quality of life measured by the 36-item Short Form Health Survey: distribution of the values at 1, 3 and 6 months after inclusion.
Note. GH = general health, SF = social functioning, HT=Health Change, PF = physical functioning, RP = role physical, RE = role emotional, BP = bodily pain, VT = vitality, MH = mental health, PCS = physical component summary, MCS = mental component summary.

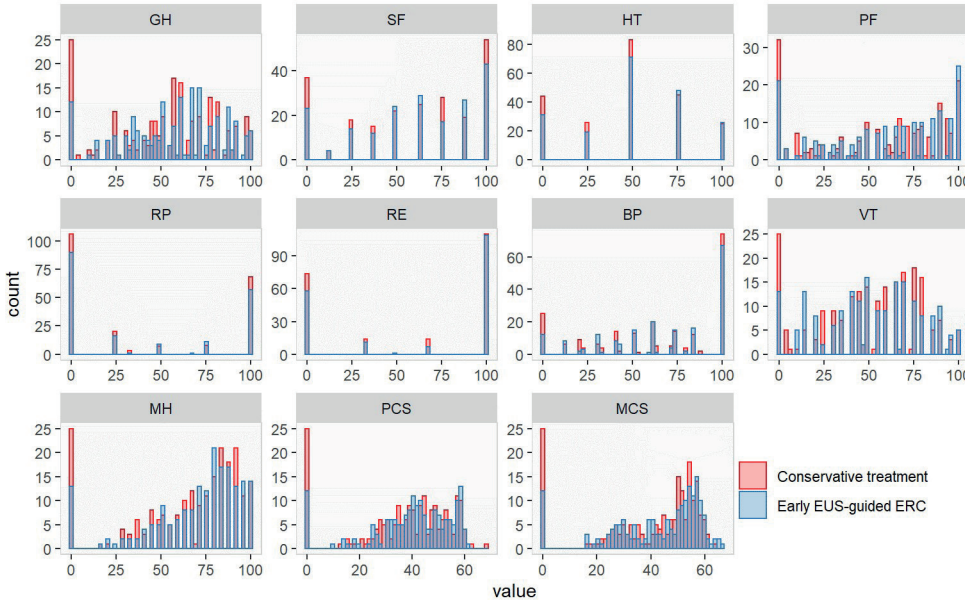

Figure S7.3 Health related quality of life measured by the 36-item Short Form Health Survey: distribution of the values across all time-points (1, 3 and 6 months) after inclusion.
Note. GH = general health, SF = social functioning, HT=Health Change, PF = physical functioning, RP = role physical, RE = role emotional, BP = bodily pain, VT = vitality, MH = mental health, PCS = physical component summary, MCS = mental component summary.

To evaluate the association between treatment and MCS and PCS, respectively as well as differences in treatment effects over time, we fitted linear mixed models that included treatment arm, time, and their interaction. To take into account correlation between repeated measurements of the same patient, a random intercept and a random effect for the time of measurement (with an unstructured variance-covariance matrix) were used.

The results are visualised in **Figure S7.4** and shown in **Table S7.5**. Shown are the expected response over time for each treatment arm under the three scenarios with corresponding 95% confidence intervals.

There was no evidence for a difference in quality of life between the two treatment strategies. Only in the extremely unlikely scenario where all patients with missing responses would have had the worst possible score, the expected quality of life would differ at six months and the score in the urgent EUS-guided ERCP group would be better than in the conservative group.

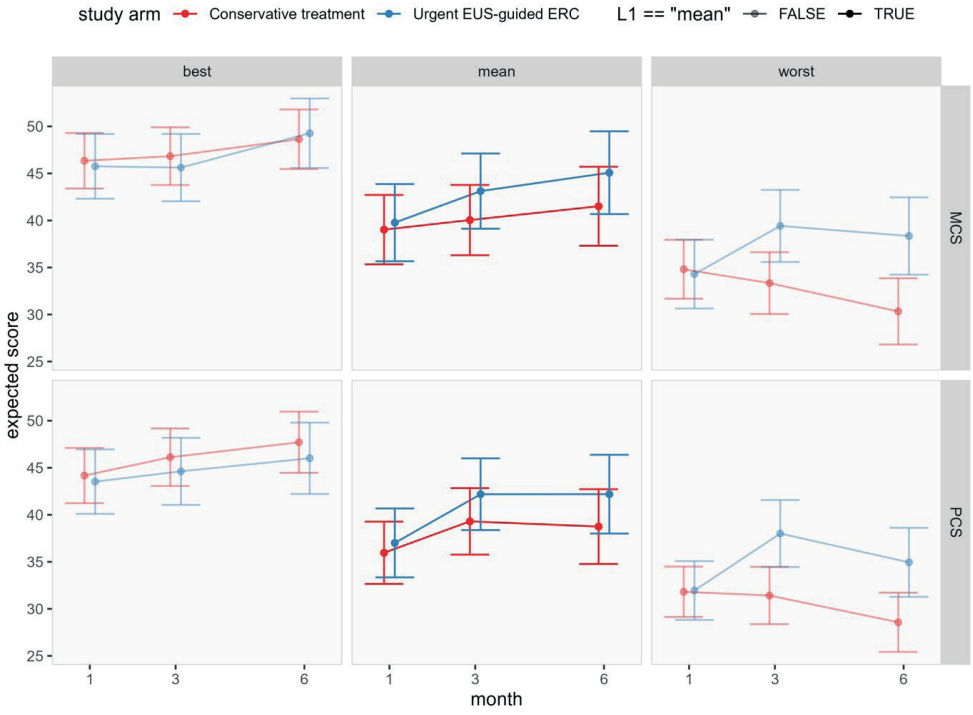

Figure S7.4 Regression coefficients and 95% confidence intervals (lower, upper) from the linear mixed models using different scenarios for the missing values.

Table S7.5. Regression coefficients and 95% confidence intervals (lower, upper) from the linear mixed models using different scenarios for the missing values.

	MCS				PCS			
Variable	**Coefficient**	**Lower**	**Upper**	**P-value**	**Coefficient**	**Lower**	**Upper**	**P-value**
Mean value imputation								
(Intercept)	39.021	35.337	42.705	0.000	35.959	32.661	39.257	0.000
Arm: Urgent EUS-guided ERC	0.747	-4.773	6.266	0.790	1.049	-3.885	5.983	0.675
Time: Month 3	1.021	-1.549	3.592	0.434	3.341	1.283	5.398	0.002
Time: Month 6	2.489	-0.904	5.883	0.150	2.788	-0.103	5.680	0.059
Arm: Urgent EUS-guided ERC: month 3	2.331	-1.385	6.047	0.218	1.836	-1.128	4.799	0.223
Arm: Urgent EUS-guided ERC: month 6	2.821	-2.035	7.678	0.253	2.396	-1.726	6.519	0.253
Worst case imputation								
(Intercept)	34.810	31.685	37.935	0.000	31.813	29.141	34.485	0.000
Arm: Urgent EUS-guided ERC	-0.512	-5.329	4.305	0.834	0.137	-3.982	4.256	0.948
Time: Month 3	-1.469	-4.081	1.144	0.270	-0.394	-2.556	1.769	0.721
Time: Month 6	-4.479	-7.688	-1.270	0.006	-3.243	-6.029	-0.457	0.023
Arm: Urgent EUS-guided ERC: month 3	6.591	2.577	10.606	0.001	6.450	3.128	9.773	0.000
Arm: Urgent EUS-guided ERC: month 6	8.528	3.597	13.459	0.001	6.238	1.956	10.519	0.004
Best case imputation								
(Intercept)	46.342	43.403	49.281	0.000	44.170	41.243	47.098	0.000
Arm: Urgent EUS-guided ERC	-0.589	-5.119	3.942	0.798	-0.643	-5.156	3.870	0.779
Time: Month 3	0.490	-2.232	3.212	0.724	1.947	-0.779	4.673	0.161
Time: Month 6	2.295	-0.823	5.412	0.149	3.538	0.400	6.676	0.027
Arm: Urgent EUS-guided ERC: month 3	-0.622	-4.805	3.561	0.770	-0.854	-5.043	3.335	0.689
Arm: Urgent EUS-guided ERC: month 6	1.225	-3.566	6.015	0.616	-1.055	-5.878	3.767	0.667

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Chapter 8

Clinical outcome of endoscopic therapy in patients with symptomatic pancreas divisum: a Dutch cohort study

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ABSTRACT

Background and aim: Although the majority of patients with pancreas divisum (PDiv) are asymptomatic, a subgroup present with recurrent pancreatitis or pain for which endoscopic therapy may be indicated. The aim of this study was to evaluate success rates and long-term outcomes of endoscopic treatment in patients with symptomatic PDiv.

Methods: A multicenter, retrospective cohort study was performed. Patients with symptomatic PDiv presenting with recurrent acute pancreatitis (RAP), chronic pancreatitis (CP), or chronic abdominal pancreatic-type pain (CAP) who underwent endoscopic retrograde cholangiopancreatography (ERCP) between January 2000 and December 2019 were included. The primary outcome was clinical success, defined as either no recurrent episode of acute pancreatitis (AP) for RAP patients, no flares for CP patients, or absence of abdominal pain for patients with CAP after technically successful ERCP.

Results: In 60 of 81 patients (74.1%) a technically successful papilla minor intervention was performed. Adverse events were reported in 30 patients (37%), with post-ERCP pancreatitis in 18 patients. The clinical success rate for patients with at least 3 months of follow-up was 42.6%, with higher rates of success among patients presenting with RAP (44.4%) as compared to those with CP (33.3%) or CAP (33.3%). Long-term sustained response was present in 40.9% of patients with a technically successful intervention. In patients with RAP who did not completely respond to treatment, the mean number of AP episodes after treatment decreased significantly from 3.5 to 1.1 per year, and subsequently the interval between AP episodes increased from 278 to 690 days ($P = 0.0006$). A potential predictive factor of failure of clinical success after technically successful ERCP, at univariate analysis, was male sex (OR=0.25, $P = 0.02$).

Conclusion: Endoscopic therapy in patients with symptomatic PDiv is moderately effective, with its highest yield in patients presenting with RAP. Future studies are needed to assess factors predictive for success of endoscopic therapy and potential risk factors for relapse after ERCP.

INTRODUCTION

Pancreas divisum (PDiv) is the most common pancreatic anomaly and is present in approximately 2% to 10% of the general population (1-3). PDiv results from failure of fusion of the ventral and dorsal pancreatic ducts during embryogenesis (4). Subsequently, pancreatic exocrine secretions are predominantly drained through the relatively small duct of Santorini and minor papilla into the duodenum.

Although the majority of patients with PDiv are asymptomatic, there are subgroups with either recurrent symptoms of acute pancreatitis (RAP), flares of chronic pancreatitis (CP) or chronic abdominal pancreatic-type pain (CAP) (5-7). A relative obstruction of outflow of pancreatic juice through the minor papilla has been proposed as a cause of recurrent pancreatitis (6,7). Endoscopic treatment may relieve symptoms in patients with PDiv and can be considered in patients with recurrent and/or severe symptoms (8,9). It aims at improving ductal outflow, by either performing a minor papilla sphincterotomy or stenting in case of a dorsal pancreatic duct stricture.

While endoscopic therapy in the management of patients with symptomatic PDiv is commonly applied in clinical practice, there is limited high-quality evidence to support this strategy. Only one small randomized trial in patients with RAP has been published, the results of which were hampered because it was not blinded and the sample size consisted of only 19 patients (10). Several retrospective studies have reported a significant improvement in the disease course for symptomatic patients with PDiv after endoscopic therapy, although reported efficacy rates are highly variable, ranging from 8% to 94% (8,11). These results are difficult to interpret and to compare, given the significant variations in the definition of successful therapy, as well as large variations in definitions of subgroups of PDiv patients. In the majority of the studies, a subjective endpoint, self-perceived improvement, was used, and sample sizes were rather small. As a result, the exact role of endoscopic therapy in the management of symptomatic PDiv remains unclear.

Given the low incidence of symptomatic PDiv, multicenter studies are required to obtain a more accurate estimate of the yield of endoscopic therapy and to identify potential predictors of success. This current multicenter study aimed to analyze the short-term and long-term efficacy and safety of endoscopic treatment in a large cohort of patients with symptomatic PDiv, with uniform definitions of outcome and subgroups of patients (i.e. RAP, CP and CAP). In addition, predictive factors for successful endoscopic treatment were studied.

METHODS

Study design and study population

A multicenter retrospective cohort study was performed in the Departments of Gastroenterology and Hepatology at three Dutch tertiary referral centers for

pancreaticobiliary diseases. Patients with symptomatic PDiv who underwent endoscopic retrograde cholangiopancreatography (ERCP) with the primary intention to perform a minor papilla sphincterotomy and/or dorsal duct plastic stent placement between January 2000 and December 2019 were identified from local endoscopy databases (Endobase or Clinical Assistant (RVC)). In this dedicated electronic endoscopic reporting system, all endoscopic procedures and reports are prospectively registered. Patients were eligible for inclusion if symptomatic PDiv had been confirmed prior to ERCP at consultation at the outpatient clinic and after exclusion of other causes of pancreatitis by a standardized diagnostic work-up.Symptomatic PDiv was further classified according to type of clinical presentation: (1) RAP, (2) CP, and (3) CAP. RAP was defined as more than one episode of proven acute pancreatitis (i.e. 2/3 of the following; acute upper abdominal pain, lipase and/or amylase >3x upper limit of normal, signs of acute pancreatitis on computed tomography). CP was defined according to the M-ANNHEIM classification system in combination with presence of abdominal pain symptoms in combination with flare type symptoms (12). CAP was defined as pancreas-type pain as judged by the treating physician, but without a biochemically or radiologically confirmed diagnosis of either acute or chronic pancreatitis (13,14). Patients with a pancreatic malignancy were excluded from the study, as well as those who underwent a previous endoscopic intervention of the pancreatic duct. This study was conducted according to the guidelines in the Helsinki Declaration and was approved by the ethics committee of the Erasmus MC University Medical Center, Rotterdam, the Netherlands.

Data collection

Each individual patient record was systematically reviewed. Data were collected on demographical factors (e.g. age, sex), clinical factors (e.g. medication use, alcohol and nicotine consumption, symptoms and number of episodes of pancreatitis prior to ERCP), findings on imaging studies (e.g. pancreatic duct strictures or dilatation), and ERCP characteristics (e.g. use of secretin, performance of sphincterotomy and stent placement). Patient records were reviewed for the number of episodes of AP, flares of CP or CAP symptoms after treatment and procedure-related adverse events (AEs). Minor papilla sphincterotomy was performed with a pull-type sphincterotome or needle-knife precut in case of failed cannulation. Plastic stents used were 5 or 7cm in length and had a diameter of 5 or 7 Fr. Reasons for straight stent placement were presence of concomitant ductal strictures, presence of obstructive pancreatic stones, or inability to perform a safe sphincterotomy. In these patients, a sphincterotomy over the stent was considered at repeat ERCP. Secretin was administered when the minor papilla could not be identified and/or cannulation failed by decision of the endoscopist. For all patients, the maximum follow-up time was based on data availability in individual medical records after ERCP.

Study outcomes

The primary outcome of the study was clinical success of endoscopic treatment, which was defined as either no recurrent episode of AP for RAP patients, no flare of CP for CP patients, or absence of abdominal pain for patients with CAP, at 3 months after technically successful ERCP. Long-term success was defined as sustained clinical response for a period of 12 months after ERCP. Secondary study outcomes were technical success, defined as performance of minor papilla sphincterotomy and/or deployment of a stent in the dorsal

duct, short-term and long-term complications, and predictors for either success or relapse after technically successful endoscopic treatment.

Statistical analysis
Descriptive statistics were used for continuous and categorical variables. Continuous variables were described using mean and standard deviation for normally distributed variables or using median and range for non-normally distributed variables. Categorical variables were described using frequencies and percentages. The Shapiro-Wilk test was used to check the normality of the variables. The Student's t-test, Wilcoxon test or the Mann-Whitney U test were used to analyze continuous variables. The Chi-square test or Fisher's Exact test were used for categorical and dichotomous variables. A 2-sided $P < 0.05$ was considered statistically significant. The statistical analyses were performed using R Version 3.6.2.

RESULTS

During the study period, a total of 81 patients underwent ERCP for symptomatic PDiv. Forty-five patients (56%) were female. The mean age was 51.4 years (SD±17 years). The majority of patients referred for ERCP presented with RAP (n=66 (82%)). In these patients, the median number of AP episodes in total prior to ERCP was four (range, 2–40). The median number of AP episodes per year was three (range, 0.2–22). Baseline characteristics of the included patients are shown in **Table 1**.

Technical success
Cannulation of the minor papilla was successful in 61 of 81 patients (75%), after a median of two ERCPs per patient (range, 1–4). Of these 61 patients, 48 (79%) had successful cannulation at first intervention and 11 (18%) at second intervention. In 13 of 81 patients, secretin was administered, which resulted in successful cannulation in six of them (46%). In six patients, an endoscopic ultrasonography-guided rendezvous technique was attempted, which resulted in successful retrograde cannulation in one.

Of the 61 patients in whom cannulation was successful, 60 (48 RAP, 9 CP, 3 CAP) underwent a technically successful intervention (98%), defined as completion of minor papilla sphincterotomy and/or deployment of a stent in the dorsal pancreatic duct. A minor papilla sphincterotomy was performed in 53 of 60 patients (88%). In six patients (10%) a straight plastic stent without sphincterotomy was deployed as final treatment, and balloon dilatation of the minor papilla without sphincterotomy was performed in one patient (2%). Median stent length was 5 cm (range, 5–7) and median stent diameter was 5 Fr (range, 5–7). The stents were left indwelling for a median of 65 days (range, 48–153). After this period all stents were removed and no stents were replaced.

In 40 of 61 ERCPs (66%) with cannulation of the minor papilla, short-term prophylactic pancreatic drainage by deployment of a 5 or 7 Fr single pigtail stent was performed. Follow-up data were available for all 60 patients with a median of 26.5 months (range, 1–213).

Table 1. Baseline patient characteristics

Characteristics	Symptomatic PDiv (n = 81)
Gender	
• Female	45 (55.6)
• Male	36 (44.4)
Age (year) (mean ± SD)[1]	51.4 ± 17.4
Medical history	
• Cholecystectomy	26 (32.1)
• Hypertension	12 (14.8)
• DM II	8 (9.9)
Alcohol	
• Former alcohol abuse	4 (4.9)
• Current alcohol abuse	3 (3.7)
Smoking	
• Former smoker	20 (24.7)
• Current smoker	8 (9.9)
PDiv type	
• Complete	69 (85.2)
• Incomplete	12 (14.8)
PDiv diagnosis by	
• EUS	12 (14.8)
• MRCP	49 (60.5)
• MRCP + secretin	8 (9.9)
• MRI	8 (9.9)
• CT	2 (2.5)
• Unknown	2 (2.5)
PDiv presentation	
• RAP	66 (81.5)
• CP	12 (14.8)
• CAP	3 (3.7)
Number of AP episodes before treatment (absolute) (median (range))	4.0 (2 – 40)
No AP episodes (per year) (median (range))	2.96 (0.19 – 22.14)[2]
Pancreatic duct dilatation – mm[3]	
• Head (median (range))	3.0 (1 – 8.5)
• Corpus (median (range))	2.8 (1 – 8.6)
Prior imaging:	
• CT	8
• EUS	1
• MRCP	40
• SS-MRCP	18
• MRI	12

Values are in n (%) unless otherwise defined
PDiv, pancreas divisum; DMII, type 2 diabetes mellitus; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; CAP, chronic, abdominal, pancreatic-type pain; AP, acute pancreatitis; CT, computed tomography; SS-MRCP, secretin-stimulated magnetic resonance cholangiopancreatography.
[1]Age at first endoscopic treatment.
[2]Calculated as the number of AP episodes per year from first AP to first intervention.
[3]Measurable in 55 patients at imaging.

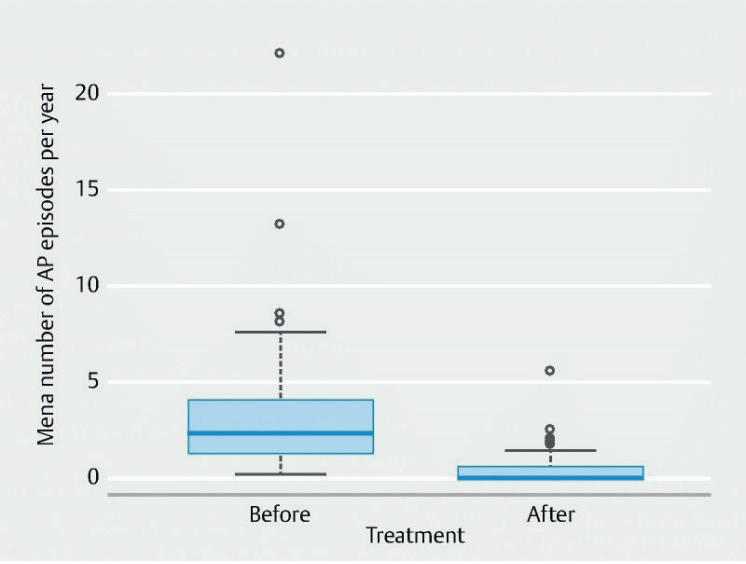

Figure 1. Box plot for mean number of AP episodes per year for RAP, before, and after treatment for patients with≥3 months of follow-up.

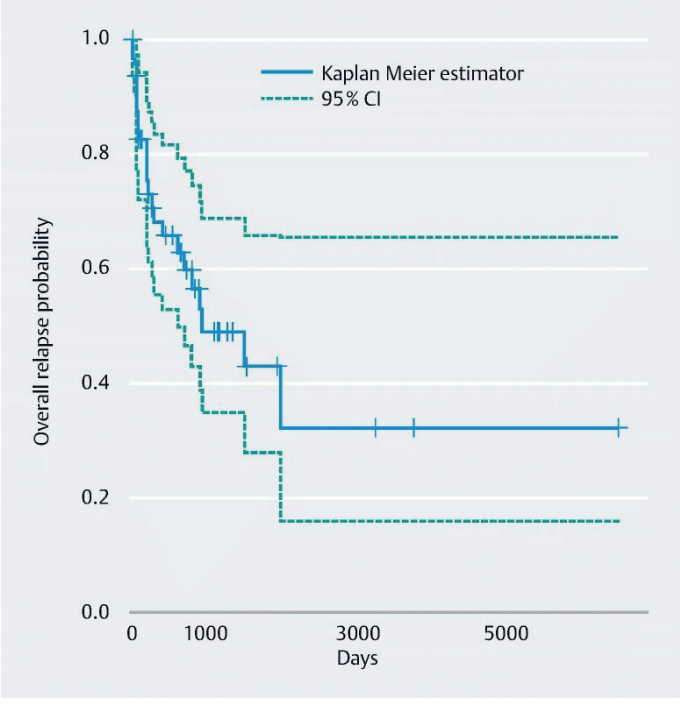

Figure 2. Kaplan-Meier curve for overall relapse probability for RAP until the first date a relapse occurred. This includes all patients, regardless of follow-up and surgeries performed.

Clinical success

Efficacy in PDiv patients with RAP

Clinical success was achieved in 23 of 48 RAP patients (48%). For patients with at least 3 months of follow-up, 20 of 45 patients (44.4%) had clinical success and for patients with at least 12 months of follow-up, 17 of 37 patients (46%) had sustained clinical success. In total, 22 patients (46%) had a RAP episode after technical successful intervention. For patients with an acute pancreatitis episode after technical successful intervention, the mean number of pancreatitis episodes per year before and after endoscopic treatment decreased from 3.5 (SD 3.1) to 1.13 (SD: 1.2) (P =0.0003), respectively (**Figure1**). Subsequently, the mean number of days between pancreatitis episodes before and after successful minor intervention increased from 278 (SD 424) to 690 (SD 623) (P =0.0003), respectively (**Figure2**). The median duct diameter was 3mm (range, 1.0–8.4). Only five patients had a dilated dorsal pancreatic duct ≥5mm (10.4%). In those patients, clinical success was achieved in four patients (80%). Of the 43 patients without dilatation, 19 patients achieved clinical success (44.2%). This was not significantly different (P =0.18). In total, 10 patients underwent MRCP with secretin prior to endoscopic treatment. Only four patients (40%) had a pathological increase of duct diameter after secretin administration. Clinical success was achieved in two patients (50%). In the patients with a normal SS-MRCP, clinical success was achieved in three patients (50%).

Of the 25 patients without clinical success, five patients underwent surgery. Two patients underwent pancreatoduodenectomy and pancreatic tail resection, respectively. Two other patients underwent a pancreatojejunostomy. They did not have an episode of pancreatitis after surgery. Progression from RAP to CP was diagnosed in a total of nine patients (18.8%) with RAP. Progression to CP was diagnosed by computed tomography in four of nine patients, magnetic resonance imaging in two of nine, and endoscopic ultrasonography in three of nine. Genetic mutations playing a role for CP development were not routinely assessed. However, in two patients, the CFTR gene was detected prior to endoscopic treatment. One patient developed a symptomatic CP, for which he underwent a pancreatic head resection. Afterwards, he was opioid dependent.

Efficacy in PDiv patients with CP

Clinical success was achieved in five of nine patients (56%). However, three patients had a follow-up shorter than 3 months. For these patients, no flare of CP was reported in the available follow-up period.

Two of the six patients (33.3%) with follow-up >3 months achieved clinical success. Out of five patients with at least 12 months of follow-up, one patient (20%) reported no flares of CP. Overall, four patients underwent surgery after ERCP. Three patients underwent a pancreatojejunostomy after endoscopic treatment, and in one patient this was combined with an additional tail resection after 1 year. In another patient a pancreatic head resection was performed. Three patients remained opioid-dependent after surgery.

Efficacy in PDiv patients with CAP

Clinical success was achieved in one of three (33.3%) CAP patients, who did not experience a relapse of abdominal pain within a total follow-up period of 11 months. The remaining two patients still had complaints of abdominal pain after endoscopic treatment.

Predictive factors for clinical successful minor intervention

Univariate logistic regression analysis was performed to analyze potential predictive factors for clinical success (**Table 2**). Male sex was significantly associated with a lower chance of clinical success (OR=0.25, P =0.02). No other associations were identified.

Table 2. Results of univariate analysis of potential predictive factors for clinical success (>3 months) after technically successful minor intervention

Univariate analysis	OR	CI	P-value
Gender (male = 1)	0.25	0.07 – 0.79	0.02
Age	1.02	0.99 – 1.05	0.296
Stent vs sphincterotomy	2.18	0.33 – 17.67	0.417
Incomplete PDiv	0.64	0.08 – 3.62	0.629
PDIV presentation			
• RAP	1.6	0.05 – 29.8	1.000
• CP	1.0	0.14 – 35.9	0.709
Number of AP episodes (absolute)	1.06	0.86 – 1.32	0.587
Pancreatic duct diameter head (in mm)	1.07	0.74 – 1.56	0.698
Minor stenosis	1.21	0.33 – 4.28	0.766

PDiv, pancreas divisum; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; AP, acute pancreatitis.

Post-procedure adverse events

AEs were reported in in 26 of 81 patients (32.1%). Post-ERCP pancreatitis was diagnosed in 18 patients (22.2%), of whom 17 had a mild and one a moderate course, according to the Revised Atlanta Classification (15). Based on the total number of procedures, the prevalence of post-ERCP pancreatitis was 18 of 148 (12.2%). Post-sphincterotomy delayed bleeding was reported in one patient (1.2%). One patient developed a pancreatic fluid collection shortly after ERCP (1.2%). In patients in whom a straight stent was placed as treatment (n=6), distal stent migration occurred in 2 (33%) and occlusion in one patient (16.7%). All stents could easily be removed and no additional treatment was necessary.

DISCUSSION

Although symptomatic PDiv is generally considered a suitable indication for ERCP, the efficacy of endoscopic treatment to relieve symptoms is unclear. In the present study, we report the technical and clinical success of ERCP in a multicenter cohort of symptomatic PDiv patients who were treated in tertiary referral centers. In this cohort with a median follow-up of 26.5 months, ERCP with minor papilla sphincterotomy or dorsal duct stent placement benefits approximately half of patients in whom cannulation of the PD was

achieved. Overall success of endoscopic treatment was however limited by moderate initial pancreatic duct cannulation rate at first ERCP and a relatively high rate of post-ERCP pancreatitis. The clinical success is highest for the subgroup of patients with RAP, as compared to CP and CAP, which is further illustrated by a significant decrease in AP episodes after ERCP compared to before the ERCP in the RAP population.

Another important finding in our series is that nearly 20% of patients with RAP progressed to CP during follow-up despite endoscopic therapy. Of note, in our clinical practice, evolution to CP is not routinely assessed and additional imaging studies are only performed in patients presenting with clinical signs of CP. The view of the theory of progression from RAP to CP can provide a rationale for early endoscopic treatment of RAP in symptomatic PDiv patients to halt progression into CP. In patients with CP the etiology of pain is more likely to be multifactorial, with not only ductal hypertension necessarily as the sole cause, but also neuropathy of intra-pancreatic nerves and central sensitization. Therefore, endoscopic therapy may be less clinically successful in this subgroup of patients.

The clinical efficacy of ERCP for PDiv in our cohort is lower as compared to previous reports. An important explanation is that we only included patients in whom symptomatic PDiv had been confirmed prior to ERCP on consultation at the outpatient clinic and after exclusion of other causes of pancreatitis with a standardized diagnostic work-up. Patients in whom an incomplete PDiv was detected during ERCP performed for other reasons, such as trans-papillary drainage of pseudocysts, were excluded. In addition, we used stringent and objective definitions for treatment outcome instead of subjective patient-reported outcomes. Tringali et al. reported a clinical success rate of 72% after a mean follow-up of 9.7 years in PDiv patients with RAP (n=48) (16). An important explanation for this higher efficacy of endoscopic treatment may be the selection of a favorable group of patients who answered the questionnaire after long-term follow-up, as the study design suggests exclusion of patients who were lost to follow-up, deceased, or developed CP. Another cohort study from the United States showed similar differences between the subgroups as our study. In 62 RAP, 22 CP, and 29 CAP patients, reported success rates were 53.2%, 18.2%, and 41.4%, respectively. However, this study was limited by the subjective nature of primary outcome measures, i.e. better or cured on a Likert scale, without needing narcotics, after one ERCP procedure (13). A meta-analysis by Michailidis et al. reported an overall clinical success rate of 67% after endoscopic treatment for PDiv (11). Success rates were reported to be 76%, 52%, and 48% for patients with RAP, CP and CAP, respectively. Important to note is that if strict objective outcome measures were used, instead of subjective measurements like self-reported pain or opioid usage, a smaller percentage of the patients reached clinical success in this review (17), which is in line with the outcome of our current study.

Overall, a high rate of post-ERCP pancreatitis was observed in our study, which ran a mild course in the majority of patients. These results are consistent with literature, and confirm that the risk of post-ERCP pancreatitis is higher in PDiv patients, as compared to other indications for ERCP (18,19). This complication risk influences the risk-benefit ratio of endoscopic treatment in patients with PDiv, and underlines the importance to identify predictors of clinical success. Additional univariate regression analysis revealed that male

sex was significantly associated with a lower chance of clinical success (OR=0.25, P=0.02). However, due to the low number of cases, multivariate regression analysis could not be performed to test for an independent association between male gender and clinical success after endotherapy. The model was at potential risk of multiple testing and finding a false-positive association. Therefore, this finding should be interpreted with caution. Michailidis et al. found in the pooled analysis that male sex seemed to predict better response rates, although this was not significant (11). To the best of our knowledge, there is no other study available describing the relationship between male sex and the effect of endotherapy, irrespective of PDiv. A larger cohort study should be performed to reliably test for the association between male sex and the effect of endotherapy in patients with PDiv. Although a dilated pancreatic duct is often presumed to be a potential predictor, dilatation of the Santorini duct as measured at imaging studies prior to ERCP was not significantly associated with clinical success. This finding calls into question whether increased ductal outflow is the main pathogenetic mechanism for symptoms in PDiv patients. However, it might well be that a relative stenosis of the minor papilla or Santorini duct is hard to identify on regular non-dynamic MRCP. Dynamic secretin-stimulated MRCP (SS-MRCP) can be helpful in revealing relative ductal abnormalities otherwise not detected on MRCP alone, with increase in the distention of the upstream portion of the duct and/or decreased pancreatic duct compliance after secretin stimulation. In our patients, SS-MRCP was not routinely performed at baseline prior to ERCP. Dorsal duct stenting was the only significant predictor of success in the meta-analysis by Michailidis et al., but given the significant heterogeneity among included studies, those results should be interpreted with caution (11). In our study, dorsal duct stent placement did not result in significantly greater treatment success as compared to minor papilla sphincterotomy alone.

Although a major strength of our study is its multicenter design with inclusion of a large number of patients, it also has some limitations, which should be considered when interpreting our results. First, data were collected retrospectively and follow-up was not standardized. This resulted in a range of follow-up time points. Despite this shortcoming, follow-up data of at least 12 months was available for 70% of the patients. The follow-up was relatively complete and systematically documented as standard follow-up intervals after endoscopic treatment were adhered to in clinical practice. Second, the sample size of our cohort may have been too small to allow for identification of predictors of clinical success in logistic regression analysis. Also, the subgroup of patients with CP and CAP was relatively small compared to RAP. Therefore, the clinical success rate in these two subgroups could be overestimated and should be interpreted with caution.

In conclusion, endoscopic treatment is effective to relieve symptoms in PDiv patients in half of patients after technically successful ERCP, and should be considered, in particular, for patients with RAP. Clinical decisions may benefit from more data pertaining to the appropriate selection of patients for ERCP to weigh risk and benefits, because the risk of post-ERCP pancreatitis in PDiv is considerable. Multicenter, preferably randomized, clinical trials in which minor papilla sphincterotomy is compared to sham treatment in PDiv patients are needed to optimize the selection of PDiv patients and to identify potential risk factors for relapse after ERCP.

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Chapter 9

Safety and efficacy of a novel resection system for direct endoscopic necrosectomy of walled-off pancreas necrosis: a prospective, international, multicenter trial

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ABSTRACT

Background and aim: Direct endoscopic necrosectomy (DEN) of walled-off pancreatic necrosis (WOPN) lacks dedicated instruments and requires repetitive and cumbersome procedures. This study evaluated the safety and efficacy of a new powered endoscopic debridement (PED) system designed to simultaneously resect and remove solid debris within WOPN.

Methods: This was a single-arm, prospective, multicenter, international device trial conducted from November 2018 to August 2019 at 10 sites. Patients with WOPN ≥6 cm and ≤22 cm and with >30% solid debris were enrolled. The primary endpoint was safety through 21 days after the last DEN procedure. Efficacy outcomes included clearance of necrosis, procedural time, adequacy of debridement, number of procedures until resolution, hospital stay duration, and quality of life.

Results: Thirty patients (mean age, 55 years; 60% men) underwent DEN with no device-related adverse events. Of 30 patients, 15 (50%) achieved complete debridement in 1 session and 20 (67%) achieved complete debridement within 2 or fewer sessions. A median of 1.5 interventions (range, 1-7) were required. Median hospital stay was 10 days (interquartile range, 22). There was an overall reduction of 91% in percent necrosis within WOPN from baseline to follow-up and 85% in collection volume. Baseline WOPN volume was positively correlated with the total number of interventions ($\rho = .363$, $P = .049$).

Conclusion: The new PED system seems to be a safe and effective treatment tool for WOPN, resulting in fewer interventions and lower hospital duration when compared with published data on using conventional instruments. Randomized controlled trials comparing the PED system with conventional DEN are needed. (Clinical trial registration number: NCT03694210.)

INTRODUCTION

Acute pancreatitis is a life-threatening disease with increasing incidence (1). Approximately 20% of acute pancreatitis patients develop necrotizing pancreatitis; consequently, about 30% of acute necrotizing pancreatitis patients develop infected necrosis, which is associated with mortality ranging between 15% and 30% (2-5). Treatment of acute necrotizing pancreatitis is crucial to prevent ongoing infection and sepsis-related multiorgan failure (6,7). Over the past decades, treatment of infected acute necrotizing pancreatitis has shifted from open surgery to minimally invasive techniques with a step-up approach. Endoscopic transluminal drainage or percutaneous drainage is performed, followed by direct endoscopic necrosectomy (DEN) or video-assisted retroperitoneal debridement when necessary. Studies have shown favorable outcomes for DEN compared to video-assisted retroperitoneal debridement with regard to adverse events (AEs) and death (8,9).

Endoscopic transluminal drainage can be achieved by placing plastic double-pigtail stents (DPSs), self-expandable metal stents (SEMSs), or lumen-opposing metal stents (LAMSs). If the patient does not improve after endoscopic drainage, DEN can be performed after entering the necrotic cavity through the fistula created by the previously placed stent. Currently, DEN is performed using conventional accessories, including snares, baskets, forceps, or retrieval nets. However, these instruments are not designed for DEN and can limit the effectiveness of necrosectomy. According to a meta-analysis by Puli et al. (10), a mean number of 4 DEN procedures is required to clear the necrotic cavity. These procedures have poor endoscopic visualization within the cavity, use instruments that lack sufficient grip on the necrotic debris, and require removal of necrotic debris into the stomach, which makes efficient removal cumbersome.

A new dedicated instrument for DEN, the EndoRotor powered endoscopic debridement (PED) system (Interscope, Inc, Northbridge, Mass, USA), was previously assessed in a pilot study that investigated its feasibility and safety for DEN in patients with walled-off pancreatic necrosis (WOPN) (11). This study demonstrated that necrotic debris could be removed in a median of 2 procedures (range, 1-7) and that no procedure-related AEs occurred. In addition, the performing endoscopist deemed the device easy and safe to use (11). In this current study we aimed to further investigate the safety and efficacy of the EndoRotor PED system for DEN of WOPN in a larger, prospective, multicenter setting.

METHODS

Study design

This investigational, prospective, single-arm trial was conducted at 10 sites (7 in the United States and 3 in Europe) and was approved by the U.S. Food and Drug Administration under an investigational device exemption (G180127, clinicaltrials.gov NCT03694210). The U.S. Food and Drug Administration governed the sample size of 30 patients with at least 15 patients enrolled in the United States. The protocol was approved by the ethics committee at each site and the Western Institutional Review Board (approval September 25, 2018,

no. 20182351). The electronic data capture system was web-based, encrypted, password protected, and was monitored by independent monitors contracted by the sponsor (Interscope Inc). All data were verified for accuracy against source documentation.

Study device

The EndoRotor PED system is intended for use in endoscopic procedures to resect necrotic tissue in symptomatic WOPN patients after EUS-guided drainage (**Figure 1**). The PED catheter is motorized and simultaneously suctions, cuts, and debrides tissue using negative pressure. The catheter is compatible with therapeutic endoscopes with at least a 3.2-mm working channel and is controlled by the endoscopist using 2 foot pedals. The EndoRotor console is set to high (1700 rotations per minute) or low (1000 rotations per minute) speed, and the vacuum is set between 50 to 550 mm Hg of negative pressure. All endoscopists in this study underwent standardized device and protocol training.

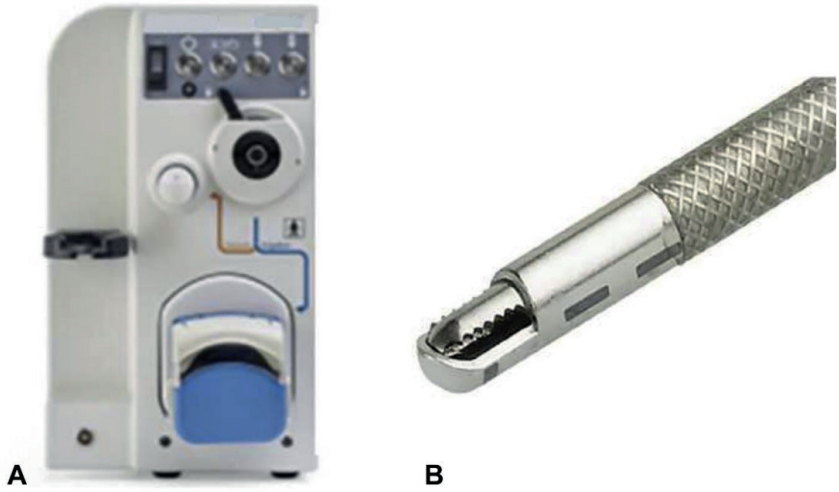

Figure 1. A, EndoRotor console. **B**, EndoRotor powered endoscopic debridement catheter.

Study endpoints

The primary endpoint was safety of the EndoRotor PED system, defined as freedom from major device-related AEs through the 21-day (±7) postnecrosectomy follow-up period. Secondary endpoints were clearance of necrosis, defined as having at least 70% of the necrotic debris removed from the WOPN assessed by contrast-enhanced CT (CECT) at the 21-day postnecrosectomy follow-up visit; total procedure time (scope-in to scope-out and start to end of debridement); adequacy of debridement after each procedure assessed endoscopically; total number of DEN procedures required to achieve clearance of necrosis; length of hospital stay (index procedure to discharge); and patient quality of life (36-Item Short Form Survey [SF-36]).

Study population

Patients were at least 22 years old with symptomatic WOPN requiring DEN and gave informed consent. Reflective of the pilot study population, patients were required to have WOPN measuring ≥6 cm and ≤22 cm with at least 30% necrosis based on baseline imaging and to have undergone EUS-guided transluminal drainage at least 2 days before the index DEN procedure to assess for potential AEs of the stent placement procedure. Exclusion criteria were patients with pseudoaneurysm ≥1 cm (per imaging), intervening gastric varices or unavoidable vessels within the access tract, dual-antiplatelet therapy or therapeutic anticoagulation that could not be withheld for the procedure, pregnant or lactating women, and any condition that in the opinion of the endoscopist was not safe for the patient to undergo the procedure.

Study procedures

CECT was performed by a radiologist at baseline to calculate collection volume using length, width, and height measurements and to assess percent necrotic tissue. Radiologic impressions were confirmed by the endoscopist. Medical history, demographics, and physical examination details were collected, and patients were asked to complete an SF-36 questionnaire.

All patients underwent EUS-guided cystogastrostomy and transluminal drainage (**Figure 2 and 3**). Depending on the institution, DEN procedures were performed using monitored anesthesia care or general anesthesia with endotracheal intubation. During each procedure, the endoscope was advanced through the cystogastrostomy into the WOPN cavity. The EndoRotor catheter was then advanced from the working channel of the endoscope, and necrosectomy was performed under direct visualization (**Video 1**, available online at www.giejournal.org). After completion of necrosectomy, the cavity was visually inspected for bleeding. DEN procedures were performed until a patient showed clinical improvement of WOPN symptoms and at least 70% of the necrotic debris was removed. At least 2 days between consecutive procedures was required for all patients. If patients were symptomatically stable after the index DEN, subsequent outpatient procedures were allowed. Those treated as inpatients were discharged from the hospital after completion of all DEN procedures. All patients entered the follow-up period when DEN procedures were considered complete. Procedural data collected included scope-in to scope-out time, concomitant procedures, EndoRotor use time, visual estimate of the percent necrosis removed, and AEs.

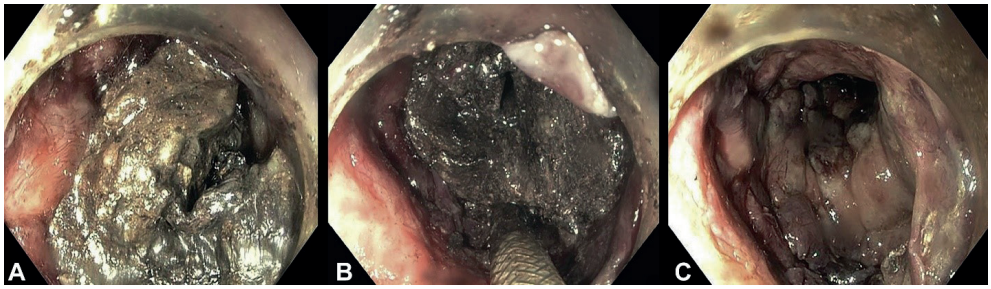

Figure 2. A, Endoscopic view of debris in the cavity through the stent. **B**, Endoscopic view of the EndoRotor debriding the necrosis. **C**, Endoscopic view of the walled-off necrosis cavity after debridement.

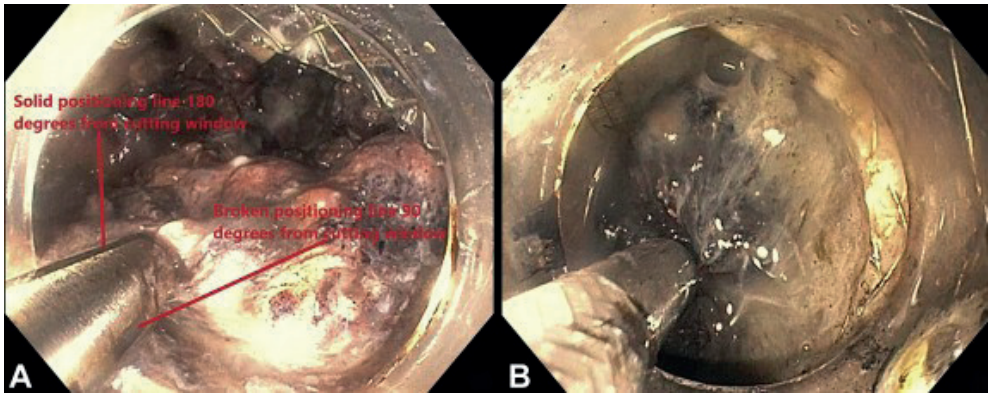

Figure 3. A, Endoscopic view of EndoRotor catheter orientation (with catheter in the lower left bottom corner) within a walled-off pancreatic necrosis. **B**, Endoscopic view of necrotic tissue being drawn into the cutting window of the EndoRotor catheter.

Follow-up

Patients were asked to return for a follow-up visit 21 days after their last DEN procedure and were assessed for AEs. A CECT was conducted by the radiologist to collect the post-DEN collection volume and percent necrotic debris, again confirmed by the study endoscopist. Surveillance endoscopy was performed at the discretion of the endoscopist, and a second SF-36 questionnaire was administered.

AEs and data safety monitoring board

All AEs were assessed for relationship to the EndoRotor device and DEN procedure per the endoscopist's opinion of causality (definite, probable, possible, or not related) and categorized according to severity, seriousness, and predictability. All serious AEs (SAEs) were adjudicated by a fully independent data safety monitoring board (DSMB) that consisted of 2 experts in pancreatic EUS-guided interventions and 1 expert in pancreatic surgery. Deidentified source documentation were provided to the DSMB for each event adjudication. Events with a definite or probable relationship were considered related.

Statistical analysis

Continuous variables were described using mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were described using frequencies and percentages. Normal distribution was assessed using histograms and the Shapiro-Wilk test. Baseline and follow-up SF-36 scores were calculated using the Wilcoxon signed-rank test. Missing data were not imputed. Correlation statistics were performed using the Spearman test to test for a correlation between the number of DEN procedures and other variables. A $P < .05$ was considered statistically significant. All statistical analyses were performed using SPSS 25.0 software (IBM Corp, Armonk, NY, USA).

RESULTS

Baseline characteristics

Between November 2018 to August 2019, 37 patients were screened for this study. Seven patients did not meet the inclusion criteria, and 30 patients were enrolled (mean age, 55 years; 60% men). The etiologies of acute necrotizing pancreatitis were biliary in 18 patients (60%), alcohol in 5 (17%), and unknown in 7 (23%). At baseline, 25 patients (83%) had pain, 5 (16%) met SIRS criteria, 5 (16%) had sepsis, and none had multiorgan failure. Demographics and medical history are shown in **Table 1**.

Twenty-six patients (87%) underwent CECT, 3 (10%) had conventional CT because of contrast allergy or renal insufficiency, and 1 (3%) had EUS by decision of their endoscopist. Mean length, width, and height of the necrotic collection were 6.5 cm (SD, 3.2), 7 cm (SD, 3.5), and 11.1 cm (SD, 3.8), respectively, and the median volume of the necrotic collection was 395 cm3 (IQR, 674; mean, 612 [SD, 556]). Median percent necrotic debris within WOPN was 75% (IQR, 40; mean, 70 [SD, 19.8]). All patients underwent EUS-guided drainage with placement of the following stent types: LAMS in 23 (76%), plastic DPS in 5 (17%), and SEMS in 2 (7%). A nasocystic drain was placed in 2 patients (7%). Baseline imaging was performed a median of 1 day before EUS-guided drainage (range, 10 days before to 42 days after) and 6 days (IQR 7) before the index DEN. Median time from stent placement to the index DEN was 7 days (IQR, 9).

Table 1. Baseline characteristics of patients undergoing direct endoscopic necrosectomy for WOPN

Characteristics	Value
Age (y (SD)	55 (15.5)
Male gender	18 (60)
Etiology of pancreatitis	
• Biliary	18 (60)
• Alcohol	5 (17)
• Unknown	7 (23)
Medical History	
• Hypertension	20 (67)
• Cardiac disease	14 (47)
• Diabetes mellitus	11 (37)
• *Type I*	1 (3)
• *Type II*	10 (33)
• Pulmonary disease	9 (30)
• Anemia	6 (20)
• Renal insufficiency	4 (13)
• Choledocholithiasis	3 (10)
• Pain	25 (83)
• SIRS	5 (1)
• Sepsis	5 (16)
Smoking	
• Current smoker	3 (10)
• Former smoker	11 (37)
Stents placed	
• LAMS	23 (76)
• SEMS	2 (7)
• Plastic DPS	5 (17)
Volume of the collection, cm^3	
• Median (IQR)	395 (674)
• Mean (SD)	612 (556)
Percent necrosis in the collection	
• Median (IQR)	75 (40)
• Mean (SD)	70 (20)

Values are n (%) unless otherwise defined.
SD, Standard deviation; IQR, interquartile range; SIRS, systemic inflammatory response syndrome.

DEN procedures and follow-up

Sixty-four DEN procedures were performed in 30 patients. Seventy-seven percent of procedures were performed using general anesthesia and 23% using monitored anesthesia care. Median number of procedures per patient was 1.5 (IQR, 2), with a median of 6 days (mean, 6; IQR, 5) between consecutive procedures. Twenty patients (67%) required 2 or less procedures to achieve resolution, 4 (13%) required 3 procedures, and 2 (7%) required 4 procedures. Three patients (10%) had more than 4 procedures, all of which were considered protocol deviations, occurred in 1 center, and were attributed to staffing and resource considerations. Finally, 1 patient (3%) underwent 2 EndoRotor procedures, with only a 10% reduction of necrosis because of dense consistency of the debris that occluded the catheter. This patient was considered an EndoRotor failure and underwent additional necrosectomy procedures using conventional instruments but was not excluded from analysis.

Mean total procedure time was 117 minutes (SD, 50) and mean EndoRotor time was 71 minutes (SD, 36). Overall median percent necrotic debris removed per procedure was 66% (IQR, 65) (**Table 2**).

Table 2. Endoscopic aassessment of percent necrosis removed from the collection per procedure and percent necrosis remaining in the collection after each procedure

Procedure	Number of patients	Necrosis removed	Necrosis remaining
1	30/30 (100%)	80 (50)	9* (25)
2	15/30 (50%)	40 (70)	20 (41)
3	9/30 (30%)	65 (78)	20 (24)
4	5/30 (17%)	25 (43)	20 (31)
5†	3/30 (10%)	-	-
6†	1/30 (3%)	-	-
7†	1/30 (3%)	-	-

Values are n/N (%) or n (%). —, Not applicable.
* Value reported for 29 of 30 subjects.
† Three subjects had more than 4 procedures, and the endoscopic assessment of necrosis removed was not captured for the fifth, sixth, and seventh procedures. After completing all direct endoscopic necrosectomy procedures in these 3 patients, the endoscopist endoscopically verified that all necrotic material had been removed.

Median hospitalization duration was 10 days (IQR, 22) after the index DEN. In 8 patients (27%) all DEN procedures were performed as outpatients, and in 2 patients (7%) the index procedures were performed as inpatients but subsequent procedures were performed as outpatients. All outpatient procedures were from U.S. hospitals. The remaining 22 patients (73%) were discharged a median of 12 days (IQR, 24) after the last DEN procedure.

At the 21-day postnecrosectomy follow-up visit, imaging confirmed at least 70% removal of the necrotic debris was achieved in 29 of 30 patients (97%). Percent necrosis within WOPN decreased to a median of 0% (IQR, 5; mean, 6% [SD, 17]), for an overall 91% reduction. Follow-up imaging was performed a median of 35 days (IQR, 19) after baseline imaging and a median of 20 days (IQR, 11.5) after the last DEN procedure. Twenty-four patients (80%) had repeat CECT, 3 (10%) had repeat conventional CT, and 1 (3%) had repeat EUS. In 2 patients (7%) follow-up imaging was not performed; 1 patient refused additional CECT and the other had endoscopy in lieu of CECT. Collection volume measurements were not performed for these patients, but percent necrotic material removed was confirmed via endoscopy. A statistically significant positive correlation was found between the number of DEN procedures performed per patient and baseline collection volume (ρ = .363, P = .049) (ie, a larger collection volume at baseline may increase the number of DEN procedures required for clinical resolution).

Adverse events

Nine SAEs and 11 non-SAEs occurred in 10 of 30 patients (33%) (**Table 3**). Of the 9 SAEs, 3 were adjudicated by the DSMB as possibly related to the DEN procedure: GI bleeding in 2 and pneumoperitoneum in 1.

Regarding the 2 GI bleeds, the first patient experienced viral gastroenteritis, pain, and vomiting 4 days after the final DEN procedure. The patient was readmitted to the hospital for endoscopic evaluation during which blood was noted to be oozing from the stomach near the flange of the LAMS. Argon plasma coagulation was applied with successful hemostasis, and the patient was discharged. The second patient experienced hemorrhagic shock, hypotension, and hematemesis 1 day after the first and the final DEN procedure. Endoscopic evaluation identified bleeding caused by the flange of a SEMS, placed after completion of DEN, abrading the collection wall. The patient received 2 applications of polysaccharide hemostatic powder, and a DPS was placed through the SEMS to prevent abrasion. The patient received a blood transfusion and platelets and recovered.

Finally, the patient who experienced pneumoperitoneum had hemodynamic instability and pain within 24 hours of the DEN procedure. Pneumoperitoneum was attributed to the endoscope being torqued within the LAMS that allowed for extravasation of free air into the peritoneal cavity. The patient was observed, and a CT performed 4 days later showed resolution of pneumoperitoneum. The patient was transferred out of the intensive care unit. The following day, the patient decompensated with shock complicated by respiratory failure, hypotension, and acute renal insufficiency because of fungemia with fungal empyema acquired from chest tube placement in the intensive care unit. The patient developed multisystem organ failure and died 10 days later. Multisystem organ failure was adjudicated by the DSMB as unrelated to the EndoRotor device or DEN procedure.

With regard to AEs, 2 of 11 were (possibly) related to the DEN procedure. In 1 patient SEMS dislocation related to the DEN procedure occurred during plastic DPS placement after completion of DEN. A second patient was diagnosed with anemia related to the LAMS abrading the posterior wall of the WOPN cavity after bloody secretions were noted from a percutaneous drain. CT showed no active bleeding or hematoma; the patient received a single blood transfusion and recovered.

Catheter limitations and misuse

Seventy-two catheters were used during the entire trial (64 procedures). Seven catheters broke because the catheters were extended beyond 160 degrees, which is against the instructions for use recommendations and limitations. The rest of the catheters functioned well when used within 120 degrees of angulation arc or less. One catheter broke at the end that connects to the suction tower. Another catheter was clogged because of thick and sticky debris and was unable to perform resection.

Quality of life

Twenty-four patients completed both the baseline and follow-up SF-36 questionnaire and were included in the analysis. A significant improvement was found in 4 domains: physical functioning (36 vs 58, P = .002), energy/fatigue (28 vs 37, P = .040), emotional well-being (61 vs 68, P = .024), and pain (32 vs 55, P = .001) (**Table 4**).

Table 3. Adverse events

	Patients (n = 30)	Severity	Device-related*	Procedure-related*
Serious adverse events				
Deep vein thrombosis	1 (3.3)	Moderate	Not related	Not related
Hematemesis	1 (3.3)	Moderate	Not related	Not related
Sepsis	1 (3.3)	Moderate	Not related	Not related
Cholestasis	1 (3.3)	Moderate	Not related	Not related
Gastrointestinal bleed	2 (6.6)	Severe (n=1), moderate (n=1)	Not related	Possible
Pneumoperitoneum	1 (3.3)	Mild	Not related	Possible
Shock with multi-organ failure resulting in death	1 (3.3)	Severe	Not related	Not related
Pancreatitis	1 (3.3)	Severe	Not related	Not related
Non-serious adverse events				
Pleural effusion	1 (3.3)	Moderate	Not related	Not related
Bacteraemia	1 (3.3)	Moderate	Not related	Not related
Diarrhea	1 (3.3)	Mild	Not related	Not related
Colitis	1 (3.3)	Mild	Not related	Not related
Dislocated stent	1 (3.3)	Mild	Not related	Definite
Anemia	1 (3.3)	Moderate	Not related	Possible
Clostridium difficile infection	1 (3.3)	Moderate	Not related	Not related
Hypokalaemia	1 (3.3)	Mild	Not related	Not related
Insomnia	1 (3.3)	Mild	Not related	Not related
Fever	1 (3.3)	Moderate	Not related	Not related
Candida oesophagitis	1 (3.3)	Moderate	Not related	Not related

Values are n (%)
* Definitions of relation to the procedure: not related, the event is because of an underlying or concurrent illness or effect of another device, drug, or intervention and is not related to the investigational device, procedure, or general surgery; possible, the event has a strong temporal relationship to the use of the investigational device, procedure, or general surgery and an alternative etiology is equally or less likely; probable, the event has a strong temporal relationship to the use of the investigational device, procedure, or general surgery and another etiology is unlikely or significantly less likely; definite, an event that can only be attributed to the use of the investigational device, procedure, or general surgery; not assessable, the event's relationship to the use of the investigational device, procedure, or general surgery cannot be assessed.

Table 4. 36-Item Short Form Survey (SF-36)

	Baseline	Follow-up	p-value
Physical functioning	36.0 (± 30.8)	57.7 (± 31.0)	0.002*
Role limitations due to physical health	11.5 (± 28.5)	25.0 (± 37.6)	0.100
Role limitations due to emotional problems	27.8 (± 41.3)	51.4 (± 48.1)	0.051
Energy/ fatigue	27.9 (± 22.0)	36.7 (± 23.2)	0.040*
Emotional well-being	60.7 (± 19.7)	68.3 (± 18.9)	0.024*
Social functioning	51.6 (± 32.6)	56.3 (± 26.6)	0.459
Pain	31.5 (± 28.4)	55.0 (± 30.4)	0.001*
General health	47.4 (± 16.2)	53.8 (± 15.3)	0.083

* A significant improvement was found at follow-up as compared with baseline ($P < .05$).

DISCUSSION

The effectiveness of DEN is currently hampered by the lack of dedicated tools designed for this indication. Instruments currently used include snares, baskets, retrieval nets, or grasping forceps that lack sufficient grip on the necrotic debris, which makes efficient removal difficult and obscures visualization during the procedure. The EndoRotor PED system is now commercially available in the United States and European Union and is the first tool that is specifically designed and indicated for DEN under direct endoscopic visualization.

A 2017 pilot study performed at 2 hospitals in Europe aimed to evaluate the safety and feasibility of the EndoRotor PED system (11). Twelve patients with WOPN were enrolled and treated with the device. Successful removal of necrotic debris was achieved in 100% of patients in a median of 2 procedures with no EndoRotor-related AEs. The performing endoscopists deemed the device easy to use and effective for safe removal of the necrotic tissue. The current study is the first prospective, international, multicenter clinical trial in which we investigated the safety and effectiveness of the EndoRotor PED system in more centers and a larger study population.

The primary endpoint in the current study was absence of major device-related AEs. No device-related SAEs were reported; however, there were 3 SAEs that were classified by the DSMB as having a relationship to the DEN procedure and not caused by the EndoRotor. Two patients were diagnosed with GI bleeding. We believe the bleeding was caused by friction of the LAMS and SEMS, respectively, and not initiated by the EndoRotor, because the cavity was visually inspected for bleeding after all DEN procedures and no bleeding was seen. Bleeding or oozing from the necrotic cavity is a relatively common AE of DEN and is described to occur in 16% of patients undergoing the procedure using conventional techniques (12). In this study, bleeding from the necrotic cavity was noted in 7% of patients, which is lower when compared to bleeding reported for conventional techniques. Furthermore, LAMS dislodgement was encountered in 1 patient (3%) in our study, whereas Bang et al. (13) reported an occurrence in 10% of patients. Overall, procedure-related SAEs occurred in 10% of patients (3/30), which is lower compared with literature reports ranging from 21% to 36% (10,12,14,15). Finally, 1 patient died because of extensive comorbidities and ongoing pancreatitis with fungemia resulting in multiorgan failure. This resulted in a mortality rate of 3% in our study, which is lower as compared with previous studies, ranging from 6% to 18% (9,12,14,16).

As for effectiveness of the device, according to baseline and follow-up imaging, an average reduction of 85% in collection volume and 91% of necrotic debris was achieved. In addition, a low median number of DEN procedures per patient (1.5) were required to successfully remove the necrotic tissue from the collection. A meta-analysis reported a mean number of 4.1 DEN procedures necessary to clear the collection when conventional techniques were used.10 A randomized controlled trial from the Netherlands in which an endoscopic step-up approach was compared with a surgical step-up approach reported a median of 2 (range, 1-4) DEN procedures per patient after endoscopic drainage using conventional techniques (9), whereas Seifert et al. (14) reported a mean of 6.2 procedures

per patient. Our study was not designed or powered to prove a difference in the number of procedures necessary per patient, but our results suggest this number is lower if the EndoRotor PED system is used; however, comparative studies assessing this point are required for a definitive answer. In addition, although borderline significant (P = .049), there might be a correlation between baseline collection volume and the number of DEN procedures required to achieve clearance.

In this study, 22 patients (73%) were discharged a median of 10 days after the index DEN, compared with a median of 14 to 29 days reported in previous studies using conventional DEN techniques (9,10,16). Of note, Bang et al. (16) reported a median of 14 days from index intervention, which comprised endoscopic drainage in their study and not necessarily DEN. In the current study, 8 patients (22%) were considered stable enough to be treated entirely as outpatients. Four (50%) of these patients required 1 procedure to achieve resolution and the remaining 4 (50%) required 2 to 3 DEN procedures. Two patients (7%) were treated as inpatients for the index procedure and had 1 or 2 subsequent outpatient DEN procedures to achieve resolution. The low number of procedures required per patient and the decrease in collection volume as well as solid necrotic debris in the collection suggest that the EndoRotor is effective for DEN.

The strengths of this study are its prospective, international, multicenter design and 100% verification of data against the source. It is therefore anticipated that these results are generalizable. Furthermore, the results of this study are consistent with those of the 2017 pilot study, which further verifies and validates our outcomes (11).

Although this study had positive outcomes with regards to the number of DEN procedures and effectiveness of the device, study limitations are small sample size, no prospective or retrospective matched cohort, lack of a central independent radiologist to measure volume and percent necrotic debris on CECT, and subjective visual endoscopic assessments by the endoscopist regarding adequacy of the debridement per DEN session. Although endoscopic assessment of necrotic tissue left in the collection is difficult, expert endoscopists participated in this study, and given the large reductions in collection volume (85%), percent necrotic debris in the collection (91%), and average percent necrosis removed per DEN session (66%), in combination with the improvement in the clinical course of the patients, we believe these are close to accurate observations. At some sites, endoscopic visualization of debris volume is standard of care during DEN sessions regardless of the debridement device.

In conclusion, this prospective, multisite device study validates the results of the previous Endorotor PED system pilot study and provides further evidence of the safety and efficacy of the system for treatment of WOPN. Patients undergoing DEN with the EndoRotor seem to require less DEN sessions and fewer days hospitalized when compared with studies using conventional instruments. However, large sample size prospective trials comparing the EndoRotor with conventional techniques are urgently needed to further evaluate the EndoRotor's clinical management impact on endoscopic WOPN treatment.

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Chapter 10

Prevalence of and risk factors for stent migration-induced duodenal perforation

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ABSTRACT

Background and aim: The safety of transpapillary biliary drainage by stent placement through endoscopic retrograde cholangiography (ERC) may be compromised by the occurrence of stent migration-induced perforation of the duodenal wall (SMDP). We aimed to assess the prevalence rate, risk factors and clinical course of SMDP.

Methods: This retrospective cohort study included all patients who underwent an ERC with biliary plastic stent placement, between January 2014 and December 2018. Patients with an SMDP were identified from our endoscopy complication registry.

Results: 1227 patients underwent an ERC, of whom 629 patients (51%) with biliary plastic stent placement; in 304 patients (25%) stents were placed for perihilar strictures. Thirteen patients with SMDP were identified. The prevalence was 2.1% for patients with biliary plastic stent placement and 4.3% for patients stented for a perihilar stricture. All SMDPs occurred in patients with a perihilar stricture and with stents ≥12 cm (range 12-20 cm). Another potential risk factor was stent insertion into the left liver lobe, which was present in 10/13 patients. In 10/13 patients SMDP was clinically suspected. 3/13 patients were asymptomatic and diagnosed at elective stent retrieval. Eight patients could be endoscopically treated with an over the scope clip. Four patients died due to abdominal sepsis despite repeated interventions.

Conclusion: SMDP is a rare but potentially life-threatening complication of ERC after transpapillary drainage for perihilar biliary strictures. Stents ≥12cm and stent insertion into the left liver lobe may be associated risk factors.

INTRODUCTION

Transpapillary biliary drainage with stent placement through endoscopic retrograde cholangiography (ERC) is a well-established treatment for bile duct obstruction due to either malignant or benign strictures or cholelithiasis. Improving biliary drainage by stent placement allows for symptom relief of jaundice, pruritus and pain, and improvement of liver function tests (1,2).

Endoscopic placement of biliary stents may be complicated by stent occlusion, potentially leading to cholangitis, often necessitating repeat ERC. In addition, plastic stent migration is regularly encountered, with reported rates between 5-10% and a trend towards higher migration rates after sphincterotomy (1,3). Fortunately, the majority of distally migrated stents pass the digestive tract uneventfully. However, distal stent migration may lead to duodenal erosion or superficial ulcers caused by the mechanical friction between the tip of the stent and the opposite duodenal wall, possibly increasing the risk of bleeding. Furthermore, pressure necrosis can eventually lead to perforation of the duodenal wall, as has been reported in case reports (4-30). Although stent migration-induced perforation of the duodenal wall (SMDP) is considered a rare complication, it is associated with serious life-threatening complications including intra-abdominal or retroperitoneal abscesses, fistulation or sepsis (1,10,31). Once perforation has occurred, early diagnosis and management including endoscopic or surgical closure of the defect are essential. Clinical presentation can be non-specific with symptoms that mimic those of cholecystitis or pancreatitis thereby obscuring early detection. As a result, a high index of suspicion is needed to diagnose this complication.

So far, SMDP has only been reported in case reports. The actual prevalence of this complication and associated risk factors are unknown. The current study aims to analyze the prevalence rate, clinical course and risk factors of SMDP in a tertiary referral center for pancreaticobiliary diseases.

METHODS

Study design and study population

A single-center retrospective cohort study was performed in our tertiary referral center. Firstly, all consecutive patients who underwent an ERC at our institution between January 2014 and December 2017, were identified from an endoscopy database (Endobase®), in which all endoscopic procedures and reports are prospectively registered. All patients who underwent an ERC with biliary plastic stent placement were included for analysis. Secondly, all patients who were diagnosed with an SMDP between January 2014 and December 2018, were identified from our endoscopy complication registry. This complication registry is maintained prospectively and updated weekly. To be able to identify all patients who were diagnosed with an SMDP that was caused by stents placed in the study period (January 2014 – December 2017), we included patients diagnosed with an SMDP until December 2018, assuming that an SMDP would occur within one year after stent placement. An SMDP was defined as a duodenal wall perforation diagnosed by endoscopy and/or computed tomography (CT) scan, with or without clinical symptoms of

abdominal pain, fever and elevated infection parameters. Of note, all patients undergoing an ERC with plastic stent placement for a hilar stricture at our institution, receive one gift of antibiotic prophylaxis pre-procedurally followed by three days of oral antibiotics post-procedurally.

This study was conducted according to the guidelines in the Helsinki Declaration and was approved by the ethics committee of the Erasmus MC University Medical Center, Rotterdam, the Netherlands.

Selection criteria for plastic stent insertion

The general approach to optimizing endoscopic drainage in operable patients with perihilar strictures was to initially drain the future liver remnant (decided after a multidisciplinary meeting involving surgeons, radiologists and oncologists). In inoperable patients, maximum drainage was attempted whilst taking care to avoid opacifying and draining atrophied segments. The initial approach was to drain with plastic stents and exchange these for uncovered SEMS after adequate drainage (based on bilirubin levels) was achieved. In all patients drainage of opacified segments was actively pursued, regardless of the initial drainage plan.

Initially center bend type stents were used, but after recognizing cases of duodenal perforation we switched to duodenal bend type stents. The use of plastic stents with a distal pigtail was considered, but due to pushability concerns in complex hilar strictures these stents have not been used in our institution.

The anatomy of patients with hilar strictures was based on both pre-operative imaging (mainly MRI/MRCP) and the cholangiogram obtained at ERCP. Transpapillary stents were used and length and diameter (either 7 or 10 French) selection were based on anatomy and expected difficulty of multiple stent placement. The use of balloon dilation of the stricture was at the discretion of the endoscopist.

Data collection

With the use of a dedicated electronic endoscopic reporting system (Endobase®) and the electronic hospital information system (HiX 6.1 HF103, ChipSoft B.V.), the following data was retrieved for all patients who underwent an ERC with plastic stent placement: demographic factors, medical history, indication of stent placement, etiology and location of the stricture, stricture dilatation before stent placement, performance of a sphincterotomy, and stent characteristics (i.e. number of inserted stents, type and bend (center or duodenal), location of the proximal tip of the stent and stent length and diameter). Furthermore, for all patients diagnosed with an SMDP, data were collected regarding clinical symptoms at presentation, date of diagnosis, treatment and outcome.

Study outcomes

The primary outcome was defined as the rate of SMDP in patients who underwent an ERC with plastic stent placement. Secondary outcomes were potential risk factors for SMDP, either disease-related or stent-related, and the treatment and clinical course of patients diagnosed with an SMDP.

Statistical analysis

Descriptive statistics were used to analyze the data. Continuous variables were described using mean and standard deviation for normally distributed variables or using median and range for non-normally distributed variables. Categorical variables were described using frequencies and percentages. A univariate logistic regression analysis was performed to identify potential risk factors. Factors included in this analysis were disease-related and stent-related factors. For stricture-related factors (i.e. etiology of the stricture and stricture dilatation prior to stent placement), only biliary ERC procedures in which a plastic stent was placed for a stricture were included for analysis. For all other factors, all biliary ERCs with plastic stent placement were included for analysis. The statistical analyses were performed using the statistical software package IBM SPSS version 25.

RESULTS

Prevalence rate and risk factors for SMDP

Between January 2014 and December 2017, in 1227 patients (mean age 61 years (SD ± 15.9 years), 54% male) a total of 2486 ERCs were performed. In 51% (629/1227) one or more biliary plastic stents were placed, encompassing a total of 1203 procedures. In 25% (304/1227) one or more biliary plastic stents were placed for a perihilar stenosis. Baseline characteristics of the patients undergoing an ERC with plastic stent placement are shown in **Table 1**.

Table 1. Baseline characteristics of patients who underwent an ERC with plastic stent placement

Characteristic	(n = 629)
Age (mean ± SD)	59.8 (15.0)
Gender (% male)	61.0
Indication for plastic stent placement (%)	
• Obstructive jaundice	50.7
• Cholangitis	18.9
• Bile leakage	11.8
• Drainage of gallstones	10.7
• Other (i.e bile duct obstruction without liver test abnormalities, abdominal pain, duodenobiliary reflux)	8.0
Median number of ERCPs per patient (range)	1 (1-14)
Sphincterotomy prior to stent placement (%)	73.1
Stenosis (%)	
• No stenosis	20.7
• Distal stenosis	31.0
• Perihilar stenosis	48.3
Dilatation prior to stent placement (%)	19.6
Number of stents in total in situ (%)	
• 1	74.9
• 2	21.6
• 3	3.0
• 5	0.2
• 7	0.3

ERC, endoscopic retrograde cholangiography; ERCP, endoscopic retrograde cholangiopancreatography.

During the study period, 13 patients were diagnosed with an SMDP. Baseline patient characteristics are shown in **Table 2**. The prevalence rate of SMDP for all biliary ERC *procedures* with plastic stent placement was 1.1% (13/1203) and 1.9% (13/701) for the *procedures* with plastic stent placement for a perihilar stricture. The prevalence rate of SMDP for all *patients* undergoing a biliary ERC with plastic stent placement was 2.1% (13/629) and 4.3% (13/304) for the *patients* with plastic stent placement for a perihilar stricture . Importantly, all patients who were diagnosed with an SMDP had a perihilar stricture. SMDP did not occur in patients in whom a stent was placed for a distal stricture or for other indications than a stricture. The stricture was malignant in 62% (8/13) and benign in 39% (5/13). In 54% (7/13) the stricture was dilated prior to stent placement. In 77% (10/13) a sphincterotomy was performed. In 54% (7/13) SMDP occurred after the first ERC with plastic stent placement. All ERCs were performed by or under direct supervision of endoscopists who are experienced in ERC. About half of patients with an SMDP had 1 stent in situ (54% (7/13)). Median stent length was 15 cm (range 12 – 20) and median stent diameter was 10 French (range 7 – 10). SMDP occurred with both duodenal bend and center bend type stents (54% (7/13) versus 46% (6/13), respectively). All stents were straight stents with a flap, from either Boston Scientific Inc. or Cook Medical Inc. No stents with a distal pigtail part were used. The location of the proximal tip of the stent was intrahepatic left in 77% (10/13), intrahepatic right in 15% (2/13) and in 8% (1/13) multiple stents were placed bilateral.

Table 2. Baseline characteristics of patients diagnosed with SMDP

Characteristic	(n = 13)
Age (mean ± SD)	62.3 (14.1)
Gender (% male)	10 (76.9)
Indication for plastic stent placement (%)	
• Obstructive jaundice	8 (61.5)
• Cholangitis	5 (38.5)
PSC (%)	2 (15.4)
Etiology (%)	
• Malignant	8 (61.5)
• Benign	5 (38.5)
Stricture location (%)	
• Distal	0 (0)
• Perihilar	13 (100)
• No stricture	0 (0)
Stricture dilatation prior to stent placement (%)	7 (53.8)
Sphincterotomy prior to stent placement (%)	10 (76.9)
Number of stents in situ (%)	
• 1	7 (53.8)
• 2	4 (30.8)
• 3	1 (7.7)
• 4	1 (7.7)
Stent length (median (range))	15 cm (range 12 – 20)
Stent diameter (median (range))	10 French (range 7 – 10)
Bend stent (% duodenal)	7 (53.8)
Proximal tip of the stent (%)	
• Intrahepatic left	10 (76.9)
• Intrahepatic right	2 (15.4)
• Both	1 (7.7)

PSC, primary sclerosing cholangitis.

In **Table 3** the results of the univariate logistic regression analysis are shown. The location of the stricture was not included in the univariate logistic regression analysis since SMDP only occurred in perihilar strictures. At univariate logistic regression, a stent placed to drain the left liver lobe and longer stent length were found to be associated with SMDP. Due to the relatively low number of SMDPs a multivariate logistic regression analysis could not be performed.

Table 3. Univariate logistic regression analysis of patient-, stricture- and stent characteristics in relation to SMDP

Characteristic	OR (95% CI)	p-value
Age	1.020 (0.980 – 1.062)	0.322
Male gender	0.550 (0.151 – 2.009)	0.366
PSC	1.421 (0.312 – 6.479)	0.650
Etiology of the stricture - malignant	1.900 (0.634 – 5.697)	0.252
Etiology of the stricture - benign	0.569 (0.185 – 1.751)	0.325
Etiology of the stricture – indeterminate	0.784 (0.101 – 6.094)	0.816
Stricture dilatation prior to stent placement	2.880 (0.960 – 8.644)	0.059
Sphincterotomy prior to stent placement	0.782 (0.214 – 2.866)	0.711
Number of stents in situ		
• 1	1	
• 2	1.530 (0.457 – 5.122)	0.490
• ≥ 3	0.951 (0.118 – 7.677)	0.962
Stent diameter	0.863 (0.567 – 1.312)	0.489
Stent length	1.329 (1.142 – 1.546)	0.000*
Proximal tip of the stent – intrahepatic left	14.064 (3.840 – 51.516)	0.000*
Proximal tip of the stent – intrahepatic right	0.994 (0.219 – 4.522)	0.994
Proximal tip of the stent – bilateral intrahepatic	0.552 (0.071 – 4.277)	0.570

SMDP, stent migration-induced duodenal perforation; PSC, primary sclerosing cholangitis.
* Factors significantly associated with SMDP at univariate logistic regression analysis (P<0.05).

Clinical course of SMDP

77% (10/13) were clinically suspected of SMDP based on their presentation with abdominal pain, fever and/or increased serum levels of inflammatory parameters. The remaining 23% (3/13) was asymptomatic and SMDP was diagnosed at elective stent retrieval. 80% (8/10) of the symptomatic patients presented within 14 days after ERC with stent placement. The median time between stent placement and diagnosis was 12 days (range 2 – 229).

The diagnosis was established by means of endoscopy alone in 39% (5/13) and in the remaining 39% (5/13) by CT scan. In 31% (4/13) the perforation was considered to be a contained perforation and could therefore be treated conservatively with only stent removal. These patients did not develop any complications nor needed additional interventions. In 62% (8/13) the perforation could be closed with an over the scope clip (OTSC) and 8% (1/13) had to undergo surgery since the perforation was too large to be successfully treated by endoscopic means. In total, 77% (10/13) received prophylactic antibiotics to prevent infection. Nevertheless, 38% (5/13) developed intra-abdominal or retroperitoneal abscesses for which they underwent percutaneous drainage. In 8%

(1/13) a percutaneous transhepatic cholangiography (PTC) drain was placed. Endoscopic nasobiliary drainage was not routinely performed in our patients. In 15% (2/13) a right hemicolectomy needed to be performed. In the first patient, the stent was perforated through the horizontal part of the duodenum and the tip of the stent had caused a false aneurysm of the ileocolic artery. The ileocolic artery had to be coiled which led to an ischemic caecum. In the second patient, a submucosal hematoma in the wall of the caecum together with an ischemic caecum was found during surgery. This was probably caused by a fistula between the duodenum and the mesocolon of the colon ascendens, which had developed after the stent perforated the duodenal wall with extensive retroperitoneal infiltration.

Finally, 31% (4/13) died due to ongoing abdominal sepsis, despite repeated endoscopic, percutaneous and/or surgical interventions. Two of these patients were diagnosed with an irresectable malignant hilar stricture and were unfit for surgery, and one elderly patient with a benign hilar stricture refused further surgical treatment after failure of endoscopic and percutaneous drainage, and wished to be discharged with palliative care at home. An overview of the clinical course of SMDP patients is shown in **Table 4**.

Figure 1 and **Figure 2** show a biliary plastic stent which is perforated through the duodenal wall on fluoroscopy during ERC and on CT scan. **Figure 3** shows the endoscopic view of a perforated biliary plastic stent through the duodenal wall and **Figure 4** shows an OTSC that has been placed over the perforation. **Figure 5** shows fluoroscopy during ERC showing no contrast leakage after the plastic stent has been removed from the duodenal wall (contained SMDP).

Figure 1. Fluoroscopy during ERC showing a biliary plastic stent perforated through the duodenal wall

Table 4. Clinical presentation, diagnosis and treatment of patients with SMDP

Case	Clinical presentation	Days after ERCP	Diagnosis	Treatment perforation	Additional treatment	Outcome
1	Abdominal pain	2	Endoscopy + CT	OTSC	Antibiotics, drainage intra-abdominal and retroperitoneal abscesses	Recovered
2	Abdominal pain, fever	3	Endoscopy	OTSC	Antibiotics, drainage retroperitoneal abscess	Recovered
3	Abdominal pain, sepsis	3	Endoscopy + CT	OTSC	Antibiotics	*Deceased*
4	Abdominal pain	4	Endoscopy + CT	OTSC	Antibiotics, drainage intra-abdominal abscesses	*Deceased*
5	Abdominal pain, fever	4	Endoscopy	OTSC	Antibiotics	Recovered
6	Abdominal pain	6	Endoscopy	OTSC	Antibiotics	Recovered
7	Complicated cholecystitis	12	Endoscopy + CT	Surgery	Antibiotics, drainage retroperitoneal abscess, right hemicolectomy	*Deceased*
8	Abdominal pain, leukocytosis	13	Endoscopy	OTSC	Antibiotics, drainage intra-abdominal and retroperitoneal abscesses	*Deceased*
9	Asymptomatic	22	Endoscopy	Conservative	-	Recovered
10	Fever, hematemesis	26	Endoscopy + CT	OTSC	Antibiotics, right hemicolectomy	Recovered
11	Asymptomatic	125	Endoscopy	Conservative	-	Recovered
12	Asymptomatic	126	Endoscopy	Conservative	Antibiotics	Recovered
13	Fever and cholestasis	229	Endoscopy	Conservative	-	Recovered

SMDP, stent migration-induced duodenal perforation; OTSC, over-the-scope-clip; CT, computed tomography

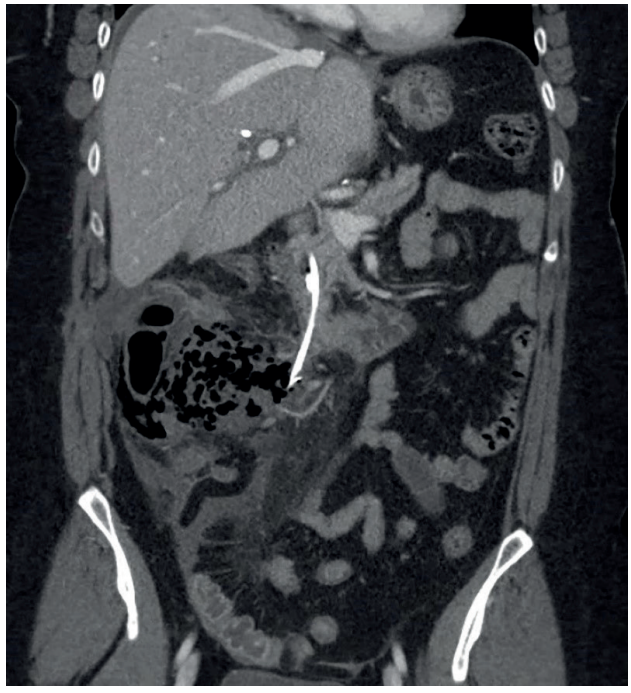

Figure 2. Fluoroscopy during ERC showing a biliary plastic stent perforated through the duodenal wall

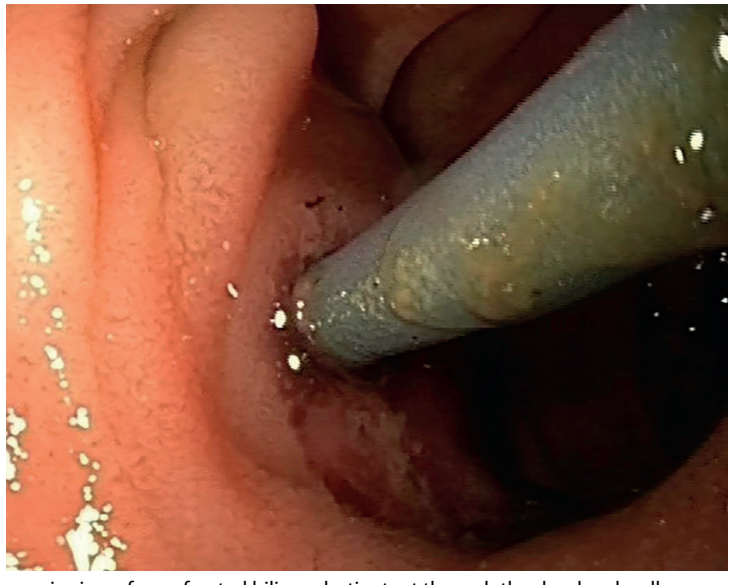

Figure 3. Endoscopic view of a perforated biliary plastic stent through the duodenal wall.

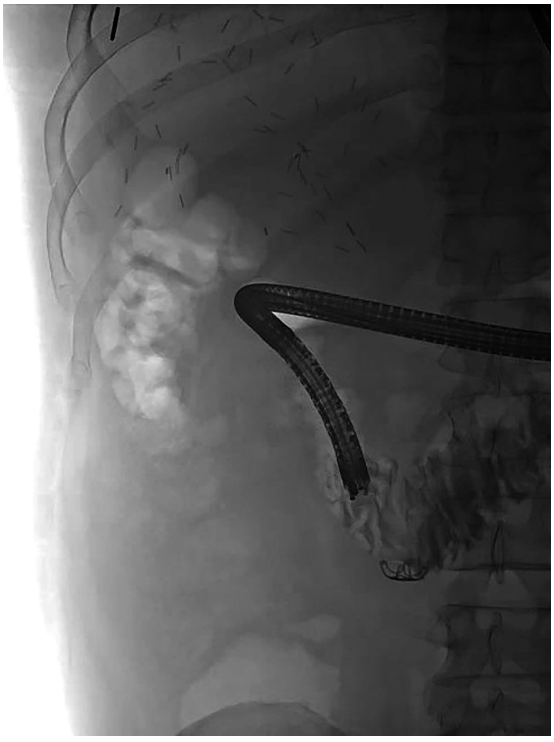

Figure 4. Endoscopic view of a perforated biliary plastic stent through the duodenal wall.

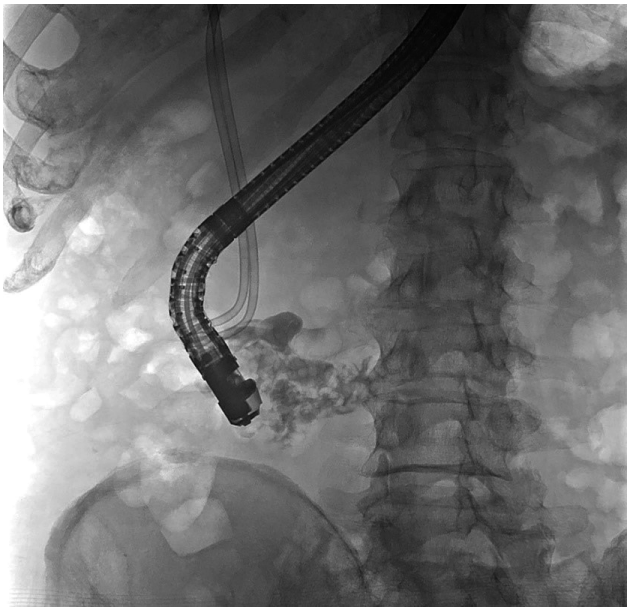

Figure 5. Fluoroscopy during ERC showing no contrast leakage after the plastic stent has been removed from the duodenal wall (contained SMDP).

DISCUSSION

Stent migration-induced perforation of the duodenal wall (SMDP) is a potentially life-threatening complication of ERC. In this study, we observed an overall SMDP prevalence rate of 1.1% in all biliary ERC procedures with plastic stent placement that were performed and a prevalence rate of 2.1% in patients after ERC with plastic stent placement. The prevalence rate in patients with stent placement for a perihilar stricture was as high as 4.3%. According to this study, the most common clinical presentation of SMDP consists of sepsis with signs of peritonism within two to four weeks after ERC for a perihilar stricture with placement of a plastic stent ≥12 cm length. In all but one patient, the perforation site could be technically successfully closed endoscopically. Nevertheless, despite endoscopic closure in combination with antibiotic therapy, 60% of patients required additional abscess drainage or surgery to treat the septic complications, and the overall mortality of SMDP was 30%.

To the best of our knowledge, this is the first study to report on the actual prevalence rate of SMDP in a large consecutive cohort of patients that undergo ERC. Previous publications only comprise case reports (4-30). Prevalence rates in our study may seem high, however, SMDP may well be an underreported complication, due to hesitation of physicians to report a complication that may be (falsely) attributed to inadequate technical skills. The results of our study show that SMDP indeed is erroneously considered a rare complication of ERC and occurs also in expert ERC centers when experienced endoscopists performed the procedure. Our results provide for the first time a plausible estimate of the actual complication rate of SMDP. Since the risk of SMDP in our study for patients with a perihilar stricture is of the same magnitude as the risk of post-ERCP pancreatitis (3.5-9.7%) and bleeding (0.3-9.6%) (32), we propose to include the risk of SMDP in the informed consent procedure for patients undergoing an ERC for a perihilar stricture.

Considering the potential lethality of SMDP, prompt diagnosis and immediate treatment are of paramount importance. In our study, the majority of the patients presented with abdominal pain and sepsis within two to four weeks after placement of a plastic stent. This is in line with previously published case reports (4,5,8,9,17,19,22-26,28-30). Symptoms of SMDP may mimic common complications of ERC, such as post-ERCP pancreatitis, cholangitis or cholecystitis. A high index of suspicion of the possibility of SMDP in patients with such symptoms is therefore warranted and the diagnostic workup often requires cross-sectional imaging. With regard to treatment, literature data are scarce. Although all symptomatic patients in our series were treated endoscopically within 24 hours after presentation, a large proportion developed abscesses despite prophylactic antibiotics. A strategy of primary surgical closure of the duodenal wall defect combined with peritoneal lavage might accelerate clinical course and improve outcome, and may be considered an adequate alternative in patients fit for surgery. In our series, four patients died due to ongoing intra-abdominal sepsis or respiratory failure. Surgical intervention was considered in all patients in case of failure of endoscopic therapy and/or persisting abdominal infection. Only one of these patients underwent surgery. It could be discussed whether this should have been performed in the remaining three patients that have deceased. However, two of them were diagnosed with progressive metastasized disease and unfit

for invasive treatment shortly after the SMDP was diagnosed. The remaining patient was diagnosed with a benign hilar stricture, but refused further surgical treatment after failure of endoscopic and percutaneous drainage and chose for palliative care at home. Our reported mortality rate may be influenced by the thigh prevalence of comorbidities in this group of patients. It is difficult to compare our rate to what has been reported previously, as most published data on SMDPs predominantly come from case reports. We have only found two reports that described patients that deceased after an SMDP (16,24). In first report this concerned a patient with benign disease who was immediately treated surgically after diagnosis of SMDP (24). In the second report this concerned a patient with metastasized disease who was also treated surgically immediately after diagnosis of SMDP (16). In both cases, despite early surgical intervention, the patients died due to ongoing abdominal infection and respiratory failure.

We did not perform endoscopic nasobiliary drainage (ENBD) routinely in patients with SMDP for several reasons: in all cases endoscopic closure of the perforation was attempted and, after apparent successful closure, this was confirmed with the administration of intraluminal contrast. Adding ENBD to endoscopic therapy was not considered to be of added value. In those patients with persistent leakage, usually confirmed via percutaneous drainage, the added value of ENBD was considered to be very limited. Lastly, the role of ENBD in our unit is, contrary to for example Asian clinical practice, very limited and typically used for patients with refractory biliary leakage after surgical procedures or trauma. The most important risk factor for SMDP in our study was the indication for biliary drainage of a perihilar stricture. All perforations occurred in patients with a perihilar stricture after the placement of a plastic stent ≥12 cm length. These findings are in line with other reports (4,5,8,13,17,23-25,27-29). Only two case reports were published in which a perforation was reported with shorter stents (9,15). Longer stent length was also associated with a higher risk of SMDP at univariate regression analysis. Another potential risk factor that we identified with univariate regression analysis was when a stent was placed to drain the left liver lobe. However, this finding should be interpreted with caution as the model was of risk of multiple testing due to the relatively low number of cases and the high number of possible risk factors tested, potentially resulting in a false-positive association (type I error). Nevertheless, the fact that stents placed into the left biliary system seem to migrate more often compared to those placed in the right biliary system could be argued as this might be the resultant of the sharper anatomical angel and more bended position of a left sided intrahepatic stent which provokes the stent to straighten due to material rigidity thereby causing outward migration. And, migration of stents deployed in the left intrahepatic ducts was also described in previously published case reports (25,27,29).

A potential solution to decrease the rate of SMDP is changing the type of stents used for drainage. In our series, all SMDPs occurred with straight plastic stents. During the study period we switched from placing straight stents with a center bend to straight stents with a duodenal bend with the hypothesis that this would decrease the risk of migration and thereby SMDP. However, our results show that SMDP occurred equally with both type of stents. The use of single or double pigtail stents could be an alternative for straight plastic stents, as they are less traumatic at its distal and/or proximal tip. However, their use for drainage of perihilar strictures is hampered by the lack of pushability to position

the stents adequately across the stricture and therefore single or double pigtail stents were not used for drainage of perihilar strictures our patients. With regard to the diameter of the stents, it could be suggested to place 7 Fr stents instead of 10 Fr stents, as the former are more flexible with possibly less risk of SMDP. In our study, SMDP occurred with both 7 Fr stents and 10 Fr stents, but only three patients had one or multiple 7 Fr stents in situ. Even though stent diameter was not statistically significant at univariate analysis, suggesting that a larger stent diameter does not increase the risk of SMDP, placement of one or multiple smaller diameter stents could still be considered, as type II statistical errors are possible with these low numbers of cases.

The use of self-expandable metal stents (SEMS) could be a promising alternative. So far, uncovered SEMS are widely used but only in patients with an irresectable malignant (hilar) stricture. However, Grünhagen et al. already showed that pre-operative deployment of an uncovered SEMS in patients with resectable hilar CCA is feasible and provides adequate biliary drainage, without the need for re-intervention and without a negative effect on surgery (33). The use of covered SEMS is not recommended in irresectable hilar CCA due to the risk of occlusion of the side braches of the intrahepatic ducts (34). However, covered SEMS are of lower risk for recurrent biliary obstruction due to tumor ingrowth. A review article by Naitoh et al. reported a shorter time to recurrent biliary obstruction with covered SEMS as compared to uncovered SEMS, but with a success rate of 100% for re-intervention when using fully covered SEMS (FCSEMS) (35). And therefore, an interesting alternative for placement of plastic stents in patients with irresectable CCA could be placement of a FCSEMS to drain the left liver lobe and placement of a plastic stent to drain the right liver lobe. Although a few case reports have been published on SMDP after insertion of a SEMS (6,10,15,20,24), in the majority of the cases the migrated stent was a covered SEMS (15,20,24). Prospective studies are needed to investigate the safety and (cost-) effectiveness of use of uncovered SEMS in patients with hilar duct strictures that are potential candidates for surgery.

To our knowledge, this is currently the largest cohort study to report on SMDP and its prevalence rate. Due to our prospectively collected complication registry, and manual review of all (>2400) endoscopy reports and radiological images, no cases of SMDP were missed. Therefore, this study for the first time provides a reliable estimate of the rate of SMDP after biliary plastic stent placement. However, some limitations of our study warrant consideration. First, as this study was a retrospective study, not all potential confounding factors could be accounted for. However, all medical records were screened for predefined items to facilitate a detailed and complete data collection. Second, due to the low number of cases and the number of examined risk factors we might have increased the risk of false-positive results (type I error), and were not able to perform a multivariate analysis. A larger cohort study with more SMDPs cases should be conducted to be able to more reliably test for associations between possible risk factors and the occurrence of SMDP.

In conclusion, this is the first study to report on the prevalence rate of SMDP in patients who undergo ERC. Despite the overall low risk of SMDP, it represents a noteworthy and clinically relevant potentially life-threatening complication of ERC after transpapillary drainage for perihilar biliary strictures. The risk of SMDP in patients referred for this indication needs to be acknowledged. In symptomatic patients after ERC for drainage of

a perihilar stricture clinicians should have a high clinical suspicion for this complication. Future studies should focus on differential means of biliary drainage for perihilar biliary stenosis to prevent the occurrence of SMDP including a more frequent use of metal stents.

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Part IV

Discussion

Chapter 11

Summary, discussion and future perspectives

SUMMARY AND DISCUSSION

This thesis aimed to better define the clinical role of advanced endoscopy in pancreaticobiliary diseases and to offer guidance for improving its outcome in patients suffering from biliary or pancreatic diseases. In the first part of this thesis a general introduction was provided on existing advanced endoscopic techniques (i.e. endoscopic retrograde cholangiopancreaticography (ERCP), endoscopic ultrasound (EUS), and single-operator cholangiopancreatoscopy (SOC)), etiology of and diagnostic approach to acute pancreatitis, treatment of acute pancreatitis and its complications, and complications of biliary stenting. In addition, the aims and outline of this thesis were described. In the second part, the clinical value of a relatively novel endoscopic technique, i.e. SOC, for use in the diagnostic and therapeutic algorithm of pancreaticobiliary diseases, was evaluated. In the third part, we focused on contributing to the body of evidence on existing diagnostic and therapeutic endoscopic interventions in biliary and pancreatic diseases. First, we investigated the role of EUS-guided removal of common bile duct stones by means of ERCP in the treatment of patients with acute biliary pancreatitis. Then, we evaluated the outcome after endoscopic therapy in patients with symptomatic pancreas divisum. Also, the safety and efficacy of a novel tissue resection tool was evaluated in the treatment of acute necrotizing pancreatitis. Finally, the prevalence, clinical course and possible risk factors for stent migration-induced duodenal perforation (SMDP) after biliary stent placement was evaluated. In the present part of the thesis, the main findings and conclusions are summarized and discussed with recommendations for future research.

Cholangiopancreatoscopy

As discussed in the introduction, important technical improvements in SOC were made over the past decades. This resulted in high quality images and better maneuverability, resulting in an increased use of SOC in clinical practice. However, due to its relative novelty, the clinical value of SOC has mainly been investigated in retrospective series. High quality prospective studies or randomized controlled trials are scarce. The ESGE and ASGE have published a technology review, including a short description of the clinical applications (1,2) and only recently a consensus guideline has been published by the Thai Association for Gastrointestinal Endoscopy (TAGE) and the Tokyo Conference of Asian Pancreato-biliary Interventional Endoscopy (T-CAP) (3). Nevertheless, current use of SOC is mainly based on personal preference and experience. Therefore, we aimed to investigate the diagnostic and/or therapeutic clinical value of SOC to better define the role of SOC in clinical practice.

In **Chapter 2**, a European survey compromising 66 questions is described, with the aim to evaluate the current clinical practice patterns of SOC regarding the applied techniques and main indications throughout Europe. This survey was conducted among 369 endoscopists who perform cholangioscopy and/or pancreatoscopy, of whom 86 completed the survey (response rate 23%), from 21 different countries. The results showed that the respondents were highly experienced in ERCP, but experience in cholangioscopy and pancreatoscopy varied greatly. Despite the varying experience in SOC, uniformity was found regarding

the indications for the technique. Cholangioscopy was mainly used for determination of biliary strictures (98.8% of respondents) and removal of bile duct stones (91.9% of respondents). Pancreatoscopy was mainly used for removal of pancreatic duct stones (89.5% of respondents). However, we found interesting differences with regard to how the technique was applied and the timing in clinical practice. Only a minority reported to have an institutional standardized biopsy protocol for targeted SOC-guided tissue sampling in biliary strictures. This is an important finding, as pathological examination still remains the golden standard. In addition, in contrast to what is recommended by guidelines (4-6), SOC with lithotripsy was reported to be used as first-line treatment for bile duct stones without prior conventional removal, i.e. ERCP with endoscopic sphincterotomy (ES) and stone extraction using a balloon or basket, and without prior ESWL for the treatment of pancreatic duct stones. Finally, according to this survey the timing of SOC in the (pre-operative) diagnostic work-up of cholangiocarcinoma (CCA) or intraductal papillary mucinous neoplasms (IPMN) varies greatly. In conclusion, the results of this survey showed consensus on the main indications for SOC, but also considerable variation in its role and timing, emphasizing the need for standardization of indications and technical performance.

Cholangioscopy

The evaluation of indeterminate biliary strictures (i.e. strictures of inconclusive nature after laboratory work-up, abdominal imaging, and ERCP with tissue sampling) is currently the most frequently used biliary indication for SOC and presents a major diagnostic challenge. Traditional diagnostic methods such as ERCP with intraductal biopsies or brush cytology have a low sensitivity for malignant strictures (7). EUS-guided biopsies provide high sensitivity and specificity, but are not preferred as diagnostic modality because of the risk of seeding in the needle tract (8). SOC enables the endoscopist to visually assess the stricture and take targeted biopsies. **Chapter 3** describes an international, multicenter, retrospective cohort study including 44 high quality videos of indeterminate biliary strictures assessed by 19 endoscopists experienced in SOC, with the aim to determine the diagnostic accuracy and interobserver agreement (IOA) for the diagnosis of indeterminate biliary strictures. The assessors were blinded for clinical information. In this study we aimed to include a representative study population, with a high pre-test probability of having CCA. The endoscopists were asked to report on the presence of cholangioscopic features that in the literature are reported to be associated with either benign or malignant pathology and make a visual appraisal regarding the etiology (i.e. benign or malignant) of the stricture. Of note, prior to video assessment no consensus was reached as to the actual appearance of each cholangioscopic feature. Meaning, each endoscopist's appraisal was based on own experience. We found moderate sensitivity (74.2%) and low specificity (46.9%) for the diagnosis of malignant biliary strictures when the endoscopists were blinded to previous clinical information. After unblinding the endoscopists, only the specificity increased significantly (odds ratio (OR) 2.1 (95% CI 1.51-2.86), $p<0.001$), suggesting that benign strictures were easier to detect when clinical information was available. These diagnostic accuracy rates were lower when compared to previous studies (9). This may be due to the fact that in these studies, the assessors were not blinded to the patient's clinical history data and that frequently a non-representative study population was included. When patients with conditions known to present diagnostic difficulty in

differentiating biliary lesions, such as primary sclerosing cholangitis (PSC), stents in situ prior to SOC and hilar strictures, were excluded from analysis, we found comparable results.

The IOA between the endoscopists regarding visual diagnosis (i.e. benign or malignant) was fair for both assessments (i.e. blinded and unblinded) and ranged from slight to moderate for the scored presence of the cholangioscopic features, that is, when no consensus was reached as to the actual appearance of the cholangioscopic features prior to assessment. Sethi et al. however previously showed that even when consensus is reached prior to assessment, the IOA still remains low (10,11). More recently, Kahaleh et al. published an updated classification system with an increased IOA after training the reviewing endoscopists. This new classification system reached an overall diagnostic accuracy of 77%, although again no PSC-cases were included in this study (12). Finally, we found that features that were previously described as being indicative for malignancy were identified in both benign and malignant strictures. This might suggest that features may overlap. In conclusion, this study showed that when cholangioscopic visual assessment is the only tool to diagnose a stricture, it is very difficult to reliably identify malignant strictures, even among very experienced endoscopists. Therefore, the actual diagnostic accuracy may even be lower in general clinical practice. Also, the results suggest that cholangioscopic features that are associated with malignancy should be further defined. Until then, tissue remains the issue and efforts should be made to improve SOC-guided biopsy sampling protocols.

Pancreatoscopy

As discussed previously, treatment of intraductal stones in patients with chronic pancreatitis (CP) is one of the main pancreatic indications for SOC. In addition, the evaluation of intraductal papillary mucinous neoplasms (IPMN) is an upcoming indication for pancreatoscopy.

Pain in CP is multifactorial, caused by inflammation, changes in the peripheral and central nervous system and by increased intraductal pressure caused by stones or strictures. Over the past years, endoscopic therapy has gained an important role in treatment of painful CP and aims at ductal decompression by means of stone or stricture treatment, or inhibition of the afferent pancreatic pain signals. **Chapter 4** provides an overview of the indications, timing, technical aspects and outcome of endoscopic therapy in patients with painful CP. This chapter has been published as a book chapter. Currently, extracorporeal shockwave lithotripsy (ESWL) is recommended as first-line treatment in case of stones >5mm, and surgery should be reserved for patients in whom endoscopic therapy is unsuccessful. Until recently, pancreatoscopy with lithotripsy was only used as second-line therapy in retrospective series, after unsuccessful ESWL, with reported ductal clearance rates ranging between 43-100% (13-15) and clinical success in 74-95% of patients (13,16). Data on technical and clinical success of pancreatoscopy with lithotripsy as first-line treatment, without prior ESWL, were still lacking.

Therefore, in **Chapter 5** we describe a prospective consecutive case series including patients with chronic calcifying pancreatitis, with stones >5mm located in the head

or neck of the pancreas, who underwent pancreatoscopy-guided electrohydraulic lithotripsy (EHL) as first-line treatment, without prior ESWL or surgery. Technical success was achieved in 24 out of 34 included patients (70.6%). Failure of technical success was mainly due to inability to achieve deep cannulation of the pancreatic duct (PD). When deep cannulation was achieved, technical success was 92.3% (n=24/26). Complete stone removal was achieved in 80% of patients after a median of 2 ERCP procedures (range 1-3) and 1 EHL procedure (range 1-2) procedure. In a considerable proportion of patients (n=19) a PD stent was placed at index procedure, to facilitate PD cannulation at the subsequent procedure. In three patients this resulted in stone fragmentation obviating the need for pancreatoscopy. Although our results seem modest compared to previous studies (pooled technical success rate 90.9%; 95% CI [88.3-95.7%] (17)), we believe that the prospective nature of this study provides a more accurate reflection of clinical practice and that these results suggest that pancreatoscopy-guided EHL could be a promising first-line treatment for patients with painful obstructive CP. A two-phase strategy could be considered for logistical considerations and to achieve higher technical success rates. In such strategy, first a stent is placed to achieve ductal access at index procedure followed by pancreatoscopy-guided EHL during the subsequent procedure. In this study, adverse events were encountered in 40% of patients, with post-ERCP pancreatitis (PEP) in 28%, although these were all mild and could be treated conservatively. Compared to ESWL these numbers are higher and may be due to the EHL procedure itself, using a significant amount of devices into the pancreatic duct together with saline solution irrigation. Finally, clinical success, defined as >50% reduction in Izbicki pain score or reduced opiate usage at 6 months follow-up, was achieved in 16/22 patients (72%). Quality of life, measured by the Short-Form Health Survey (SF-12), did not differ significantly at 6-months follow-up as compared to baseline. As CP is a chronic, benign disease, a longer follow-up is required to truly determine the improvement in patient's quality of life, which is ultimately the goal of any therapy. Therefore, we are currently performing a long-term follow-up study of the patients included in this study and will compare outcomes to patients who underwent ESWL as first-line treatment. Whether first-line pancreatoscopy-guided lithotripsy is beneficial compared to first-line ESWL is an important question, but cannot be answered by the results from this study only. Prospective comparative studies are required to directly compare the two techniques and investigate whether the results from this study can be extrapolated to other centers.

In **Chapter 6** a systematic review and meta-analysis is described summarizing the available literature on the technical success, safety, diagnostic yield and clinical utility of pancreatoscopy in the management of IPMN. IPMN may progress to high grade dysplasia or invasive carcinoma and therefore correct diagnosis and determination of the extent of the intraductal lesions is important, to determine the indication and extent of surgery. Current diagnostic modalities, such as CT, MRI, EUS and ERCP with brush cytology perform suboptimal including false positive results leading to patients undergoing unwarranted pancreatic resections.

Our overview demonstrates high overall technical success rates of pancreatoscopy, in 86-100% of patients, with a dilated PD reported as predictive factor for successful cannulation. Diagnostic accuracy rates regarding the visual diagnosis of IPMN seems to be promising,

with reported rates of 87.5-100%. However, results regarding visual predictive factors and diagnostic accuracy of pancreatoscopy-guided targeted biopsies or cytology vary widely. In addition, the clinical impact of preoperative or intraoperative assessment of the intraductal extent of IPMN, which was reported in 11 articles, varied greatly, from affecting only 13% of patients to almost all patients. Limitations of the included studies were a small sample size (<20 patients) in more than half of the studies, the retrospective nature and different diagnostic work-up protocols that were used. Therefore, from this review it remains difficult to determine the exact role of pancreatoscopy in the clinical management of IPMN. Future studies should be aimed at reaching consensus on the actual appearance of the pancreatoscopic features predictive of malignant IPMN, preferably with a high IOA. In addition, as with cholangioscopy, intraductal biopsy protocols should be improved to increase diagnostic accuracy results of pathological examination. Finally, when determining the exact role of pancreatoscopy in the diagnostic work-up of IPMN, risks and benefits should be outweighed, including adverse events and costs. Pancreatoscopy carries a risk of PEP (pooled rate 10%), although mild, and the procedure might be more costly compared to other (radiological) diagnostic tools. However, performing unwarranted surgery carries the risk of surgery-related adverse events and is also costly. Therefore, studies taking the cost-effectiveness into account are eagerly awaited.

Optimization of endoscopic strategies in biliary and pancreatic diseases

The final section of this thesis focuses on current endoscopic treatment strategies in pancreaticobiliary diseases. Over the past years the role of endoscopy in the diagnostic and therapeutic algorithm of acute pancreatitis has gained an important role. Therefore, in the third part of this thesis we aimed to contribute to the existing body of evidence by investigating both currently used and novel techniques, used for diagnosis and treatment of acute pancreatitis. In addition, a rare but potentially life-threatening complication of biliary stenting, a very frequently used procedure in daily practice, was investigated.

Acute pancreatitis

Presented in **Chapter 7** is a prospective multicentre cohort study that investigated the value of an urgent EUS-guided ERCP with endoscopic sphincterotomy (ES) in patients with a predicted severe acute biliary pancreatitis without cholangitis. In patients with predicted severe acute biliary pancreatitis with cholangitis the guidelines recommend to perform an urgent ERCP with ES. In patients with a predicted mild disease course, a conservative treatment is recommended (18-20). The previous APEC-trial, a randomized controlled trial including 232 patients, investigated whether an urgent ERCP with ES would reduce major complications and/or mortality in patients with predicted severe acute biliary pancreatitis without cholangitis, compared to a conservative treatment (21). No difference was found between the two treatment strategies, therefore supporting a conservative treatment. As discussed before, EUS would be a more reliable tool to detect stones or sludge. Therefore, the hypothesis of the current study was that urgent EUS-guided ERCP with ES could reduce major complications and/or mortality in a selected group of patients with predicted severe acute biliary pancreatitis without cholangitis and confirmed CBD stones or sludge. The outcomes were compared to the conservative

treatment group of the APEC-trial. Analysis showed that there was no significant difference in the primary composite endpoint of major complications and mortality: 34/83 (41%) and 50/113 (44%) (RR 0.93, 95%CI 0.67-1.29, p=0.65), respectively. Early EUS-guided ERCP with ES was only favourable with regard to readmissions due to biliary events (i.e. recurrent biliary pancreatitis and symptomatic choledocholithiasis) and hospital stay. In the early EUS-group stones were found in 58% of patients of whom 90% successfully underwent urgent EUS-guided ERCP with ES, after a median of 21 hours (range 17-23) after hospital admission. Further decreasing the interval does not seem realistic. Five patients with a negative initial EUS underwent an ERCP at a later stage. Three patients underwent an ERCP due to progressive cholestasis, where CBD stones were found and removed during the procedure. In the fourth patient an ERC was performed due to cholangitis caused by a CBD stenosis due to pancreatitis. The final patient underwent an ERCP for biliary stent placement to overcome biliary leakage secondary to a liver abscess. Although EUS can reliably detect stones or sludge in the CBD, thereby selecting the right patients who potentially could benefit from early stone removal and decompression, we concluded that based on the study results a conservative treatment strategy should be adapted in patients with a predicted severe acute biliary pancreatitis without cholangitis. ERCP with ES is only recommended in case of concomitant cholangitis (urgently performed) or in case of persistent choledocholithiasis (electively performed).

Another, however rare, cause of acute pancreatitis is pancreas divisum, an anatomical anomaly resulting in failure of fusion of the ventral and dorsal pancreatic ducts. Due to its low incidence, there is limited data on the clinical success of endoscopic therapy in this subgroup of patients. Therefore, **Chapter 8** describes a multicentre, retrospective cohort study including patients that underwent endoscopic therapy, i.e. minor papilla sphincterotomy or dorsal duct stent placement, for symptomatic pancreas divisum (PDiv). Symptomatic PDiv was classified according to the clinical type of presentation: 1) recurrent acute pancreatitis (RAP), 2) CP, defined according to the M-ANNHEIM classification, and 3) chronic abdominal pain (CAP), defined as pancreas-type pain, without a biochemically or radiologically confirmed diagnosis of acute of chronic pancreatitis. In total, 81 patients were included, with moderate initial successful cannulation (74%), resulting in repeated ERCP procedures (median 2 procedures (range 1-4)), with subsequent risk of PEP. Clinical success, defined as no relapse episodes of RAP or CP, or absence of CAP, at 3 months follow-up, was achieved in approximately half of the patients (42.6%), with highest success rates for RAP patients (44%), compared to 33% for both CP and CAP patients. Sustained clinical success after 12 months was highest for RAP patients (46%). In addition, for the subgroup of RAP patients that did experience relapse episodes after endoscopic therapy, the number of episodes per year decreased significantly from 3.5 to 1.13, with a significantly increased interval between consecutive episodes. Adverse events occurred in 32% of patients, with PEP being most frequently diagnosed in 22%.

In our study, clinical success rates are lower as compared to previous reports, which may be due to strict inclusion criteria and definitions of study outcomes: previous reports mainly included subjective patient-reported outcomes. Only a small number of patients with CP and CAP were included in our study, making it difficult to determine the effect of endoscopic therapy in these subgroups of patients. Based on the results of this study it seems that RAP patients benefit most from endoscopic therapy; however the risk of

PEP, which is not negligible, should be outweighed against the possible advantages. In addition, it could be argued whether it is worthwhile to perform endoscopic therapy early in the disease course to prevent progression to CP. In the current cohort, 20% (9 patients) of RAP patients progressed to CP, of whom only 2 had initial clinical successful endoscopic treatment.

In the majority of patients with acute pancreatitis the disease will have a mild course with rapid favourable recovery. However, approximately 20% of patients with acute pancreatitis will develop acute necrotizing pancreatitis (ANP), with necrosis of the pancreatic parenchyma and/or peripancreatic tissue. About 30% of patients with ANP will develop infected necrosis, which is associated with high mortality rates between 15% and 30% (22-24). Treatment of infected necrosis is therefore virtually always necessary. A dedicated, effective tool for endoscopic removal of pancreatic necrosis is currently lacking. In **Chapter 9**, we evaluated a novel resection tool, the EndoRotor® PED™ system, designed for endoscopic resection of necrotic tissue. A previous study including 12 patients showed that the tool was safe and effective in removing pancreatic necrosis in this patient group, requiring less procedures than previously reported regarding the use of conventional techniques (25). We found in the present study that a median of 1.5 procedures (range 1-3) was required to completely remove the necrotic tissue, with the majority of patients requiring less than 2 procedures. This is lower as compared to what has been reported on conventional accessories, such as baskets or biopsy forceps (median of 4 (range 1-7)) (26). Overall, a 91% reduction in percentage necrosis in the collection was achieved and an 85% reduction in collection volume. Only in one patient additional conventional instruments were used to remove the necrotic tissue due to a thick and sticky consistency of the debris. Adverse events were encountered in 33% of patients; 9 serious adverse events (SAEs) and 11 non-SAEs. The most important outcome of this study is that no device-related SAEs occurred and use of the device seems safe, similar to the previous study. Of the nine SAEs, three SAEs were adjudicated by the data safety monitoring board as 'possibly' related to the necrosectomy procedure. In two patients a bleeding occurred, one and four days post-procedure, respectively. In both patients endoscopic evaluation showed bleeding from the gastric or collection wall, caused by abrasion of the flange of the metal stent to the wall, which was placed to create a fistula for transluminal drainage. In the third patient, a pneumoperitoneum occurred, caused by the endoscope being torqued within the metal stent that allowed for extravasation of free air into the peritoneal cavity. Another important outcome of this study is that the application of the system seems feasible for its intended use, that is removal of infected necrosis. However, this study lacked a comparative group, impeding direct comparison to conventional tools. Currently, an international, multicenter randomized controlled trial is being conducted comparing conventional tools alone versus the EndoRotor® PED™ system plus conventional tools if needed. The aim is to investigate the clinical value of the EndoRotor® PED™ system in the debridement of necrotic tissue. A cost-effectiveness analysis is included in this trial.

Duodenal perforation after biliary stenting

As endoscopy in pancreaticobiliary diseases has gained an important role for diagnostic and therapeutic purposes, knowledge regarding frequently encountered procedure-related adverse events is important. Post-ERCP pancreatitis, bleeding and perforation are among

the most frequently occurring adverse events (27). As procedures become more complex since more complex conditions are being treated, such as hilar cholangiocarcinoma, awareness of other rare and potentially life-threatening complications is required for timely recognition and adequate treatment. **Chapter 10** demonstrates the results of a retrospective cohort study investigating the prevalence rate, risk factors and clinical outcome of patients with stent migration-induced duodenal perforation (SMDP). Thirteen patients with an SMDP were identified from our endoscopy registry over a period of four years. This correlates with a prevalence of 2.1% for patients undergoing an ERCP with biliary plastic stent placement and 4.3% for patients with plastic stent placement for a perihilar stricture. All SMDPs occurred in patients with a perihilar stricture. The majority of symptomatic patients presented within 14 days after stent placement and could be treated either conservatively or with an Over-The-Scope-Clip. Still one third of patients died due to ongoing abdominal sepsis, despite repeated interventions and initial successful closure of the perforation. Potential risk factors included longer stents and stents placed in the left intrahepatic duct. However, due to the small number of cases and subsequent risk for overfitting, these results should be interpreted with caution. Larger cohort studies including more cases are needed to more reliably identify possible risk factors. We concluded that SMDP is an important complication to recognize and propose to include the risk of SMDP in the informed consent procedure for patients undergoing ERCP with plastic stent placement for perihilar strictures, since the risk of SMDP in this subgroup of patients in this study is of the same magnitude as the risk of PEP or bleeding (27).

CONCLUSIONS AND FUTURE PERSPECTIVES

In this thesis, we focused on different aspects of advanced pancreaticobiliary endoscopy, including currently existing and novel techniques, with the aim to improve diagnosis and treatment of patients suffering from biliary or pancreatic diseases. As mentioned in the introduction, over the past decades endoscopy has gained an important role in diagnosis and treatment of pancreaticobiliary diseases. However, compared to other fields of gastrointestinal endoscopy, pancreaticobiliary endoscopy is relatively new. Until recently we relied on radiological visualization of ductal structures and surgery was the primary treatment modality. It is only since the introduction of SOC that we are now able to visualize intraductal structures. Studies have shown promising results regarding the visual diagnosis of CCA and malignant IPMN and have tried to identify features that are predictive of malignancy. However, we and others have shown that there still is great interobserver variation, even among endoscopists experienced in SOC, and that features of benign and malignant disease may overlap. In order to improve the clinical value of SOC it is important to overcome this variation and to reach an international consensus on the appearance of the features and the subsequent predictive value for malignant or benign disease. Until a valid classification system is established, tissue remains the issue, and studies should be conducted optimizing the tissue acquisition protocol for SOC-guided targeted biopsies. Previous studies have shown that taking multiple biopsies increases the sensitivity rate for detecting malignancy (28,29). In addition, the bite-on-bite technique for tissue sampling, where a second biopsy bite is taken directly on top of the first biopsy bite, might be of added value for pancreaticobiliary lesions. Due to the small diameter of the ductal lumen and biopsy forceps, obtaining adequate tissue

samples for pathological examination remains challenging. Studies should be conducted investigating the optimal biopsy protocol, including the optimal number of biopsy bites and/or bite-on-bite biopsies.

In the future, artificial intelligence (AI) might be of added value. In other fields of gastrointestinal endoscopy, such as colonoscopy, AI has already shown its value. There might also be a role for AI in pancreaticobiliary endoscopy. Even though research regarding AI in pancreaticobiliary diseases is still scarce, some studies indicate a good diagnostic accuracy (30). With regard to biliary strictures, Saraiva et al. recently published a pilot study reporting an overall accuracy of 95%, with a sensitivity of 95% and a specificity of 92% of AI in identifying malignant strictures (31). However, we would need very large, standardized, databases of cholangioscopic and pancreatoscopic images with a definite pathological diagnosis to sufficiently train and validate AI. To achieve this, international collaboration between endoscopists is required, together with collaborations with scientists and engineers.

With regard to therapeutic indications of SOC, in particular SOC-guided lithotripsy, data presented in this thesis illustrate that SOC-guided lithotripsy using EHL holds promise as first-line treatment of pancreatic duct stones. Treatment of bile duct stones is not covered in this thesis. As an alternative to using EHL, SOC-guided lithotripsy can be performed with laser lithotripsy. High-quality studies directly comparing clinical outcomes using these two modalities are awaited. An advantage of SOC-guided lithotripsy might be the ability to simultaneously treat strictures and that the endoscopist is in full control of the treatment and not dependent on ESWL facility, enhancing a more wide spread availability. We believe that SOC performance is best carried out in high-volume expert centers as it is a technically challenging procedure requiring expertise of the performing endoscopist.

Finally, we have shed new light on the clinical value of advanced pancreaticobiliary endoscopy in the treatment of acute pancreatitis. As acute pancreatitis is one of the main indications for pancreaticobiliary endoscopy, it is an important field of research with continuous developments. This thesis contributes to the optimization of endoscopic treatment in patients with acute pancreatitis and promising data are presented regarding a novel tool for resection of pancreatic necrosis. Although multicenter, most data are based on small sample sizes and results should be validated in larger, prospective, comparative randomized controlled trials. As continuous improvements are made and innovations developed, it is possible to treat more complex patients endoscopically. However, this also leads to occurrence of seemingly rare complications, as highlighted in this thesis. Therefore, these patients should preferably be treated in a multidisciplinary setting, including endoscopists, radiologists and surgeons, selecting the right patient for endoscopic treatment.

The results of this thesis provide new insight in the clinical value of SOC, a relatively new endoscopic modality, and aids to the existing body of evidence regarding endoscopic treatment of pancreaticobiliary diseases, in particular acute pancreatitis. It addressed scientific gaps for future research, with the aim to further improve diagnosis and treatment for patients with pancreaticobiliary diseases.

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Chapter 12

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING EN DISCUSSIE

Dit proefschrift heeft tot doel de klinische rol van geavanceerde endoscopie bij pancreaticobiliaire ziekten beter te definiëren en handvatten te bieden voor het verbeteren van de uitkomst ervan bij patiënten die lijden aan ziekten van de galwegen of pancreas. In het eerste deel van dit proefschrift wordt een algemene introductie gegeven over de huidige geavanceerde endoscopische technieken (d.w.z. Endoscopische Retrograde Cholangiopancreatografie (ERCP), endo-echografie (EUS), single-operator cholangiopancreaticoscopie (SOC)), de etiologie en diagnostiek van acute pancreatitis, de behandeling van acute pancreatitis en de daarmee geassocieerde complicaties, en complicaties die gerelateerd zijn aan biliaire stent plaatsing. Daarnaast zijn de doelen en opzet van dit proefschrift beschreven. In het tweede deel is de klinische waarde geëvalueerd van een relatief nieuwe endoscopische techniek, cholangiopancreaticoscopie, voor gebruik in het diagnostische en therapeutische algoritme van pancreaticobiliaire ziekten. In het laatste en derde deel van dit proefschrift hebben we ons gericht op het bijdragen aan de huidige literatuur over reeds bestaande diagnostische en therapeutische endoscopische interventies voor aandoeningen van galwegen en pancreas. Ten eerste is de rol van EUS-geleide vroege verwijdering van galstenen uit de ductus choledochus middels ERCP onderzocht, voor de behandeling van patiënten met acute biliaire pancreatitis. Ook is het klinische succes onderzocht van endoscopische therapie bij patiënten met een symptomatische pancreas divisum, en is de veiligheid en effectiviteit geëvalueerd van een nieuw instrument voor weefselresectie voor de behandeling van acute necrotiserende pancreatitis. Ten slotte zijn de prevalentie, het klinische beloop en mogelijke risicofactoren geëvalueerd voor door stentmigratie geïnduceerde duodenumperforatie (SMDP), na plaatsing van een biliaire stent.

Cholangiopancreatoscopie

Zoals reeds besproken in de introductie zijn er de afgelopen decennia belangrijke technische verbeteringen in SOC doorgevoerd. Dit heeft geresulteerd in een betere manoeuvreerbaarheid en beelden van hoge kwaliteit, wat heeft geleid tot een toename in het gebruik van SOC in de klinische praktijk. Gezien SOC een relatief nieuwe endoscopische techniek is, is de klinische waarde voornamelijk onderzocht in retrospectieve series. Prospectieve studies van hoge kwaliteit of gerandomiseerde studies zijn schaars. De ESGE en ASGE hebben een review gepubliceerd ten aanzien van de techniek, waarin ook kort de klinische toepassingen zijn beschreven (1,2). Zeer recentelijk is er een consensus richtlijn gepubliceerd door de Thai Association for Gastrointestinal Endoscopy (TAGE) and the Tokyo Conference of Asian Pancreato-biliary Interventional Endoscopy (T-CAP) (3). Desalniettemin is het huidige gebruik van SOC voornamelijk gebaseerd op persoonlijke voorkeur en ervaring. Om die reden wilden we de diagnostische en/of therapeutische waarde van SOC verder onderzoeken om de rol van SOC in de klinische praktijk beter te definiëren.

In **Hoofdstuk 2** is een Europese survey beschreven, bestaande uit 66 vragen, met als doel het gebruik van SOC in de huidige klinische praktijk in Europa te evalueren, met betrekking

tot de toegepaste technieken en meest gebruikte indicaties. De survey werd gehouden onder 369 endoscopisten die cholangioscopie en/of pancreatoscopie verrichten, van wie 86 de survey hebben afgerond (responspercentage 23%), uit 21 verschillende landen. De resultaten toonden aan dat de respondenten veel ervaring hadden in ERCP, maar zeer wisselende ervaring in cholangioscopie en pancreatoscopie. Ondanks de wisselende ervaring in SOC, was er uniformiteit in de meest gebruikte indicaties. Cholangioscopie werd voornamelijk gebruikt voor het determineren van galwegstricturen (98.8% van de respondenten) en het verwijderen van galstenen (91.9% van de respondenten). Pancreatoscopie werd voornamelijk gebruikt voor het verwijderen van pancreasstenen (89.5% van de respondenten). Interessante verschillen werden echter gevonden in de toepassing van de techniek en de timing in de klinische praktijk. Slechts een minderheid meldde een gestandaardiseerd biopsieprotocol te hebben voor het nemen van gerichte, SOC-geleide biopten van biliaire stricturen. Dit is een belangrijke bevinding, aangezien pathologisch onderzoek nog steeds de gouden standaard is. Bovendien, in tegenstelling tot wat wordt aanbevolen door richtlijnen (4-6), werd gerapporteerd dat SOC met lithotripsie werd gebruikt als eerstelijnsbehandeling zonder voorafgaande conventionele verwijdering van galstenen, d.w.z. ERCP met sfincterotomie en steen extractie middels een ballon of basket, en zonder voorafgaande ESWL voor de behandeling van pancreasstenen. Ten slotte liet deze survey zien dat de timing van SOC in de (preoperatieve) diagnostische work-up van cholangiocarcinoom (CCA) of intraductale papillaire mucineuze neoplasmata (IPMN) sterk varieert. Concluderend lieten de resultaten een consensus zien ten aanzien van de belangrijkste indicaties voor SOC, maar ook aanzienlijke variatie in de rol en timing ervan, wat de noodzaak benadrukt voor het standaardiseren van indicatie en technisch gebruik.

Cholangioscopie

De evaluatie van biliaire stricturen van onduidelijke aard (d.w.z. op basis van laboratorium onderzoek, beeldvorming en ERCP met weefsel onderzoek) is op dit moment de meest voorkomende indicatie voor SOC en vormt een grote diagnostische uitdaging. Traditionele diagnostische methodes zoals ERCP met intraductale biopten of brush cytologie hebben een lage sensitiviteit voor het detecteren van maligne stricturen (7). EUS-geleide biopten hebben een hogere sensitiviteit en specificiteit, maar hebben niet de voorkeur als diagnostische modaliteit vanwege het risico op verspreiding van maligne cellen over het naald traject (8). Door middel van SOC kan de endoscopist intraductale structuren nu visueel beoordelen en gerichte biopten nemen. **Hoofdstuk 3** beschrijft een internationale, multicenter, retrospectieve cohort studie waarin 44 hoge kwaliteit video's van biliaire stricturen van onduidelijke aard zijn beoordeeld door 19 endoscopisten met ervaring in SOC, met het doel de diagnostische waarde en de interbeoordelaar overeenstemming (interobserver agreement – IOA) van SOC te bepalen voor het diagnosticeren van biliaire stricturen. Hierbij werden de beoordelaren geblindeerd voor alle klinische informatie. In deze studie wilden we een representatieve studie populatie includeren, met een hoge vooraf kans op het hebben van CCA. De endoscopisten werden gevraagd om de aanwezigheid van cholangioscopische kenmerken te scoren, welke in de literatuur zijn beschreven als geassocieerd met benigne of maligne pathologie, en om hun oordeel te geven over de etiologie van de strictuur (d.w.z. benigne of maligne) op basis van de visuele beoordeling. Ter verduidelijking, voorafgaand aan de

video beoordelingen werd geen consensus bereikt over de daadwerkelijke uiterlijke verschijnsvorm van elk cholangioscopisch kenmerk. Dat betekent dat de beoordeling van elke endoscopist over de aanwezigheid van de verschillende cholangioscopische kenmerken gebaseerd was op eigen ervaring. Er werden een matige sensitiviteit (74.2%) en een lage specificiteit (46.9%) gevonden voor het diagnosticeren van maligne galwegstricturen, wanneer de endoscopisten geblindeerd waren voor eerdere klinische informatie. Na het deblinderen van de endoscopisten, verbeterde alleen de specificiteit significant (odds ratio (OR) 2.1 (95% CI 1.51-2.86), p<0.001), suggererende dat benigne stricturen beter te identificeren zijn wanneer de klinische informatie beschikbaar is. Deze diagnostische waarden zijn lager dan wat in de literatuur is gerapporteerd (9). Dit kan te maken hebben met het feit dat beoordelaren in eerdere studies niet geblindeerd waren voor de klinische voorgeschiedenis van de patiënt en dat er vaak een niet-representatieve onderzoekspopulatie werd geïncludeerd. Wanneer patiënten uit de analyse werden geëxcludeerd met aandoeningen die een bekende diagnostische uitdaging vormen bij het differentiëren van biliaire laesies, zoals primaire scleroserende cholangitis (PSC), stents in situ voorafgaand aan SOC of hilaire stricturen, werden vergelijkbare resultaten gevonden.

De IOA tussen de endoscopisten voor de visuele diagnose (d.w.z. benigne of maligne) was matig voor beide beoordelingen (d.w.z. geblindeerd en ongeblindeerd) en varieerde van gering tot redelijk voor de gescoorde aanwezigheid van de cholangioscopische kenmerken, wanneer er voorafgaand aan de beoordelingen geen consensus was over de daadwerkelijke uiterlijke verschijningsvorm van de verschillende cholangioscopische kenmerken. Echter, Sethi et al. toonde eerder aan dat zelfs wanneer er wel consensus werd bereikt voorafgaand aan de beoordeling, de IOA nog steeds laag was (10,11). Meer recentelijk heeft Kahaleh et al. een hernieuwd classificatiesysteem gepubliceerd waarbij de IOA verbeterde na training van de beoordelende endoscopisten. Dit nieuwe classificatiesysteem bereikte een overall diagnostische accuratesse van 77%, hoewel er ook in deze studie geen patiënten met PSC waren geïncludeerd (12). Ten slotte vonden we dat kenmerken die in de literatuur eerder werden beschreven als indicatief voor een maligniteit, in onze studie werden geïdentificeerd in zowel benigne als maligne stricturen. Dit kan erop wijzen dat kenmerken kunnen overlappen tussen benigne en maligne stricturen. Concluderend toonde deze studie aan dat wanneer de visuele beoordeling op basis van cholangioscopie het enige middel is om een strictuur te diagnosticeren, het erg moeilijk is om op betrouwbare wijze maligne stricturen te identificeren, zelfs door zeer ervaren endoscopisten. Derhalve kan de werkelijke diagnostische waarde zelfs lager zijn in de algemene klinische praktijk. De resultaten suggereren ook dat de cholangioscopische kenmerken die geassocieerd zijn met een maligniteit beter moeten worden gedefinieerd. Tot die tijd blijft pathologie de gouden standaard en moet het protocol voor SOC-geleide biopsie verbeterd worden.

Pancreatoscopie

Zoals eerder besproken, is de behandeling van intraductale stenen bij patiënten met chronische pancreatitis (CP) een van de belangrijkste indicaties voor pancreatoscopie. Daarnaast is de evaluatie van IPMN een opkomende indicatie voor pancreatoscopie.

Pijn bij CP is multifactorieel en wordt veroorzaakt door ontsteking, veranderingen in het perifere en centrale zenuwstelsel en door verhoogde intraductale druk veroorzaakt door stenen of stricturen. Endoscopische therapie heeft de afgelopen jaren een prominente rol gekregen bij de behandeling van pijn in het kader van CP en is gericht op ductale decompressie door middel van steen- of strictuurbehandeling, of remming van de afferente pijnsignalen van de pancreas. **Hoofdstuk 4** geeft een overzicht van de indicaties, timing, technische aspecten en uitkomst van endoscopische therapie bij patiënten met pijn bij CP. Dit hoofdstuk is als boekhoofdstuk verschenen. Op dit moment wordt extracorporele schokgolf lithotripsie (ESWL) aanbevolen als eerstelijnsbehandeling in geval van stenen groter dan 5 mm, en wordt geadviseerd een operatie te reserveren voor patiënten bij wie endoscopische therapie niet succesvol is. Tot voor kort werd pancreatoscopie met lithotripsie alleen gebruikt als tweedelijnstherapie in retrospectieve series, na onsuccesvolle ESWL, met gerapporteerde volledige verwijdering van de stenen in 43-100% van de patiënten (13-15) en klinisch succes bij 74-95% (13,16). Data over technisch en klinisch succes van pancreatoscopie met lithotripsie als eerstelijnsbehandeling, zonder voorafgaande ESWL, ontbreken echter nog.

Derhalve werd een prospectieve cohort studie verricht, beschreven in **Hoofdstuk 5**, van patiënten met chronische calcificerende pancreatitis, met stenen van groter dan 5 mm in de kop of hals van de pancreas, die pancreatoscopie-geleide elektrohydraulische lithotripsie (EHL) als eerstelijnsbehandeling ondergingen, zonder voorafgaande ESWL of operatie. Technisch succes werd behaald bij 24 van de 34 geïncludeerde patiënten (70.6%). Het falen van technisch succes kwam voornamelijk door het onvermogen om diepe canulatie van de ductus pancreaticus (PD) te verkrijgen. Wanneer wel diepe canulatie werd bereikt, was het technische succes 92.3% (n=24/26). Volledige steenverwijdering werd bereikt bij 80% van de patiënten na een mediaan van 2 ERCP-procedures (range 1-3) en 1 EHL-procedure (range 1-2) procedure. Bij een aanzienlijk deel van de patiënten (n=19) werd bij de index procedure een PD-stent geplaatst om de PD-canulatie bij de daaropvolgende procedure te vergemakkelijken. Bij drie patiënten resulteerde dit in steenfragmentatie, waardoor pancreatoscopie niet nodig was. Hoewel onze resultaten slechter lijken in vergelijking met eerdere studies (gepoold technisch succes 90.9%; 95% CI [88,3-95,7%] (17)), zijn wij van mening dat het prospectieve karakter van deze studie een betere weerspiegeling geeft van de klinische praktijk en dat deze resultaten suggereren dat pancreatoscopie-geleide EHL een veelbelovende eerstelijnsbehandeling zou kunnen zijn voor patiënten met pijn bij chronische calcificerende pancreatitis. Om logistieke redenen en om een hoger technisch succes te behalen, kan een tweefasen-strategie worden overwogen. In een dergelijke strategie wordt eerst een stent geplaatst om ductale toegang te verkrijgen bij de index procedure, gevolgd door pancreatoscopie-geleide EHL tijdens de daaropvolgende procedure. In deze studie traden complicaties op bij 40% van de patiënten, waarvan post-ERCP pancreatitis (PEP) bij 28% van de patiënten, welke echter alle mild verliepen en conservatief konden worden behandeld. Vergeleken met ESWL zijn deze aantallen hoger hetgeen te maken kan hebben met de EHL-procedure zelf, waarbij een significant aantal instrumenten in de PD wordt geïntroduceerd en waarbij tegelijk geflushed wordt met zoutoplossing.

Ten slotte werd klinisch succes bereikt in 16/22 patiënten (72%), gedefinieerd als >50% vermindering van de Izbicki-pijnscore of verminderd opiaatgebruik na 6 maanden follow-up. De kwaliteit van leven, gemeten door middel van de Short-Form Health Survey (SF-12), verschilde niet significant na 6 maanden follow-up ten opzichte van baseline. Aangezien CP een chronische, goedaardige ziekte is, is een langere follow-up nodig om de verbetering in kwaliteit van leven van de patiënt goed te kunnen bepalen, wat uiteindelijk het doel van elke therapie is. Om die reden loopt er momenteel een lange-termijn follow-up studie van de patiënten die in de huidige studie zijn geïncludeerd. Hierin zullen deze uitkomsten worden vergeleken met de lange-termijn uitkomsten van patiënten die een eerstelijnsbehandeling met ESWL hebben ondergaan. Of eerstelijns pancreatoscopie-geleide lithotripsie gunstig is in vergelijking met eerstelijns ESWL is een relevante vraag, maar kan niet alleen worden beantwoord met de resultaten van deze studie. Prospectief vergelijkend onderzoek is nodig om de twee technieken direct te kunnen vergelijken en om te onderzoeken of de resultaten van deze studie geëxtrapoleerd kunnen worden naar andere centra.

In **Hoofdstuk 6** wordt een systematische review en meta-analyse beschreven waarin de beschikbare literatuur wordt samengevat over het technische succes, de veiligheid, de diagnostische waarde en de klinische toegevoegde waarde van pancreatoscopie bij de diagnostiek en behandeling van IPMN. IPMN heeft het risico zich te ontwikkelen tot hooggradige dysplasie of invasief carcinoom. Daarom is een correcte diagnose en bepaling van de intraductale extensie van de laesie van belang om de juiste indicatie en uitgebreidheid van de operatie te kunnen bepalen. Huidige diagnostische modaliteiten, zoals CT, MRI, EUS en ERCP met brush cytologie, presteren suboptimaal, inclusief fout-positieve resultaten, wat ertoe leidt dat patiënten onnodige pancreasresecties ondergaan.

Ons overzicht toont een hoog overall technisch succespercentage van pancreatoscopie, in 86-100% van de patiënten, waarbij een verwijde PD als voorspellende factor voor succesvolle canulatie wordt gerapporteerd. De diagnostische waarde van de visuele diagnose van IPMN op basis van het beeld lijkt veelbelovend, met gerapporteerde percentages van 87.5-100%. Echter, resultaten met betrekking tot visuele voorspellende kenmerken en de diagnostische waarde van gerichte biopten of cytologie middels pancreatoscopie lopen sterk uiteen. De klinische impact van preoperatieve of intraoperatieve beoordeling van de intraductale uitbreiding van IPMN werd gerapporteerd in 11 artikelen, en resultaten varieerden sterk. Hierbij werd gerapporteerd dat bevindingen invloed hadden op het beleid, wisselend van in 13% van de patiënten tot bijna alle patiënten. Beperkingen van de geïncludeerde studies waren een kleine studie populatie (<20 patiënten) in meer dan de helft van de studies, het veelal retrospectieve karakter en de verschillende diagnostische protocollen die werden gebruikt. Daarom blijft het op basis van dit review moeilijk om de exacte rol van pancreatoscopie in de klinische praktijk rondom IPMN te bepalen. Toekomstige studies moeten gericht zijn op het bereiken van consensus over de daadwerkelijke uiterlijke verschijningsvorm van de pancreatoscopische kenmerken die voorspellend zijn voor maligne IPMN, bij voorkeur met een hoge IOA. Bovendien moeten, net als bij cholangioscopie, de protocollen voor intraductale biopsie worden verbeterd om de diagnostische waarde van pathologisch onderzoek te verbeteren. Ten slotte, bij het bepalen van de exacte rol van pancreatoscopie in de diagnostische work-up van IPMN,

moeten de risico's en voordelen worden afgewogen, inclusief bijwerkingen en kosten. Pancreatoscopie brengt een risico met zich mee van PEP (gepoold percentage 10%), hoewel mild, en de procedure kan duurder zijn in vergelijking met andere (radiologische) diagnostische middelen. Het uitvoeren van (onnodige) operaties brengt echter het risico met zich mee van operatie-gerelateerde complicaties en is ook kostbaar. Er wordt dan ook uitgekeken naar studies die rekening houden met de kosteneffectiviteit.

Optimalisatie van endoscopische strategieën voor ziekten van galwegen en pancreas

Het laatste deel van dit proefschrift richt zich op de huidige endoscopische behandelstrategieën bij pancreaticobiliaire ziekten. In de afgelopen jaren heeft de rol van endoscopie in het diagnostische en therapeutische algoritme van acute pancreatitis een belangrijke rol ingenomen. Het derde deel van dit proefschrift beoogt bij te dragen aan de huidige literatuur door zowel bestaande als nieuwe technieken te onderzoeken die worden gebruikt voor diagnostiek en behandeling van acute pancreatitis. Daarnaast werd een zeldzame maar potentieel levensbedreigende complicatie van biliaire stentplaatsing, een veel gebruikte interventie in de dagelijkse praktijk, onderzocht.

Acute pancreatitis

In **Hoofdstuk 7** wordt een prospectieve multicenter cohort studie beschreven die de waarde onderzocht van een vroege EUS-geleide ERCP met endoscopische sfincterotomie (ES) bij patiënten met een voorspeld ernstige acute biliaire pancreatitis, zonder cholangitis. Bij patiënten met voorspeld ernstige acute biliaire pancreatitis met cholangitis raden de richtlijnen aan om een vroege ERCP met ES te verrichten. Bij patiënten met een voorspeld mild ziektebeloop wordt een conservatieve behandeling aanbevolen (18-20). De eerder uitgevoerde APEC-studie, een gerandomiseerde studie met 232 patiënten, onderzocht of een vroege ERCP met ES ernstige complicaties en/of mortaliteit zou verminderen bij patiënten met voorspeld ernstige acute biliaire pancreatitis zonder cholangitis, in vergelijking met een conservatieve behandeling (21). Er werd geen verschil gevonden tussen de twee behandelstrategieën, wat een conservatieve behandeling ondersteunt. Zoals eerder besproken, zou EUS een betrouwbaardere modaliteit zijn om stenen of sludge te detecteren. De hypothese van de huidige studie was dat een vroege EUS-geleide ERCP met ES ernstige complicaties en/of mortaliteit zou kunnen verminderen bij een geselecteerde groep van patiënten met een voorspeld ernstige acute biliaire pancreatitis zonder cholangitis, met middels EUS bevestigde stenen of sludge in de CBD. De uitkomsten zijn vergeleken met de conservatieve behandelgroep van de APEC-trial. Analyse toonde dat er geen significant verschil was in het primaire samengestelde eindpunt van ernstige complicaties en mortaliteit: 34/83 (41%) en 50/113 (44%) (RR 0.93, 95%CI 0.67-1.29, p=0.65), respectievelijk. Wel toonde de vroege EUS-groep gunstigere resultaten ten aanzien van heropnames als gevolg van biliaire events (d.w.z. recidiverende biliaire pancreatitis en symptomatische choledocholithiasis) en duur van de ziekenhuisopname. In de vroege EUS-groep werden stenen gevonden bij 58% van de patiënten van wie 90% met succes een vroege EUS-geleide ERCP onderging, na een mediaan van 21 uur (range 17-23) na ziekenhuisopname. Verdere verkorting van dit interval

lijkt niet realistisch. Vijf patiënten met een negatieve initiële EUS ondergingen in een later stadium een ERCP. Drie patiënten daarvan ondergingen een ERCP vanwege progressieve cholestase, waarbij tijdens de procedure CBD-stenen werden gevonden en verwijderd. Bij de vierde patiënt werd een ERCP uitgevoerd vanwege cholangitis veroorzaakt door een CBD-stenose als gevolg van de pancreatitis. De laatste patiënt onderging een ERCP voor plaatsing van een biliaire stent ter behandeling van gallekkage secundair aan een leverabces. We concludeerden dat EUS betrouwbaar is voor het detecteren van stenen of sludge in de CBD, waardoor de juiste patiënten geselecteerd kunnen worden die mogelijk baat hebben bij vroege steenverwijdering en decompressie. Echter, op basis van de onderzoeksresultaten moet een conservatieve behandelingsstrategie worden toegepast bij patiënten met een voorspeld ernstige acute biliaire pancreatitis zonder cholangitis. ERCP met ES wordt alleen aanbevolen bij gelijktijdige cholangitis (als spoedingreep) of bij persisterende choledocholithiasis (als electieve ingreep).

Een andere, hoewel zeldzame, oorzaak van acute pancreatitis is pancreas divisum, een anatomische anomalie die resulteert in het falen van de fusie van de ventrale en dorsale PD. Vanwege de lage incidentie zijn er beperkte data over het klinische succes van endoscopische therapie bij deze subgroep van patiënten. **Hoofdstuk 8** beschrijft een multicenter, retrospectieve cohort studie van patiënten die endoscopische therapie ondergingen vanwege een symptomatisch pancreas divisum (PDiv), bestaande uit een sfincterotomie van de papilla minor of plaatsing van een stent in de dorsale ductus. Symptomatische PDiv werd geclassificeerd volgens het type klinische presentatie: 1) recidiverende acute pancreatitis (RAP), 2) CP, gedefinieerd volgens de M-ANNHEIM-classificatie, en 3) chronische buikpijn (chronic abdominal pain - CAP), gedefinieerd als pancreas-gerelateerde pijn, zonder een biochemisch of radiologisch bevestigde diagnose van acute of chronische pancreatitis. In totaal werden 81 patiënten geïncludeerd, met een matige initiële succesvolle canulatie (74%), resulterend in herhaalde ERCP-procedures (mediaan 2 procedures (range 1-4)), met het bijbehorende risico op PEP. Klinisch succes, gedefinieerd als geen recidief episode van RAP of CP, of afwezigheid van CAP, werd na 3 maanden bereikt bij ongeveer de helft van de patiënten (42.6%), met het hoogste succes percentage voor RAP-patiënten (44%), vergeleken met 33% voor zowel CP- als CAP-patiënten. Aanhoudend klinisch succes na 12 maanden was het hoogst voor RAP-patiënten (46%). Bovendien nam voor de subgroep van RAP-patiënten die wel recidieven doormaakten na endoscopische therapie, het aantal episodes per jaar significant af van 3.5 naar 1.13, met een significant groter interval tussen de opeenvolgende episodes. Complicaties traden op bij 32% van de patiënten, waarbij PEP het vaakst werd gediagnosticeerd (22%).

In onze studie is het percentage klinisch succes lager in vergelijking met eerdere studies, wat mogelijk verklaard kan worden door de strikte inclusiecriteria en definities van studie uitkomsten in de huidige studie: eerdere studies bevatten voornamelijk subjectieve patiënt-gerapporteerde uitkomsten. Slechts een klein aantal patiënten met CP en CAP werd in onze studie geïncludeerd, waardoor het moeilijk was om het effect van endoscopische therapie bij deze subgroepen patiënten te bepalen. Op basis van de resultaten van deze studie lijkt het erop dat RAP-patiënten het meeste baat hebben bij endoscopische therapie; het risico van PEP, dat niet verwaarloosbaar is, moet echter worden afgewogen

tegen de mogelijke voordelen. Daarnaast zou kunnen worden beargumenteerd dat het de moeite waard is om vroeg in het ziektebeloop endoscopische therapie uit te voeren om progressie naar CP te voorkomen. In het huidige cohort ontwikkelde 20% (9 patiënten) van de RAP-patiënten uiteindelijk CP, van wie er slechts 2 een initiële klinische succesvolle endoscopische behandeling hadden.

Bij de meeste patiënten met acute pancreatitis zal de ziekte een mild beloop hebben met snel gunstig herstel. Ongeveer 20% van de patiënten met acute pancreatitis zal echter acute necrotiserende pancreatitis (ANP) ontwikkelen, met necrose van het pancreasparenchym en/of peripancreatisch weefsel. Ongeveer 30% van de patiënten met ANP zal geïnfecteerde necrose ontwikkelen, wat gepaard gaat met hoge mortaliteit, tussen 15% en 30% (22-24). Behandeling van geïnfecteerde necrose is daarom vrijwel altijd noodzakelijk. Echter, een specifiek instrument dat geschikt is voor effectieve endoscopische verwijdering van pancreasnecrose ontbreekt nog. In **Hoofdstuk 9** evalueerden we een nieuw instrument, het EndoRotor® PED™-systeem, ontworpen voor endoscopische resectie van necrotisch weefsel. Een eerdere studie met 12 patiënten toonde aan dat het instrument veilig en effectief was bij het verwijderen van pancreasnecrose bij deze patiëntengroep, en dat er minder procedures nodig waren dan eerder gerapporteerd voor het gebruik van conventionele technieken, zoals een basket of biopsietang (25). In de huidige studie vonden we dat een mediaan van 1.5 procedure (range 1-3) nodig was om het necrotische weefsel volledig te verwijderen, waarbij de meerderheid van de patiënten minder dan 2 procedures nodig had. Dit is lager vergeleken met wat is gerapporteerd over conventionele technieken (mediaan van 4 procedures (range 1-7)) (26). Gemiddeld genomen werd een reductie van 91% van het percentage necrose in de collectie bereikt en een reductie van 85% van het totale collectievolume. Slechts bij één patiënt werden aanvullende conventionele instrumenten gebruikt om de necrose te verwijderen vanwege een dikke en plakkerige consistentie van het debris. Complicaties traden op bij 33% van de patiënten; 9 ernstige complicaties (serious adverse events – SAE's) en 11 niet ernstige complicaties (non- serious adverse events – non-SAE's). De belangrijkste uitkomst van dit onderzoek is dat er geen SAE's zijn opgetreden gerelateerd aan het instrument en dat het gebruik van het apparaat veilig lijkt, vergelijkbaar met de uitkomsten van het vorige onderzoek. Van de negen SAE's werden drie SAE's door de Data Safety Monitoring Board beoordeeld als 'mogelijk' gerelateerd aan de necrosectomie-procedure. Bij twee patiënten trad een bloeding op, respectievelijk één en vier dagen na de procedure. Bij beide patiënten toonde endoscopische inspectie een bloeding uitgaande van de maagwand of de wand van de collectie, veroorzaakt door wrijving van de uiteinden van de metalen stent tegen de wand, welke was geplaatst om een fistel te creëeren voor transluminale drainage. Bij de derde patiënt trad een pneumoperitoneum op, veroorzaakt door het bewegen van de endoscoop in de metalen stent, waardoor extravasatie van vrije lucht in de peritoneale holte mogelijk was. Een andere belangrijke uitkomst van dit onderzoek is dat de toepassing van het systeem bruikbaar lijkt voor het beoogde indicatie, namelijk het verwijderen van geïnfecteerde pancreasnecrose. De huidige studie miste echter een vergelijkende groep, waardoor directe vergelijking met de huidige conventionele instrumenten niet mogelijk was. Momenteel wordt een internationale, multicenter gerandomiseerde studie uitgevoerd waarin het gebruik van de conventionele instrumenten alleen wordt vergeleken met het EndoRotor® PED™-

systeem plus eventueel conventionele tools indien nodig. Het doel is te onderzoeken wat de klinische waarde is van het EndoRotor® PED™-systeem in het verwijderen van pancreasnecrose. In deze studie is ook een kosteneffectiviteitsanalyse opgenomen.

Duodenumperforatie na biliaire stentplaatsing
Aangezien endoscopie bij pancreaticobiliaire ziekten een grote diagnostische en therapeutische rol heeft, is kennis over veel voorkomende procedure-gerelateerde complicaties van groot belang. Pancreatitis, bloeding en perforatie na ERCP behoren tot de meest voorkomende complicaties (27). Naarmate procedures complexer worden omdat complexere aandoeningen worden behandeld, zoals hilair CCA, is bewustzijn van andere zeldzamere en mogelijk levensbedreigende complicaties vereist voor tijdige herkenning en adequate behandeling. **Hoofdstuk 10** geeft de resultaten weer van een retrospectieve cohort studie die de prevalentie, risicofactoren en klinische uitkomst van patiënten met stentmigratie-geïnduceerde duodenumperforatie (SMDP) onderzocht. Dertien patiënten met een SMDP werden geïdentificeerd uit ons endoscopieregister over een periode van vier jaar. Dit komt overeen een prevalentie van 2.1% voor alle patiënten die een ERCP ondergingen voor het plaatsen van een biliaire plastic stent, en 4.3% voor alle patiënten met plaatsing van een biliaire plastic stent voor een perihilaire strictuur. Alle SMDP's traden op bij patiënten met een perihilaire strictuur. De meerderheid van de symptomatische patiënten presenteerde zich binnen 14 dagen na plaatsing van de stent en kon conservatief of met een Over-The-Scope-Clip worden behandeld. Desalniettemin overleed een derde van de patiënten als gevolg van aanhoudende abdominale sepsis, ondanks herhaalde interventies en aanvankelijke succesvolle sluiting van de perforatie. Mogelijke risicofactoren waren onder meer langere stents en plaatsing van stents in het linker intrahepatische systeem. Vanwege het kleine aantal cases en daarbij het risico op overfitting, moeten deze bevindingen echter met voorzichtigheid geïnterpreteerd worden. Grotere cohort studies met meer cases zijn nodig om mogelijke risicofactoren betrouwbaarder te identificeren. We concludeerden dat SMDP een belangrijke complicatie is om te herkennen en wij stellen voor om het risico op SMDP op te nemen in het informatie gesprek voor patiënten die een ERCP zullen ondergaan voor het plaatsen van een plastic stent wegens een perihilaire strictuur. Dit gezien het risico op SMDP in deze subgroep patiënten in onze studie even groot is als het risico op PEP of bloeding (27).

CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

In dit proefschrift hebben we ons gericht op verschillende aspecten van geavanceerde pancreaticobiliaire endoscopie, inclusief huidige en nieuwe technieken, met als doel diagnostiek en behandeling van patiënten met ziekten van galwegen of pancreas te verbeteren. Zoals vermeld in de inleiding, heeft endoscopie de afgelopen decennia een belangrijke rol gekregen bij diagnostiek en behandeling van pancreaticobiliaire ziekten. In vergelijking met andere gebieden binnen de gastro-intestinale endoscopie, is pancreaticobiliaire endoscopie nog relatief nieuw. Tot voor kort vertrouwden we op radiologische visualisatie van ductale structuren en chirurgie was de primaire behandelingsmodaliteit. Pas sinds de introductie van SOC zijn we nu in staat om intraductale structuren te visualiseren. Studies hebben veelbelovende resultaten opgeleverd met

betrekking tot de visuele diagnose van CCA en maligne IPMN en hebben geprobeerd visuele kenmerken te identificeren die voorspellend zijn voor een maligniteit. Wij en anderen hebben echter aangetoond dat er nog steeds een grote variatie bestaat tussen beoordelaren, zelfs onder endoscopisten met veel ervaring in SOC, en dat kenmerken van benigne en maligne pathologie elkaar kunnen overlappen. Om de klinische waarde van de SOC te verbeteren, is het belangrijk om deze variatie te beperken en een internationale consensus te bereiken over het uiterlijke verschijningsvorm van de kenmerken en de bijbehorende voorspellende waarde voor maligne of benigne pathologie. Totdat een gedegen classificatiesysteem is opgesteld, blijft pathologie de gouden standaard en moeten er studies worden uitgevoerd om het biopsie-protocol voor SOC-geleide gerichte biopten te optimaliseren. Eerdere studies hebben aangetoond dat het nemen van meerdere biopsieën de gevoeligheid verhoogt voor het detecteren van een maligniteit (28,29). Daarnaast kan de bite-on-bite-techniek voor weefselafname, waarbij een tweede biopt direct bovenop het eerste biopt genomen wordt, van toegevoegde waarde zijn voor pancreaticobiliaire laesies. Vanwege de kleine diameter van het ductale lumen en de biopteur is het een uitdaging om voldoende weefsel voor pathologisch onderzoek te verkrijgen. Studies naar het optimale biopsie-protocol, inclusief het optimale aantal biopten en/of bite-on-bite-biopten, zijn nodig.

In de toekomst kan kunstmatige intelligentie (AI) van toegevoegde waarde zijn. Op andere gebieden binnen de gastro-intestinale endoscopie, zoals colonoscopie, zijn al aanwijzingen voor deze toegevoegde waarde van AI. Er is mogelijk ook een rol voor AI bij pancreaticobiliaire endoscopie. Hoewel onderzoek naar AI bij pancreaticobiliaire ziekten nog schaars is, wijzen sommige studies op een goede diagnostische waarde (30). Ten aanzien van biliaire stricturen, heeft Saraiva et al. onlangs een pilotstudie gepubliceerd met een overall diagnostische accuratesse van 95%, een sensitiviteit van 95% en een specificiteit van 92% van AI voor het identificeren van maligne stricturen (31). Er is echter een zeer grote, gestandaardiseerde database nodig van cholangioscopie en pancreatoscopie beelden welke reeds een definitieve pathologische diagnose hebben, om AI voldoende te kunnen trainen en valideren. Om dit te bereiken is internationale samenwerking tussen endoscopisten nodig, met daarbij ook samenwerking tussen onderzoekers en technici.

Ten aanzien van de therapeutische indicaties van SOC, met name SOC-geleide lithotripsie, illustreren de gegevens gepresenteerd in dit proefschrift dat deze techniek wanneer uitgevoerd middels EHL veelbelovend is als eerstelijnsbehandeling van PD stenen. De behandeling van galwegstenen wordt in dit proefschrift niet beschreven. Naast electrohydraulisch, kan lithotripsie ook verricht worden als laser lithotripsie (LL). Goede, prospectieve studies die deze twee modaliteiten vergelijken zijn gewenst. Het voordeel van SOC met lithotripsie kan zijn dat stricturen gelijktijdig behandeld kunnen worden en dat de endoscopist de behandeling volledig onder controle heeft en niet afhankelijk is van de ESWL-faciliteit, wat een grotere beschikbaarheid mogelijk maakt. Wij zijn echter wel van mening dat SOC het best kan worden uitgevoerd in grote expertisecentra, omdat het een technisch uitdagende procedure is die expertise van de uitvoerende endoscopist vereist.

Ten slotte hebben we nieuw licht geworpen op de klinische waarde van geavanceerde pancreaticobiliaire endoscopie bij de behandeling van acute pancreatitis. Aangezien acute pancreatitis een van de belangrijkste indicaties is voor pancreaticobiliaire endoscopie, is het een belangrijk, zich continue ontwikkelend onderzoeksgebied. Dit proefschrift draagt bij aan de optimalisatie van de endoscopische behandeling bij patiënten met acute pancreatitis en veelbelovende data zijn gepresenteerd ten aanzien van een nieuw instrument voor de resectie van pancreasnecrose. Hoewel multicenter, zijn de meeste data gebaseerd op kleine studiepopulaties en moeten de resultaten worden gevalideerd in grotere, prospectieve, gerandomiseerde studies. Door continue verbeteringen en innovaties is het mogelijk om steeds complexere patiënten endoscopisch te behandelen. Dit leidt echter ook tot het optreden van schijnbaar zeldzame complicaties, zoals in dit proefschrift beschreven. Daarom moeten deze patiënten bij voorkeur worden behandeld in een multidisciplinaire setting, inclusief endoscopisten, radiologen en chirurgen, waarbij de juiste patiënt voor endoscopische behandeling wordt geselecteerd.

De resultaten van dit proefschrift bieden nieuw inzicht in de klinische waarde van SOC, een relatief nieuwe endoscopische modaliteit, en hebben bijgedragen aan de huidige literatuur met betrekking tot de endoscopische behandeling van pancreaticobiliaire ziekten, in het bijzonder acute pancreatitis. Het biedt aanknopingspunten voor verder wetenschappelijk onderzoek, met als doel de diagnostiek en behandeling van patiënten met pancreaticobiliaire ziekten verder te verbeteren.

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Part V

Appendices

Chapter 13

Abbreviations

ABBREVIATIONS

AC	Adenocarcinoma
AE	Adverse event
ALT	Alanine-aminotransferase
AP	Acute pancreatitis
APACHE	Acute Physiology and Chronic Health Evaluation
ASA score	American Society of Anesthesia Physical status Classification System
ASGE	American Society for Gastrointestinal Endoscopy
BD-IPMN	Branch-duct intraductal papillary mucinous neoplasms
BMI	Body Mass Index
CA19.9	Cancer antigen 19.9
CAP	Chronic abdominal pancreatic-type pain
CBD	Common bile duct
CCA	Cholangiocarcinoma
CDM	Clinical decision making
CECT	Contrast-enhanced CT
CPB	Celiac plexus block
CI	Confidence interval
CP	Chronic pancreatitis
CRP	C-reactive protein
CT	Computed tomography
DEN	Direct endoscopic necrosectomy
DMII	Type 2 Diabetes Mellitus
DPS	Double-pigtail stent
DSMC	Data Safety Monitoring Committee
d-SOC	Digital single-operator cholangioscopy
EHL	Electrohydraulic lithotripsy
ENBD	Endoscopic nasobiliary drainage
ERC	Endoscopic retrograde cholangiography
ERCP	Endoscopic retrograde cholangiopancreatography
ERP	Endoscopic retrograde pancreatography
ES	Endoscopic sphincterotomy
ESGE	European Society of Gastrointestinal Endoscopy
ESWL	Extracorporeal shock wave lithotripsy
ET	Endoscopic therapy
EUS	Endoscopic ultrasonography

FC-SEMS	Fully covered self-expandable metal stents
FISH	Fluorescence in situ hybridization
FNA	Fine-needle aspiration
Fr	French
FU	Follow-up
GI	Gastro-intestinal
HGD	High grade dysplasia
ICU	Intensive care unit
IDUS	Intraductal ultrasonography
IOA	Inter-observer agreement
IOP	Intraoperative pancreatoscopy
IPMN	Intraductal papillary mucinous neoplasms
IPOC	Indirect peroral cholangiopancreatoscopy
IQR	Interquartile range
LAMS	Lumen-opposing metal stents
LGD	Low grade dysplasia
LL	Laser lithotripsy
MCS	Mental Component Summary
MD-IPMN	Main-duct intraductal papillary mucinous neoplasms
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MT-IPMN	Mixed-type intraductal papillary mucinous neoplasms
NBI	Narrow-band imaging
NPV	Negative predictive value
OR	Odds ratio
OTSC	Over-the-scope clip
PCS	Physical Component Summary
PD	Pancreatic duct
PDiv	Pancreas divisum
PED	Powered endoscopic debridement
PEP	Post-ERCP pancreatitis
POP	Peroral pancreatoscopy
PPV	Positive predictive value
PSC	Primary sclerosing cholangitis

PTC	Percutaneous transhepatic cholangiography
RAP	Recurrent acute pancreatitis
RR	Risk ratio
ROSE-TIC	Rapid onsite evaluation of touch imprint cytology
SAE	Serious adverse event
SD	Standard deviation
SEMS	Self-expandable metal stent
s-EUS	Secretin-enhanced EUS
SF-12	12-Item Short-Form Health Survey
SF-36	36-Item Short-Form Health Survey
SIRS	Systemic Inflammatory Respons Syndrome Score
SMDP	Stent migration-induced perforation of the duodenal wall
s-MRCP	Secretin-enhanced MRCP
SN	Sensitivity
SP	Specificity
SS-MRCP	Secretin-stimulated MRCP
US	Ultrasound
WOPN	Walled-off pancreatic necrosis

Chapter 14

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Chapter 15

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Urgent endoscopic ultrasound-guided endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis (APEC-2): a multicentre prospective study
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Submitted

The role of pancreatoscopy in the diagnostic work-up of intraductal papillary mucinous neoplasms: a systematic review and meta-analysis
P.M.C. Stassen*, D.M. de Jong*, B. Groot Koerkamp, M. Ellrichmann, P.I. Karagyozov, A. Anderloni, L. Kylänpää, G.J.M. Webster, L.M.J.W. van Driel, M.J. Bruno, P.J.F. de Jonge, European Cholangioscopy Group
*Both authors contributed equally
Endoscopy, 2022, PMID 35668651

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P.M.C. Stassen*, S.E. van der Wiel*, J.W. Poley, D.M. de Jong, P.J.F. de Jonge, M.J. Bruno
*Both authors contributed equally
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Endoscopy International Open, 2021, PMID 34222643

Clinical practice patterns in indirect peroral cholangiopancreatoscopy: outcome of a European survey
P.M.C. Stassen, P.J.F. de Jonge, G.J.M. Webster, M. Ellrichmann, A.J. Dormann, M. Udd, M.J. Bruno, V. Cennamo, European Cholangioscopy Group; and the German Spyglass User Group
Endoscopy International Open, 2021, PMID 34790534

Diagnostic accuracy and interobserver agreement of digital single-operator cholangioscopy for indeterminate biliary strictures
P.M.C. Stassen, G. Goodchild, P.J.F. de Jonge, N.S. Erler, A. Anderloni, V. Cennamo, N.I. Church, I. Fernandez-Urien Sainz, M.T. Huggett, M.W. James, D. Joshi, L. Kylänpää, W. Laleman, M.K. Nayar, K.W. Oppong, J.W. Poley, J.R. Potts, A. Repici, M. Udd, J.J. Vila, T. Wong, M.J. Bruno, G.J.M. Webster, European Cholangioscopy Group
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Diagnostic performance of a CT based scoring system for diagnosis of anastomotic leakage after esophagectomy: comparison with subjective CT assessment.
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Chapter 16

PhD portfolio

PHD PORTFOLIO

Name PhD student:	Pauline Maria Catharine Stassen
PhD period:	April 2018 – April 2021
Promotor:	Prof. dr. M.J. Bruno
Co-promotor:	dr. P.J.F. de Jonge
Department Erasmus MC:	Gastroenterology and Hepatology

Courses and workshops	
	Year
BROK cursus, Consultatiecentrum Patiëntgebonden Onderzoek (CPO), Erasmus MC, Rotterdam	2018
Systematic Literature Retrieval in PubMed workshop, Erasmus MC, Rotterdam	2018
Systematic Literature Retrieval in other databases workshop, Erasmus MC, Rotterdam	2018
EndNote workshop, Erasmus MC, Rotterdam	2018
Basic Introduction course on SPSS, Erasmus Postgraduate School for Molecular Medcine (MolMed), Erasmus MC, Rotterdam	2018
Workshop on Microsoft Excel 2010: Basic, Erasmus Postgraduate School for Molecular Medicine (MolMed), Erasmus MC, Rotterdam	2019
Hands-on-training: Get your PhD done – with Outlook and Onenote, Erasmus Postgraduate School for Molecular Medcine (MolMed), Erasmus MC, Rotterdam	2019
Integrity in scientific research, Dept. of Medical ethics and Philosophy, Erasmus MC, Rotterdam	2019
Biomedical English Writing Course, Erasmus Postgraduate School for Molecular Medcine (MolMed), Erasmus MC, Rotterdam	2020

Oral presentations	
	Year
Investigator meeting European Cholangioscopy Group, United European Gastroenterology (UEG) Week, Vienna, Austria	2018
Prevalence of and risk factors for biliary stent-migration induced duodenal perforation, Digestive Disease Days, Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven, The Netherlands	2019
Investigator meeting European Cholangioscopy Group, United European Gastroenterology (UEG) Week, Barcelona, Spain	2019
Diagnostic accuracy and interobserver agreement of digital single-operator cholangioscopy for indeterminate biliary strictures, Digestive Disease Week, Chicago, United States of America	2020
Safety and efficacy of a novel resection system for direct endoscopic necrosectomy of walled-off pancreas necrosis: a prospective, international, multicenter trial, Digestive Disease Week, Chicago, United States of America	2020
Diagnostic accuracy and interobserver agreement of digital single-operator cholangioscopy for indeterminate biliary strictures, ASGE 2020 Leaders in Endoscopy	2020
Investigator meeting European Cholangioscopy Group, United European Gastroenterology (UEG) Week, Amsterdam, The Netherlands	2020
Diagnostic accuracy and interobserver agreement of digital single-operator cholangioscopy for indeterminate biliary strictures, United European Gastroenterology (UEG) Week, Amsterdam, The Netherlands	2020

Safety and efficacy of a novel resection system for direct endoscopic necrosectomy of walled-off pancreas necrosis: a prospective, international, multicenter trial, United European Gastroenterology (UEG) Week, Amsterdam, The Netherlands	2020
Diagnostic accuracy and interobserver agreement of digital single-operator cholangioscopy for indeterminate biliary strictures, Spylive live UK day, London, United Kingdom	2020
Diagnostic accuracy and interobserver agreement of digital single-operator cholangioscopy for indeterminate biliary strictures, European Society of Gastrointestinal Endosocopy (ESGE) days	2021
Cancelled due to COVID-19	
Diagnostic accuracy and interobserver agreement of digital single-operator cholangioscopy for indeterminate biliary strictures, European Society of Gastrointestinal Endosocopy (ESGE) days, Dublin, Ireland	2020
Pancreatoscopy-guided electrohydraulic lithotripsy for the treatment of obstructive pancreatic duct stones: a prospective consecutive case series, European Society of Gastrointestinal Endosocopy (ESGE) days, Dublin, Ireland	2020

Poster presentations	
	Year
Prevalence of and risk factors for biliary stent-migration induced duodenal perforation, United European Gastroenterology (UEG) Week, Barcelona, Spain	2019
Prevalence of and risk factors for biliary stent-migration induced duodenal perforation, Digestive Disease Week, Chicago, United States of America	2020
Pancreatoscopy-guided electrohydraulic lithotripsy for the treatment of obstructive pancreatic duct stones: a prospective consecutive case series, United European Gastroenterology (UEG) Week, Amsterdam, The Netherlands	2020
Clinical practice patterns of indirect peroral cholangiopancreatoscopy: an international survey, United European Gastroenterology Week, Amsterdam, The Netherlands	2020
Cancelled due to COVID-19	
Clinical practice patterns of indirect peroral cholangiopancreatoscopy: an international survey, Poster podium presentation, European Society of Gastrointestinal Endosocopy (ESGE) days, Dublin, Ireland	2020

Attended (inter)national conferences	
	Year
Digestive Disease Days, Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven, The Netherlands	2018
United European Gastroenterology (UEG) Week, Vienna, Austria	2018
Pancreasdag, Gouda, The Netherlands	2018
London Live Endoscopy, London, United Kingdom	2018
Digestive Disease Days, Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven, The Netherlands	2019
United European Gastroenterology (UEG) Week, Barcelona, Spain	2019
Digestive Disease Week, Chicago, United Stated of America (online conference)	2020
United European Gastroenterology (UEG) Week, Amsterdam, The Netherlands (online conference)	2020
Spylive UK day, London, United Kingdom (online conference)	2020
London Live Endoscopy, London, United Kingdom (online conference)	2020
Pancreasdag (online conference)	2020
Digestive Disease Days, Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven, The Netherlands	2021
European Society of Gastrointestinal Endoscopy (ESGE) days (online conference)	2021

Attended seminars	
	Year
Journal clubs, department of Gastroenterology and Hepatology, Erasmus MC, Rotterdam	'18 – '21
Weekly HPB meeting, Erasmus MC, Rotterdam	'18 – '21
Casuistische bespreking, NVGE	2019

Educational activities and lecturing	
	Year
Supervising research master student	'19 – '20
Lecture on behalf of the Dutch Pancreatitis Study Group, bachelor students Erasmus University	2019

Extracurriculair	
	Year
Board member Promeras, representing board of all PhD students, Erasmus MC, Rotterdam	'18 – '20
PhD committee, Erasmus MC, Rotterdam	2019
Editor 4Abstracts, endoscopy section	'19 – '21

Chapter 17

Dankwoord

DANKWOORD

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Chapter 18

About the author

ABOUT THE AUTHOR

Pauline Maria Catharine Stassen was born on August 25th 1991, in Maastricht, the Netherlands. She grew up in Rotterdam and attended secondary school at 'Montessori Lyceum Rotterdam'. After her graduation in 2009 she worked as laboratory assistant at the Laboratory of Experimental Intensive Care and Anesthesiology at the Academisch Medisch Centrum, Amsterdam for six months and thereafter lived in Sydney, Australia, for six months attending the Australian College of English to obtain her Cambridge Certificate of Advanced English. In 2010 she moved to Utrecht and started studying International Business Administration. In 2011 she was admitted to medical school at the Vrije Universiteit, Amsterdam. She graduated medical school in 2018. During her medical study she performed her scientific research project at the department of Upper GI surgery at the University Medical Center Utrecht, where she worked for an additional six months as student researcher. After obtaining her Bachelor's degree in 2015, Pauline moved to Amsterdam and performed her clinical rotations in different hospitals in the Netherlands and the Pedriatrics and Gynaecology rotation in Sint Maarten. During her final rotations she developed a special interest in the field of Gastroenterology and Hepatology.

After graduating medical school in 2018 Pauline shortly worked as resident not in training at the department of Gastroenterology and Hepatology at the Noordwest Ziekenhuisgroep, Alkmaar, before she started her PhD program in April 2018 at the Erasmus MC University Medical Center Rotterdam, under supervision of prof. dr. M.J. Bruno and dr. P.J.F. de Jonge. During her PhD trajectory, Pauline was active board member of Promeras, a representing body for all PhD students at the Erasmus MC University Medical Center Rotterdam and served as member of the PhD committee.

In June 2021 she started as resident not in training at the department of Internal Medicine at the Reinier de Graaf Gasthuis, Delft. From December 2021 onwards she started her Internal Medicine residency at the Reinier de Graaf Gasthuis, as part of her Gastroenterology and Hepatology residency at the Erasmus MC University Medical Center Rotterdam. Together with Stijn, Pauline now lives in Rotterdam.