Optimizing performance and techniques in advanced pancreatobiliary endoscopy

SOPHIA ELISABETH VAN DER WIEL

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Colophon

Cover design:	Erwin Timmerman
Layout and design:	Eefke Schreur - Meilink
Printing:	Optima Grafische communicatie

The work presented in this thesis was conducted at the Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, The Netherlands.

Printing of this thesis was financially supported by Erasmus Universiteit Rotterdam, Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, Nederlandse Vereniging voor Gastroenterologie

OPTIMIZING PERFORMANCE AND TECHNIQUES IN ADVANCED PANCREATOBILIARY ENDOSCOPY

Optimalisatie van prestaties en technieken
in geavanceerde pancreatobiliaire endoscopie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. A.L. Bredenoord

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
dinsdag 31 mei 2022 om 10.30 uur

door

Sophia Elisabeth van der Wiel
geboren te Amsterdam

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotor:	Prof.dr. M.J. Bruno
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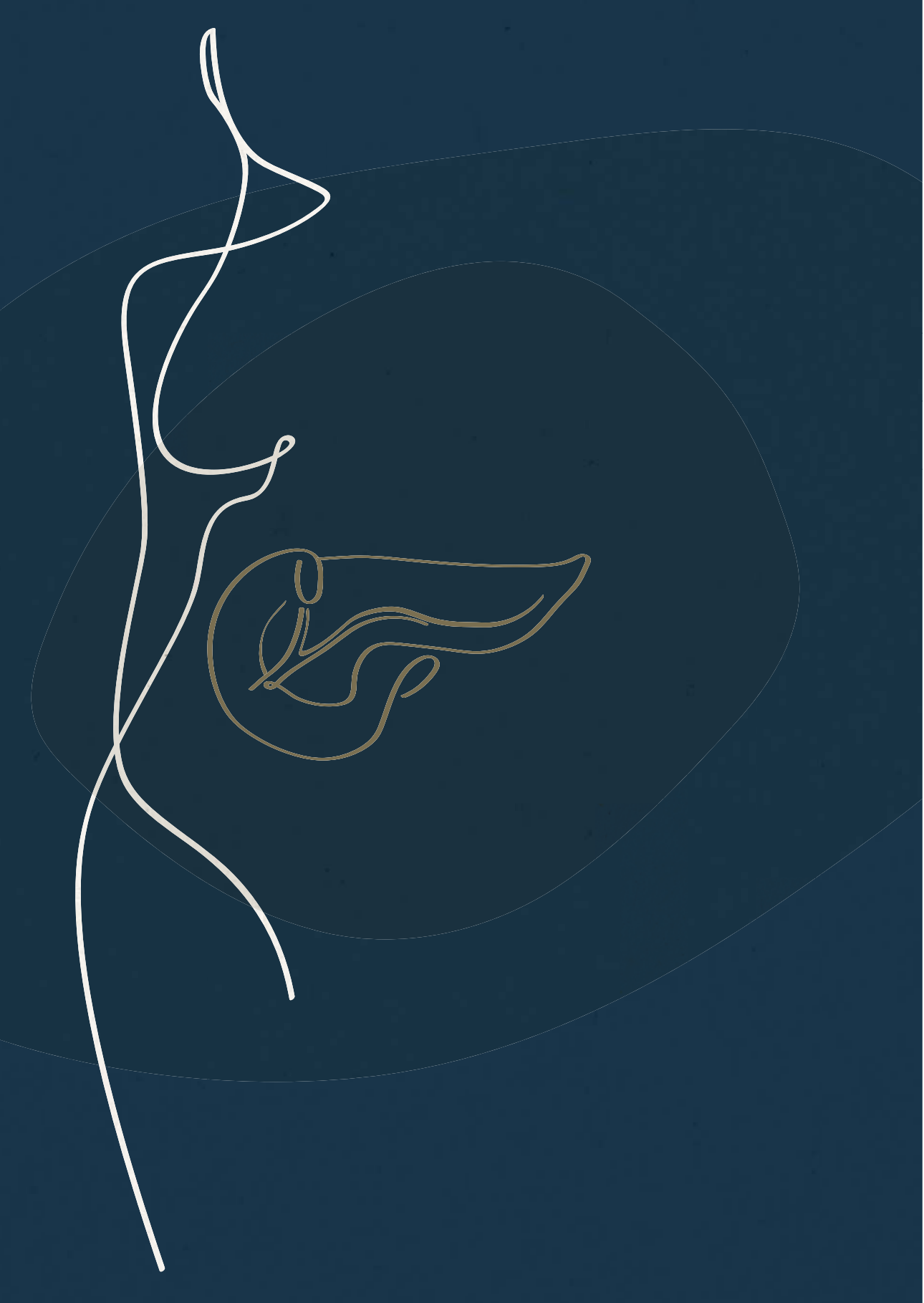

PART I

Introduction

1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

GENERAL INTRODUCTION

This thesis focuses on three aspects of advanced hepatopancreatobiliary endoscopy. Part I contains the introduction of this thesis. Part II focusses on simulator training in gastrointestinal endoscopy, specifically training in endoscopic retrograde cholangiopancretography (ERCP). The thirth part of the thesis evaluates the outcome of mandatory ERCP registration in the Netherlands, and in the fourth part of the thesis we describe various advanced endoscopic procedures and techniques in the hepatopancreatobiliary and duodenal tract.

Simulator training in gastrointestinal endoscopy

Simulator training is well known to train aviation and military personnel. Simulated environments provide a platform to allow trainees to acquire knowledge and build a framework of basic skills. The aim of simulation-based training is to better prepare trainees for the real-life situation with the possibility to extensively and repeatedly train relevant tasks combined with theoretical background.

Gastrointestinal endoscopy is an important modality to diagnose and treat gastrointestinal disorders[1]. Traditionally, trainees learn to perfom endoscopy by hands-on training in a clinical setting under the supervision of a trained endoscopist, the apprenticeship model. However, there are several drawbacks to this approach, training occurs in a stressfull environment with an overload of new information to process, with a subsequent higher complication risk, and increased patient discomfort[2]. In the last decades, there has been an increasing movement to integrate simulation-based training in training curricula for teaching endoscopy as an attractive alternative for teaching both psychomotor and perceptual skills. Numerous simulators are available, classified in mechanical simulators, live animal models, ex vivo models and virtual reality computer simulators, but all training models have its own strengths and limitations. Mechanical simulators can simulate aspects of endoscopic procedures, but mostly lack to replicate realistic tissue simulation. The most realistic experience is being provided by bio-simulated models and live animal models, however major drawbacks include the inability to repeatedly perform the procedure, costs, and ethical concerns. Virtual reality simulators can be programmed to replicate different types of procedures, patient discomfort and complication management, but these types of simulators are expensive. In recent years, several simulators have been validated for training purposes. Validity assessment of simulators can be performed on different levels. Simulators should replicate the look and feel of real-life tissue (ie, face validity) and should have the ability to both distinguish between a novice and an expert operator (i.e., construct validity)[3]. Studies on the

efficacy of simulator-based training in gastrointestinal endoscopy, mostly describe the benefit of simulation-based training in the early learning curve of the trainees[4].

Of all gastrointestinal endoscopic procedures ERCP is considered one of the most technically demanding procedures. The procedure may result in life-threatening complications[5]. ERCP is a procedure to treat diseases of the pancreatobiliary system which combines the use of endoscopy and fluoroscopy and it requires significant training and expercience to maximize success and patient outcomes. ERCP has a long learning curve and because of its complexity regarded as an advanced endoscopic procedure. It is associated with a high complication rate. To acquire competence, current guidelines recommend at least 200 ERCP procedures[6], however there is growing evidence that competency should be established by objective performance criteria rather than a numerical threshold of procedures performed[7-9]. Therefore, simulation-based training seems ideally suited as a training platform for ERCP. Strinkingly however, is the lack of scientific data on the application of endoscopic simulators in training ERCP and currently only six simulators have been described[10-15]. In this thesis we validate a novel mechanical ERCP simulator and we evaluate the learning curves of novice trainees in training ERCP.

Mandatory ERCP registration in the Netherlands

Measuring and monitoring quality in healthcare is a growing topic of interest. In 2018, the World Health Organisation issued the following definition of healthcare: *"the extent to which health care services provided to individuals and patient populations improve desired health outcomes. In order to achieve this, health care must be safe, effective, timely, efficient, equitable and people-centred*." In recent years, quality measurement and assurence of endoscopic procedures has gained increased awareness. The quality of health care can be measured by comparing the performance of an individual or a group of individuals with an ideal or benchmark[16]. Both the American Society of Gastrointestinal Endoscopy (ASGE)[17] and the European Society of Gastrointestinal Endoscopy (ESGE)[18] published guidelines with quality indicators for endoscopic procedures. More specific, in 2018 the ESGE published a list of key performance measures for ERCP en endoscopic ultrasound (EUS)[19]. These performance measures are intented to set a standard and provide a framework to measure, compare, and improve the quality of both ERCP and EUS. Both guidelines recommend to focus mainly on quality indicators related to outcome, such as cannulation rate, stent placement and successful stone extraction. In 2014, Ekkelenkamp *et al*. evaluated the quality of ERCP in the Netherlands based on a voluntary registration through self-assessment, main outcome measures were bile duct cannulation (CBD) rate and procedural success[20]. This study was an important step up in the awareness of quality assurance in ERCP in the Netherlands. Since January 2016, all endoscopist are required to document and register procedural aspects and outcomes of

all ERCP procedures in a nationwide registry. In this thesis we describe how this mandatory registry had led to an increase in quality of ERCP outcomes and how this compares to the ESGE benchmarks.

Advanced endoscopic procedures

Endoscopic management of pancreatic necrosis in acute necrotizing pancreatitis
Over the years, the incidence and number of hospital admissions for acute pancreatitis have increased in Western countries, possible explanations for this observation are increasing alcohol intake and more patients with gallstone-related pancreatitis due to increasing obesity worldwide[21]. In approximately 80% of patients, the clinical course is mild. Unfortunately, a more complicated course is seen in up to 20% of patients who may develop acute necrotizing pancreatitis (ANP). Acute (infected) necrotizing pancreatitis is accompanied by significant rates of early organ failure (38%), the need for intervention (38%), and results in up to 15% of patients in death[22]. Pancreatic necrosis is the precence of non-viable pancreatic parenchyma, but in most cases peripancreatic tissue is involved as well (75-80% of patients)[23]. Initially, open surgery was the most widely used approach in patients with infected walled-of pancreatic necrosis, however due to high morbidity and mortality rates, a shift is seen towards more minimally invasive techniques such as endosconography-guided transluminal drainage of walled-of necrosis and direct endoscopic necrosectomy (DEN)[24]. Several studies have reported on the outcome of DEN with a decrease of morbidity and mortality rates compared to open surgery[25, 26]. Unfortunately, a major drawback of this technique is the lack of dedicated and effective instruments for adequate endoscopic removal of necrotic tissue. A variety of tools, originally developed for other indications, are being used to grasp and hold the necrotic tissue, but often lack sufficient grip, making the procedure time consuming and often marginally effective, in particular when necrosis is more sticky. In this thesis we evaluated a novel mechanical tool to facilitate endoscopic necrosectomy.

Endoscopic management of obstructive pancreatic duct stones in chronic pancreatitis
Chronic pancreatitis (CP) is a severe condition characterized by an irreversible and progressive inflammatory process, resulting in progressive fibrosis, and the destruction of exocrine and endocrine tissue. The most common clinical presentation is abdominal pain. The cause of the pain is considered multifactorial, including increased intraductal and parenchymal pressure, which can be caused by either strictures of the main pancreatic duct (MPD), stones, or a combination of both[27]. Stones <5mm can potentially be extracted by endoscopic retrograde pancreaticography (ERP) alone, but success rates in case of larger stones are low[28]. Therefore, extracorporeal Shock Wave Lithotripsy (ESWL) combined with subsequent ERP is recommended in case of stones >5mm and has high

success rates up to 93 percent pertaining fragmentation of stones[29]. However, this approach is accompanied by several drawbacks such as costs, limited availability and the need for multiple ESWL sessions. A potential alternative could be pancreatoscopy-guided intraductal lithotripsy, currently mostly used as second-line therapy after failed ESWL. Data on this technique are limited and from retrospective, non-consecutive, series and intraductal laser (LL) or electrohydraulic lithotripsy (EHL) have provided discordant success rates for stone fragmentation (47–91 %) in small case series, after failure of ESWL to fragment stones[30-32]. We performed a prospective cohort study on pancreatoscopy-guided endoscopic intraductal lithotripsy as first line treatment in patients with chronic pancreatitis and obstructive main pancreatic duct stones.

Endoscopic resection of ampullary adenomas

Lesions of the ampulla of Vater are relatively rare and account for approximately 7-10% of periampullary lesions[33]. The most common benign tumors arising from the ampulla of Vater are adenomas[34]. Initially, ampullary adenomas were resected surgically, but a transition is seen to endoscopic resection of a selection of tumors of the ampulla of Vater due to improved endoscopic techniques[35-37]. Endoscopic ampullectomy (EA) has lower morbidity and mortality rates compared to surgical procedures[34, 37]. Success rates of endoscopic ampullectomy have been reported mostly based on retrospective case series with procedural success and outcome ranging from 42 to 92%. This broad range appears largely to be dependent on the extent of the tumor. Adenoma can be confined to the papilla, laterally spreading beyond the ampulla, or also extend intraductally. Data on endoscopic removal of the latter two more advanced adenoma of the ampulla of Vater are limited. We performed a retrospective study on outcome of endoscopic ampullectomy in a large cohort of patients with adenomas of the ampulla of Vater.

AIMS OF THE THESIS

The general aim of this thesis was to improve health care for patients with a disease of the hepaticopancreaticobiliary and duodenal tract. In **Chapter 1,** the aims of this thesis are outlined.

Good performance of health care starts with solid training to achieve compentency. In part II of the thesis, the value of simulator-based training for training novices is investigated. Simulator-based training becomes a more accepted tool in training residents at the beginning of their endoscopic career due to the burdensome for both trainees and patients of learning endoscopic procedures on real patients. **Chapter 2** provides an overview on simulator training in gastrointestinal endoscopy. We review current avail-

able validated simulators in training oesophagogastroduodenoscopy, colonoscopy, ERCP and EUS, and discuss limitations of current simulators and their training options. In **Chapter 3** and **Chapter 4** a novel mechanical ERCP simulator, the Boškoski-Costamagna mechanical ERCP Trainer is subjected to a formal scientific validation. In Chapter 3 we investigate the construct validaty, face validity and the didactic value of this simulator as a training tool for novices based on the judgement of ERCP experts. We assessed face validity for a novel synthetic papilla, designed as an extension to the Boškoski-Costamagna mechanical ERCP Trainer to train biliary sphincterotomy in Chapter 4. After this formal validation, we determine the impact of a two-day hands on training course with the use of the Boškoski-Costamagna mechanical ERCP Trainer, on the learning curve of novice trainees while performing specific clinical tasks in **Chapter 5**.

An important step in improving health care is creating awareness of one's own performance. In part III, **Chapter 6**, of the thesis, we evaluate the outcomes of mandatory ERCP registration in the Netherlands with data retrieved from a prospectively maintained gastrointestinal endoscopy database. We aim to evaluate change in performance outcomes compared to a previously performed study in the Netherlands and we determine whether performance measures according to the ESGE standards are met.

In part IV of the thesis we focus on advanced endoscopic procedures. Quality improvement of endoscopic techniques can be focussing on diagnostic skill and accuracy, but as well improvements in technique create opportunities to facilitate procedures and minimalize patient burden. In **Chapter 7** we assess the technical feasibility, safety and clinical outcome of the EndoRotor as a novel automated tool for the endoscopic removal of pancreatic necrosis in patients with acute necrotizing pancreatitis. In the second chapter of this part of the thesis, **Chapter 8**, the PELstone study is described, which is a prospective study investigating the effect of pancreatoscopy-guided electrohydraulic lithotripsy as treatment for obstructive distal main pancreatic duct stones in patients with chronic pancreatitis. We aimed to investigate the impact of pancreatoscopy-guided EHL as first line treatment. Finally, we retrospectively illustrate the success of endoscopic resection of ampullary adenomas in **Chapter 9**. We divide papillary adenomas in three categories, adenomas confined to the papilla, lateral spreading adenomas and thise with intraductal extention to gain insight in the endoscopic removal of different types of adenomas with regard to procedural success, complications and long-term outcomes.

Finally, in **Chapter 10**, a general discussion is provided in which the results of all studies from this thesis are integrated and recommendations for training, clinical practice and future research are outlined.

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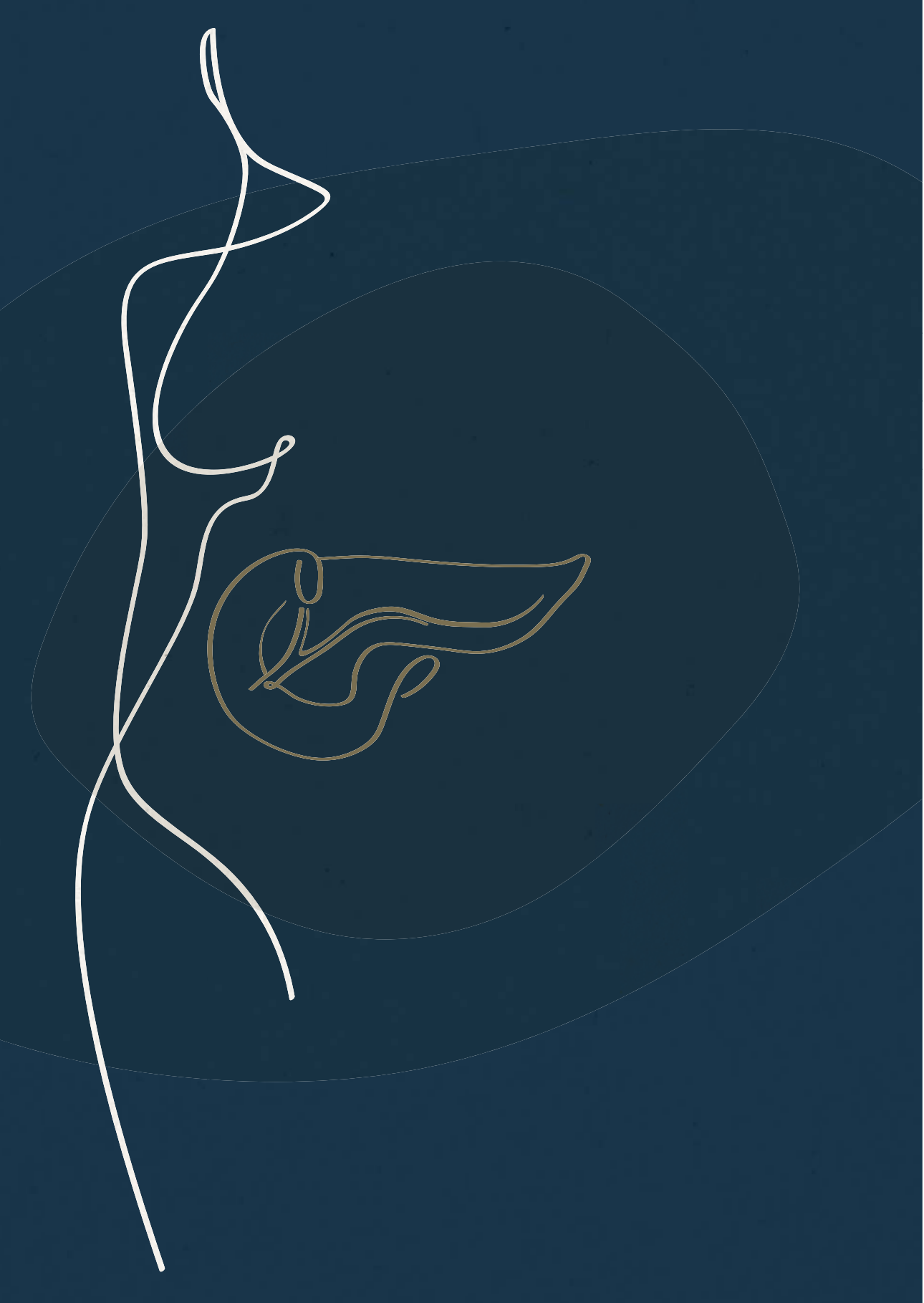

PART II

Simulation-based training in ERCP

2

Simulator training in gastrointestinal endoscopy: From basic training to advanced endoscopic procedures

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Best Practice & Research Clinical Gastroenterology, 2016

ABSTRACT

Simulator-based gastrointestinal endoscopy training has gained acceptance over the last decades and has been extensively studied. Several types of simulators have been validated and it has been demonstrated that the use of simulators in the early training setting accelerates the learning curve in acquiring basic skills. Current GI endoscopy simulators lack the degree of realism that would be necessary to provide training to achieve full competency or to be applicable in certification. Virtual Reality and mechanical simulators are commonly used in basic flexible endoscopy training, whereas ex vivo and in vivo models are used in training the most advanced endoscopic procedures. Validated models for the training of more routine therapeutic interventions like polypectomy, EMR, stenting and haemostasis are lacking or scarce and developments in these areas should be encouraged.

Introduction

During the last decades simulation-based training has gained more acceptance in teaching basic endoscopy skills to novice endoscopists. Traditionally, trainees learn to perform endoscopy by hands- on training in a clinical setting under the supervision of a trained endoscopist, the so-called master apprentice model. The main benefit of this teaching method is on-the-job training under one-on-one supervision by an experienced endoscopist offering immediate feedback. However, taking the first steps in flexible endoscopy while performing procedures on actual patients has certain drawbacks. It is learning by 'trial and error', which potentially increases patient discomfort and risk of complications. It also adds extra time to each procedure affecting capacity and economics[1]. An important drawback of such an approach is that with this type of training it is difficult for novices to appropriately process feedback in a stressful situation with an overload of new information. The approach of 'see one, do one and teach one' therefore seems outdated and no longer appropriate in the modern education of medical professionals, in particular in their early learning curve. Skillslabs and simulators offer the potential to train in a dedicated 'learning environment'. This is a safe environment for trainees where no possible harm can be done to patients. Stress factors related to doing a procedure in a live patient are eliminated to create an optimal setting for training. In this particular learning environment, it is also entirely possible to combine hands-on training with thorough theoretical teaching. Exercises can be repeated multiple times in small building blocks or specific scenario's until fully mastered. In recent years, a number of studies have been published on simulator training, usually describing the benefit of simulator training in the early learning curve towards competency. A recent systematic review demonstrated moderate quality evidence for simulator-based training in forward viewing flexible endoscopy and ERCP. The review reveals that the use of virtual reality simulators in the early training setting accelerates the learning of practical skills[2]. However, the literature on simulator training for more advanced therapeutic procedures is scarcer, aside from studies on managing acute gastrointestinal bleeds or advanced endoscopic resection in ex vivo or in vivo animal models. A realistic simulation model for polypectomy, one of the most frequently performed therapeutic procedures, is still lacking among currently available simulators. Compared to the aviation or automotive industry, we can only acknowledge with envy that we are miles behind when it comes to realistic medical simulators. In this chapter we will outline the well-established role of simulators in basic endoscopy training and elaborate on the role of (virtual reality (VR)) simulators, mechanical models, ex vivo and in vivo models for training in advanced endoscopic procedures.

Available simulators

The first simulators for flexible endoscopy were developed in the 1960s. In general there are four types of simulators: 1) mechanical simulators, 2) live animal models, 3) ex-vivo models and 4) VR computer simulators. The first endoscopic simulators were mechanical models, designed especially for training sigmoidoscopy and colonoscopy. Live animal models seem to be the most realistic compared to mechanical models with haptic feedback resembling that of human tissue, although there are distinct differences in wall thickness and orientation of various organs, resulting in a slightly different 'feel'. Live animal models have certain drawbacks including the costs involved, the fact that they can only be used in specially equipped facilities, that they cannot be used indefinitely, and that many ethical concerns have been raised by the public[4]. A good alternative for live animal models are ex-vivo models, composite and explanted animal organ simulators. These models consist of a combination of plastic parts and explanted animal organs obtained from slaughterhouses. They overcome some of the aforementioned limitations of the live animal models and have proven useful in specific training scenarios. Currently VR simulators are the most promising tools. They are available plug-and-play, making it accessible for trainees to train at their own pace and procedures can be repeated as many times as desired.

The optimal training model or simulator has to show the highest degree of content validity as well as concurrent validity. This means that the system has a high level of resemblance to the real life activity and that performance on the model should be readily transferrable to the real life activity, in casu patient-based endoscopy. Lesser, but more commonly used forms of validity are expert and construct validity. These terms describe the degree of realism as judged by experts and the ability of the simulator to distinguish different levels of competence[3]. The reliability of a simulator relates to its ability to provide consistent results with minimal errors of measurement. The most commonly used test is the test-retest reproducibility. It predicts to what extent a subject can 'beat the test' by repeated assessment[5].

Role of simulators in basic forward viewing flexible endoscopy training

Advanced therapeutic endoscopy has proven itself as an effective and safe first-line treatment for the management of early gastrointestinal neoplasia, pancreaticobiliary disease and many more conditions. Conditions formerly restricted to the domain of surgeons are now managed using minimally invasive endoscopic techniques, not only with considerably less morbidity and mortality, but also superior post-procedural functional results. Moreover, diagnostic endoscopic procedures are gaining importance largely as a result of the initiation of colorectal cancer screening programs in many countries worldwide. As a consequence, the increasing number and in particular the higher complexity

of endoscopic procedures demands more skilled endoscopists able to perform these procedures in a competent manner. Simulation-based learning programs have proven to be of added value, they can effectively speed up the learning process in the early stages of training, avoid patient harm and lower one-on-one instructor time. Consequently, the use of simulators in the early training phase in different gastrointestinal procedures is gaining acceptance and several simulators have been validated for this purpose[2, 6].

Oesophagogastroduodenoscopy

Oesophagogastroduodenoscopy (upper gastrointestinal endoscopy, OGD) is widely used for the diagnosis and treatment of oesophageal, gastric and small bowel conditions. In general, it is a safe and well-tolerated procedure. A variety of technical and cognitive aspects must be mastered in order to perform a high-quality examination. Although OGD is a common gastrointestinal (GI) procedure, studies concerning simulator-based training are scarce compared to colonoscopy. A possible explanation might be the fact that by gaining competency to perform a colonoscopy, where the need for endoscope handling and manoeuvring is much higher, performing OGD seems relatively easy. Several simulators have been developed for training OGD: mechanical models, in vivo- and ex-vivo animal models and VR simulators. The only validated VR-simulator for training upper endoscopy is the 'GI Mentor' virtual reality computer simulator (Fig. 1)[7,8].

Not much is known about the validation and use of mechanical models for basic training in upper GI endoscopy. Most models appear inappropriate for training as the level of competency gained by the trainee has been negligible[9]. The best known ex-vivo model is the Erlangen Endo-Trainer[10]. The model is mostly appreciated for training bleeding situations and seems to offer a good training scenario. Validation studies or studies on learning curves are however few. These include three studies that used the 'GI Mentor' VR simulator, to evaluate the learning curve in simulator-based OGD training[11-13]. The main outcome measures in these studies were procedure time and time to reach specific landmarks such as passing the oesophagus and the pylorus and intubating the duodenum. Secondary outcomes were intubation time, movement techniques, procedural success rates and patient outcome such as pain and discomfort. All these studies have shown that simulator-trained participants, compared to controls, have a significantly lower overall procedure time and a significantly improved technical accuracy. The simulator-trained group also appears to operate more independently compared to the controls. The training with these simulators was of no benefit to experienced endoscopists[7, 11-14].

The model has an added value in training novice endoscopists , but the effect of training overall seems to be limited. One study showed that the effect of simulation-based train-

ing was still visible after the first 60 endoscopic procedures as measured by a shorter procedure time, but not with regards to neither the technical and diagnostic accuracy nor the patients' comfort levels[12]. Another important finding was that performance scores derived from the simulator, did not correlate with performance scores given by blinded experts[15, 16]. These findings suggest that the virtual reality simulator training in OGD offers limited added value to patient-based training and only in the very early learning period[12,14, 17-19].

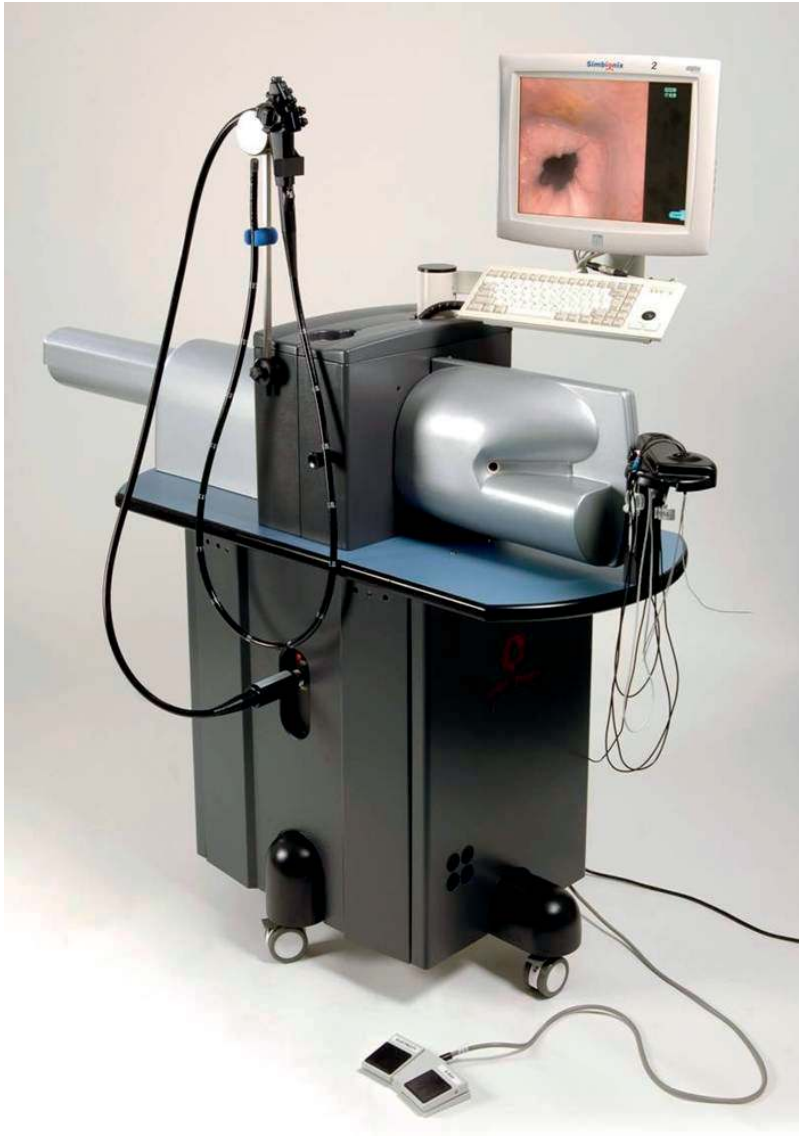

Figure 1. The Simbionix GI Mentor II.

Colonoscopy

The use of simulators in colonoscopy training has been extensively studied and remains a topic of ongoing research. Multiple studies have been performed in which mechanical, ex vivo and VR simulators have been validated for training colonoscopy[2]. The Kyoto Kagaku Colonoscope Training model is currently the only mechanical model that has been validated. Performance on this model has been shown to correlate well with the level of expertise of endoscopists as measured by caecal intubation in patient-based endoscopy[20]. A validation study using an ex vivo bovine colon model demonstrated good construct, expert and concurrent validity. A strong correlation was seen between performance on the model and outcome during patient-based colonoscopy, suggesting the potential of an effective tool for assessment of competency[21]. The most convincing evidence currently available in training colonoscopy is on VR simulators. Multiple validation studies have been performed, evaluating three different VR simulators; The Simbionix GI Mentor II (Fig. 1), the Olympus Endo TS-1 VR Simulator (Fig. 2) and the CAE Endo VR Simulator, formerly known as the AccuTouch Immersion Medical Computer Simulator[2, 7, 14, 16, 17, 21-32]. All of these simulators appear to be valid for basic colonoscopy training. Training on VR colonoscopy simulators focusses mainly on intubation skills. There are hardly any data available on training withdrawal skills and mucosal inspection or therapeutic procedures like polypectomy. Most studies had a randomized design, comparing simulator-based training versus no training followed by routine patient-based training or comparing simulator-based training versus patient-based training followed by patient-based assessment[33-42]. It has been demonstrated that simulator training leads to improved performance compared to no training lasting up to the first 80 colonoscopies in humans and that simulator training compared to patient-based training results in equal performance in the early phase of learning. A recent study using the GI Mentor demonstrated increased performance during patient-based colonoscopy after prolonged training on the simulator. After an average of 60 simulator procedures the learning effect on the simulator itself ceased which coincided with observations in patient-based colonoscopy. This tells us that when the learning effect on the simulator stops, the same applies for the transfer to patient-based endoscopy and the time has come to continue training in a human setting. The simulator derived learning effect can probably be extended when the degree of realism of the simulator increases. This observation is a well-known concept in high fidelity aviation simulators[43]. Based on currently available evidence, the effectiveness of simulator-based training in speeding up the early learning curve, thereby reducing patient's burden has been well established. The use of simulators in colonoscopy is therefore strongly recommended prior to performing patient-based endoscopy. To get the most out of simulator training it seems to make sense to train up to the point where the learning effect on the simulator itself levels off.

This provides the opportunity to offer tailored training programs to novice endoscopists and determine when to commence patient-based endoscopy on an individual basis.

Figure 2. The Olympus Endo TS-1 VR simulator.

Role of simulators in advanced endoscopy training

Endoscopic retrograde cholangiopancreatography

Endoscopic Retrograde Cholangiopancreatography (ERCP) is considered an advanced endoscopic procedure and, in most countries, is not part of the routine training of novice endoscopists. It is one of the most technically demanding and high-risk procedures in

GI endoscopy. Serious life-threatening short-term and long-term complications may arise as a result of an ERCP procedure, including post-ERCP pancreatitis, bleeding and perforation. It requires a great deal of training and an extensive number of procedures to achieve competency. Nowadays diagnostic ERCP procedures are considered obsolete, meaning that all ERCP procedures are performed with a therapeutic intent. In order to minimize patient risk, trainees need to be properly trained both clinically as well as technically and exposed to high numbers of procedures under the guidance of experts before reaching a status of competency. Simulator-based training seems ideally suited as a training platform for this complex procedure before embarking on real life procedures. Surprisingly, there is very limited data available concerning endoscopic simulators in ERCP training. A total of 6 simulators have been described, including mechanical simulators, a model utilizing ex vivo porcine organs, the anesthetized pig model and computer models. Known mechanical simulators with a module for ERCP training include the X-Vision ERCP Training system and the ERCP Mechanical Simulator (EMS)[44, 45]. These models are made out of aluminum, plastic and rubber components, with either a synthetic or ex vivo papilla and provide the possibility to train with real endoscopes and accessories. Selective bile duct or pancreatic duct cannulation can be practiced with selective stent placement, balloon dilatation, brush cytology and, in some, sphincterotomy. Practicing stone extraction has not been described in any of the models. Primary outcome parameters in studies evaluating the mechanical model are successful selective cannulation of the biliary duct and the time required to complete several procedures. Both models are able to distinguish between novice endoscopists and experienced endoscopists by means of expert assessment. After a short mechanical simulator training course a higher number of successful cannulation rates was seen in simulator-trained participants in patient-based ERCPs[45-48]. This improved performance was only described for the first 25 consecutive procedures in humans as follow-up time was limited. Live anesthetized porcine models also have been used as a model for ERCP training. This model has been shown to be adaptable to all procedural aspects of ERCP including cannulation, stent placement and sphincterotomy. After a two-day hands-on training course participants showed an increase in confidence scores, especially in performing more complex procedures like needle-knife pre-cut sphincterotomy[49, 50]. Puzzlingly, confidence in performing basic skills did not increase. The Erlangen Endo Trainer can also be equipped with an ERCP module, consisting of an ex vivo porcine stomach model with attached biliary system. It allows trainees to train with a real endoscope and accessories. The model has been extensively used in ERCP training workshops[51, 52]. The Erlangen Endo Trainer, as well as the live animal model, scored high on realism and the model seems most useful in teaching basic ERCP skills[10, 52]. The only validated VR endoscopy simulator in ERCP is the Simbionix GI Mentor II VR Simulator. The model is able to differentiate between novices and experts in time to complete procedures and time to

reach the papilla; however the model received a low score for realism[53]. Recently, a study was performed using the CAE Endo VR Simulator. This simulator provides a platform for training in diagnostic procedures, however it seems not to be useful in measuring change in performance over time and assessing competency[54]. Sedlack et al. performed a comparison validation study including the Erlangen Endo Trainer, the live porcine model and the GI Mentor II. The study concluded that each model has the potential to be included in training programs; however the Erlangen Endo Trainer scored highest on indices of realism, usefulness and performance. The GI Mentor II scored significant lower at indices of realisms but is easier to incorporate in a training program[52]. The most common performance parameter in simulator-based training in ERCP is successful cannulation rate. This measure reflects only part of the complexity and diversity of this therapeutic procedure. A successful biliary cannulation is a prerequisite to complete a therapeutic procedure successfully but is not a good predictor for successful ERCP procedure. All of these simulators show definite training potential, but based on the scant scientific data available, a definite recommendation for a well-described training program cannot be provided.

Endoscopic ultrasound

Since the description of the first transgastric pancreatic pseudocyst drainage using a linear echo endoscope by Grimm et al., endosonography (EUS) has rapidly changed from a mere diagnostic tool to a technique with advanced therapeutic capabilities[55]. Notably, the advanced EUS therapeutic procedures have a marked overlap with ERCP and demand a great deal of expertise and experience. Although the need for highly skilled endoscopists is obvious, validated simulators or models for training are lacking. There are only a few reports on simulator-based training in EUS. A learning effect by repeated exercise and improvement of performance during EUS procedures in the live porcine model was demonstrated by Barthet et al. but no formal attempts at validation or transfer of competence to a patient-based setting have been made[56]. Advanced endoscopic resections such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are typically trained in a simulator-based setting using animal models. Both ex vivo and in vivo models are used. The ex vivo model is mostly used for training bleeding complications. These topics are discussed in a separate paragraph below.

Advanced therapeutic procedures

Simulator-based training has demonstrated its use in training the basic skills in GI endoscopy. However, as GI endoscopy is no longer a merely diagnostic procedure, this obviates the need for training an increasing diversity of advanced therapeutic procedures outside the standard clinical scenario. Unfortunately we must acknowledge that there is very limited evidence to support training of these procedures in a skillslab environment.

Standard polypectomy or endoscopic mucosal resection (EMR) are perfect examples of techniques that currently cannot be trained in any of the models or VR simulators with a degree of resemblance that comes close to the real thing. A few studies using the Erlangen Endo Trainer have demonstrated a positive effect of simulator-based training for certain interventional skills like endoscopic haemostasis and perforation closure. Haemostasis was simulated using several techniques and a significant improvement has been documented in performing successful injection or coagulation therapy[4, 10, 57]. The transfer of these skills to patient-based endoscopy and its impact in real-life practice is usually not described, so from a scientific point of view we cannot conclude that training in these models is useful. However, as these training scenarios closely resemble the clinical setting, using the same instruments, it seems common sense that training in these models will at least partially improve the skills necessary to apply these techniques.

Advanced endoscopic resections

Pre-malignant and early neoplastic lesions are commonly detected in clinical practice. Interventional endoscopy, namely endoscopic submucosal dissection (ESD) and complex endoscopic mucosal resection (EMR) have replaced surgery for the treatment of many of these conditions. EMR of large lesions can be technically demanding and allows for en bloc resection of lesions up to 20-25mm. Lesions larger than this typically require piecemeal EMR which can complicate histological staging in some settings and can be considered a limitation regarding early cancers, depending on the location in the GI tract[58]. In these situations, ESD seems to be the resection technique of choice, but it is technically more challenging and has a more prolonged learning curve[59-62]. In the appropriate setting, ESD is comparable to surgery in terms of oncological outcomes, cancer free survival and recurrence, but with considerably lower costs, operative time, hospital stay, complication rates and mortality[63]. ESD had a widespread dissemination in Eastern countries but a relatively slow diffusion in Western countries due to its complexity, the requirement for considerable endoscopic skills, the high potential of serious adverse events and the difficulty in achieving adequate funding for these complex endoscopic procedures. A learning curve in performing successful ESD procedures has been demonstrated, and more experienced endoscopists have higher rate of en bloc resection, reduced procedure duration and fewer adverse events, mostly related to perforations[64, 65]. Therefore, a pre-patient training program is recommended before ESD is performed in the clinical setting[64, 66, 67]. The differences between the East and West support the use of simulators for ESD training in the West, whereas in the East, where expert supervision and suitable learning cases are easily available, a simulator phase may not be necessary[68]. Pure mechanical simulators and VR simulators are not ideal when addressing advanced endoscopic resection training, due to the inability to reproduce the elasticity, tissue properties and tactile feedback of human tissue[69]. Workshops with animal models

are being organized in many specialized training centres with the potential to aid in speeding up the learning process and achieve initial competence in ESD in a safe learning environment with direct one-on-one expert supervision. This is especially relevant where there are few adequate cases in clinical practice, and expert supervision is not readily available or hard to organize[70-72]. Simulation with explanted animal organs like the oesophagus, stomach and colon, facilitates the execution of therapeutic endoscopic procedures in a more realistic fashion with lower costs compared to mechanical simulators[73]. Ex vivo models have the advantage of being easy to assemble, more affordable and raising less ethical issues when compared to live animal models. On the other hand, the ex vivo model lacks a certain degree of realism due to its inability to bleed, although modifications can permit simulated blood flow and bleeding[64, 73-75]. Harvested organs can be attached to insertion tubes or assembled in plastic models, thus oesophageal, gastric and colonic models are available[76-79]. The Erlangen Active Simulator for Interventional Endoscopy (EASIE) was the pioneer and is the best known model, in which explanted organs are mounted in a human shaped plastic torso[80]. It has been suggested that ex vivo models cannot substitute in vivo training to acquire competence in ESD because even fresh cadaveric animal tissue is stiffer and generally more robust than live human tissue which alters the ESD technique. It is advised that learners proceed to live animal models soon after acquiring adequate basic ESD skills on explanted organs[72, 74]. Animal models, generally anesthetized pigs, have breathing movements, heart beats, peristalsis, intraluminal secretions, tissue reaction to injection and electrocautery, and abdominal distension which more closely resembles the human setting. It is possible to deal with adverse events, such as bleeding and perforation in a more realistic setup. Usually, the submucosal injection is more difficult compared to human cases, with a lesser degree of bleeding, and often more fibrosis. The orientation of various organs can be different and pathological scenarios are generally difficult to be reproduced[64, 71, 74, 81]. The thickness and stiffness of the gastric porcine mucosal layer appears to be different from the human stomach[82]. In fact, mucosal layer in this model is thinner in the proximal stomach and thicker in the distal area, particularly at the level of the greater curvature, where ESD is more challenging than in a similar human procedure. It has been suggested that the greater curvature, particularly the distal part of the porcine stomach is the least suitable place for ESD training[83]. Initial attempts ought to be in the gastric antrum and then progress can be made to more proximal regions of the stomach and other organs such as the oesophagus or colon[70, 76, 78]. Validity and clinical benefit of training ESD in this model and subsequent complication management has not been well established and is currently being investigated by our study group. Nevertheless, by training in the animal model it is possible to recognize a learning curve regarding procedure time, completeness of procedures and adverse events. A study demonstrated that the mean resection time was significantly decreased for porcine gastric ESDs in the second half

of the study cases[71]. In another study, two novice endoscopists were able to decrease procedure times, perforation rate and achieve 100% en bloc resection after accomplishing 30 gastric ESDs in an ex vivo porcine model[77]. The rates of endoscopic closure for colorectal perforations by two non-experts increased from 40 and 60% in the first five cases compared to 100% in the last five procedures[75]. Lastly, four endoscopists without any ESD experience were able to perform uneventful human gastric ESD after training in ex and in vivo animal models, thereby demonstrating the transfer of skills to a patient-based setting[72]. Based on the few studies that are available on this subject, a minimum of 10 to 30 gastric ESD procedures in the animal model should be recommended before moving to human cases[77, 84, 85]. Performing ESD in the oesophagus is more demanding than gastric ESD. This is in part due to the thinner muscle layer and the tubular shape of the oesophagus which provides a limited space to work in[67]. It has been demonstrated that by training in ex vivo models for oesophageal ESD, endoscopists with experienced in gastric ESD, were able to reduce the operation time and the number of deep injuries to the muscularis propria after ten procedures, when the five initial ESDs were compared to the final five[76]. Colorectal ESD is technically the most demanding. Difficult positioning and an increased risk for adverse events, mostly perforations, make it particularly challenging, even for the expert endoscopist. Training is therefore essential and animal models may play an essential role[74, 86]. Live animal models for colorectal ESD are difficult to prepare as it requires adequate bowel preparation before attempting any procedure. For colorectal ESD training, porcine and bovine ex vivo models have demonstrated their feasibility[75, 79]. In a study using an ex vivo model for colonic ESD, technical proficiency increased over ten procedures. In the first two cases, incomplete resections and perforations occurred, whereas in the following cases procedure time decreased and no further adverse events occurred[78].

A glance at the future

Numerous simulators have been developed over the last decades. The aim of simulator-based training is to provide a platform for training in a specialized learning environment and the possibility to repeat procedures in order to gain competence before performing patient-based endoscopic procedures. Ideally, this reduces patient's burden and results in well-trained, well-prepared and to some extent competent endoscopists. Current simulators, whether (VR) simulators, ex vivo or in vivo models, are still lacking the degree of realism that would be necessary to achieve full competency at a level where certification could be applicable. The conclusion of a large overview of our current state is that simulators have proven their value in training novice endoscopists through their first steps in the world of flexible endoscopy. As well as at the far end of the spectrum, where they can be used to train a select group of experienced endoscopists in advanced endoscopic resection techniques. The large part in between seems to be void. The best

example is the standard polypectomy training. A simulation-based scenario is not available for this kind of rather routine procedures, which however incur risks of adverse events and which is performed by virtually all endoscopists. Future research is needed to focus mainly on common therapeutic interventions such as polypectomy and EMR of sessile polyps up to two centimeter, stricture dilatation, stent placement and bleeding scenarios like variceal bleeds using rubber band ligation or endoscopic therapy for ulcer bleeds. Studies should focus on validating and improving the performance of the models, but also on the transfer of skills to patient-based settings, a step that is often omitted but that is in fact the only proof of concurrent validity. Another vast area in the broad arsenal of GI endoscopists includes ERCP and endosonography. Endosonography is no longer a diagnostic procedure for the few where little harm is done but is widely practiced with an increasing number of therapeutic possibilities. This makes EUS more complex. The therapeutic procedures have a particularly significant overlap with ERCP and demand a great deal of expertise. It seems that we have just touched the tip of the iceberg when it comes to simulation-based training for ERCP and EUS. This is in huge contrast with the fast developments in therapeutic indications and possibilities that these procedures offer. Models for ERCP training are already available but the full potential of these models have not yet been established, as well as their impact on clinical practice. Regarding EUS, data are even more scarce.

In a world where we are striving for more transparency in competency and procedural outcomes, simulation-based training is bound to have an increasingly important role. Certification and credentialing of simulator derived expertise would be the next logical step to ensure an optimal safety environment for everybody involved. The final stage of learning will always be to some extent patient-based. Our goal is that when this stage is reached we are dealing with trainees who have been well prepared by simulation-based scenarios.

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3

Face and construct validity of a novel mechanical ERCP simulator

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Endoscopy International Open, 2018

ABSTRACT

Background and Aims: Simulation-based training has become an important pillar in competence-based medicine. However, limited data are available on the use of simulators in ERCP training. We aimed to determine the face and construct validity of the Boškoski-Costamagna mechanical ERCP Trainer, and to assess its didactic value, as judged by experts.

Methods: Participants were divided into four groups based on ERCP lifetime experience: novices, intermediate, experienced, and experts. Participants performed several standardized assignments on the simulator. Outcome parameters included times to complete the procedure, ability to cannulate both ducts, number of attempts to cannulate the common bile duct and pancreatic duct, number of inadvertent pancreatic duct cannulations, successful stent placement, and successful stone extraction. All experts filled out a questionnaire on the simulator's realism and didactic value.

Results: Novices (N=11) completed the total procedure in 21:09 (min:sec), intermediates (N=5) in 10:58, experienced (N=8) in 06:42 and experts (N=22) in 06:05. Experts were significantly faster than novices (Kruskal-Wallis test $p<0.000$). Experts rated the realism of the simulator 7.12 on a ten-point Likert scale. The potential as a training tool of the simulator in training novices was rated 3.91 on a four-point Likert scale, and there was a high agreement among experts to include the simulator in the training of novice endoscopists (3.86 on a four-point Likert scale).

Conclusions: The novel Boškoski-Costamagna ERCP simulator demonstrates good face and construct validity. ERCP experts highly agree on the didactic value and added value of this simulator in the training curriculum of novice endoscopists.

INTRODUCTION

Endoscopic Retrograde Cholangiopancreatography (ERCP) is considered to be an advanced endoscopic procedure and is one of the most technically demanding and high-risk procedures in gastrointestinal endoscopy. The procedure may result in life-threatening short-term and long-term complications, and therefore, ERCP carries a higher risk for morbidity and mortality than most other endoscopic procedures[1]. Achieving competence in ERCP requires a great deal of training and an extensive number of procedures, but there is still no consensus on the assessment of a trainee's competence. Currently, in most training centers around the world, threshold numbers are still used as a surrogate for competency and certification. The first publications concerning the minimal number of ERCP procedures that must have been completed to gain technical competence were published back in the early 1990s and report numbers ranging from 100 to 180 procedures[2-4]. The current guideline of the American Society for Gastrointestinal Endoscopy (ASGE) recommends mastery of at least 200 ERCP procedures to gain competence[5]. However, a recent study of Cotton et al. describes that only a minimal number of hospitals in the United States of America adhere to these guidelines[6]. Thereby, there is growing evidence that competence should be established by objective performance criteria[7-9].

Nowadays, trainees learn to perform ERCP by hands-on training in a clinical setting on real patients under the supervision of a trained endoscopist: the so-called master apprentice model. This setting offers immediate feedback from an experienced endoscopist, but it also has certain drawbacks. Trainees learn by 'trial and error', which potentially increases patient discomfort and the risk of complications and prolonged procedure time, which has additional economic consequences. Simulators offer the potential to train in a dedicated 'learning environment, offering a less stressful situation with less potential risks and the opportunity to endlessly repeat specific tasks.

Simulator-based gastrointestinal endoscopy training has gained acceptance over recent decades and has been extensively studied. Multiple simulators have been validated and it has been demonstrated that the use of simulators in gastrointestinal endoscopy accelerates the early learning curve of trainees[10-13]. The proven value of simulator-based training has led to the recommendation of the introduction of gastrointestinal simulators in the curriculum for endoscopist being trained in forward viewing endoscopy[12]. Simulator-based training seems ideally suited as a training platform for ERCP, due to the complexity of this procedure and its associated complications. Although simulator training in ERCP has been possible for quite some time now, there is very limited scientific data on application of endoscopic simulators in ERCP in training novice endoscopists. Six simulators have been described in the literature. Nevertheless, despite their definite

training potential, the applicability of each of the simulators as a certified training tool has not been demonstrated. Before using a novel simulator as a training tool, it is essential to carry out a study to scientifically determine its validity. Studies evaluating face and construct validity demonstrate the appropriateness of using a simulator for training or assessment[14,15]. Validity assessment of a medical simulator can be performed on different levels. One of the most commonly used forms of validation is face validity, in which a defined group of subjects are asked to judge the degree of resemblance between a training simulator and the real activity. This is often combined with construct validity. This describes the degree to which the assessment can discriminate between different experience levels. The most powerful evidence is gained through concurrent validity, in which performance on the system is compared with outcomes from an established assessment method designed to measure the same skills or attributes. This implies that experience gained by training on the simulator results in improved performance in patient-based procedures[13-15].

The Boŝkoski-Costamagna ERCP Trainer is a novel mechanical ERCP training model developed and produced by Cook Medical (Cook Medical, Limerick, Ireland) in close collaboration with the Digestive Endoscopy Unit of the Gemelli Hospital in Rome, Italy (dr. Boŝkoski and prof. dr. Costamagna). It is designed to guide trainees on how to correctly position the endoscope in front of the papilla, in order to attain a proper axis and to achieve deep cannulation from where several therapeutic interventions can be performed, such as plastic or metal stent placement and stone extraction[16]. An initial report has been published by Jovanovic et al. showing the potential value of the model[17]. However, no attempt was made to scientifically assess the validity of the model. The present study had three aims: to determine whether the simulator can distinguish between endoscopists with different levels of experience (construct validity); to evaluate the extent to which the ERCP simulator simulates actual ERCP procedures (face validity); and to assess the value of the simulator as a training tool, as judged by experts.

METHODS

Simulator

The Boškoski-Costamagna ERCP Trainer (Cook Medical, Limerick, Ireland) is a mechanical endoscopic simulator (Figure 1 & Figure 2). The simulator has been designed in order to train residents on correct positioning of the endoscope, based on the knowledge that a successful ERCP procedure is much dependent upon the ability to achieve an optimal position of the scope tip in front of the papilla. The model consists of a metal framework with the oesophagus, stomach, and duodenum constructed from plastic. The various papillae are made out of latex with both bile and pancreatic ducts inserted in different

varieties intended to resemble known anatomical variations. The simulator enables the use of a real endoscope and commonly used equipment. The model can be placed on a table and real time fluoroscopy image is made visible on a secondary screen using a small camera. (Figure 3) The Boškoski-Costamagna ERCP Trainer can simulate different patient positions (prone, oblique and supine) and a variety of ERCP procedures: scope insertion, wheel and elevator handling, selectively cannulating the bile and pancreatic duct, stone extraction, and both metal and plastic stent insertion. The level of difficulty can be adjusted based on the variations of the papillary anatomy and biliopancreatic junction[16]. The currently used version during the entire study is the second generation of the ERCP Trainer.

Figure 1. The Boškoski-Costamagna ERCP Trainer.

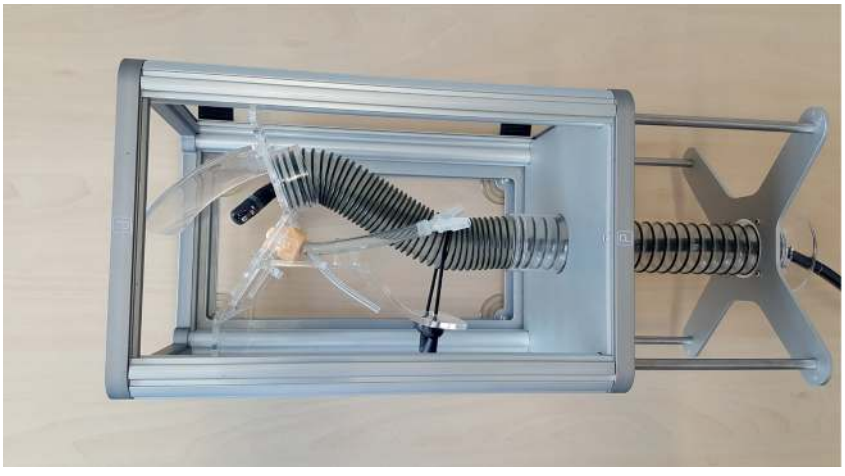

Figure 2. The Boškoski-Costamagna ERCP Trainer: perspective from above.

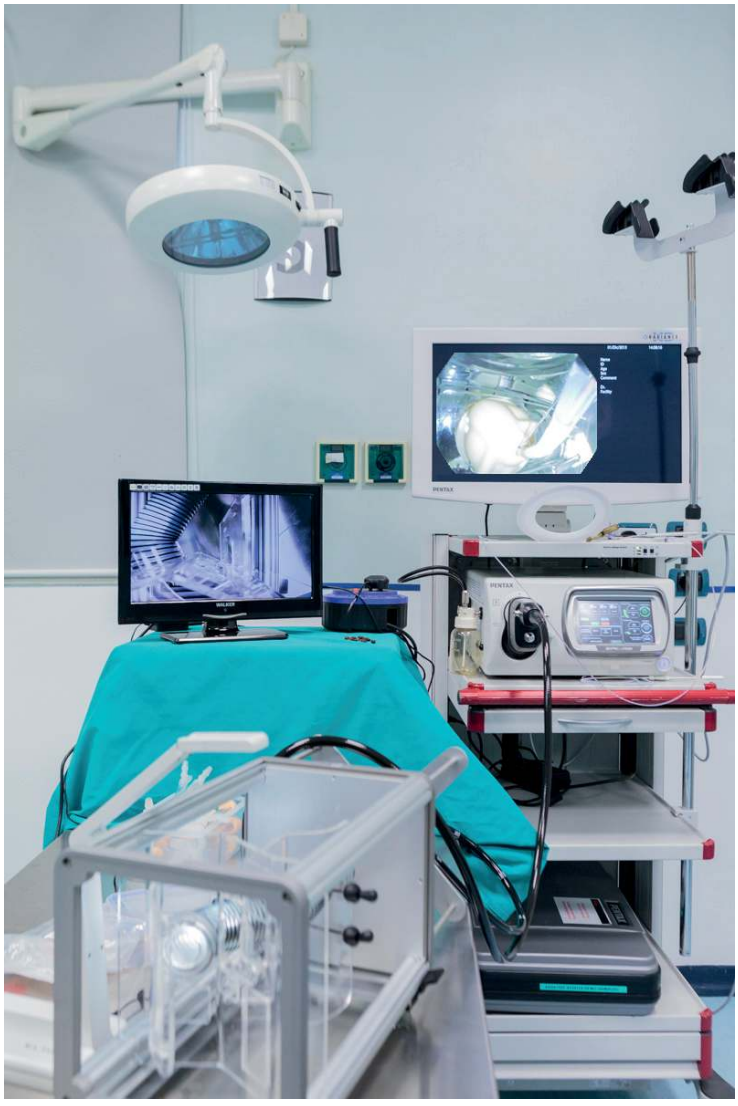

Figure 3. Complete simulator set-up.

Participants

We included four groups of participants in this study: novices, intermediates, experienced, and experts. The participants were divided into these groups based on lifetime ERCP experience. There is no consensus in the literature when it comes to numbers expressing experience levels in ERCP. Therefore we attempted to define the groups according to the most reported numbers in the literature[18-20]. The bar for the expert group was deliberately raised to 2500 ERCPs lifetime to reassure an expert group with an undisputed reputation. The first group, the novices, was defined as participants with

less than 50 lifetime ERCPs. The second group, the intermediates, had a lifetime experience of 50 to 600 ERCPs. The third group consisted of experienced participants with a lifetime experience of 601 to 2500 ERCPs. Based on previous studies concerning ERCP, we assumed that experts would be twice as fast in the completion of the ERCP simulator assignments compared to novices[19,21,22]. A sample size calculation reveals a minimal sample of seven participants both in the novice and expert groups to achieve a power of 0.80. All participants were invited for a simulator session in a similar private conference room either in our hospital, during a national conference of the Dutch Society of Gastroenterology in Spring 2016 or during the Digestive Disease Week in May 2016. During the procedures the participants were assisted by five alternating endoscopy nurses from the Erasmus MC with a broad experience in assisting ERCP procedures and good English conversation skills.

Questionnaire

All participants filled out a questionnaire on demographics, medical experience, and endoscopy experience. Endoscopy experience included the numbers of various endoscopic procedures performed annually and estimated lifetime numbers. Additionally, participants were asked about previous experience with other medical simulators. After performing a standardized set of assignments on the simulator, experts were asked to rate their appreciation of the realism of the ERCP Trainer. Appreciation was expressed on a 10-point Likert scale[23], varying from very unrealistic (1) to very realistic (10). Questions were asked about the realism of the simulator setup, anatomical representation, difficulty, the handling of the endoscope, haptic feedback, and imaging. Additionally, experts were asked to evaluate the didactic value of the Boškoski-Costamagna ERCP Trainer on a 4-point Likert Scale.

ERCP Simulation

All participants were invited to perform six standardized assignments. The first assignment was to establish a correct position of the endoscope in front of the papilla to gain a proper axis for cannulation. The second assignment was to cannulate the common bile duct (CBD) during which the number of unintentional pancreatic duct (PD) cannulations was also scored. The same applied for PD cannulation and unintentional CBD cannulations. Next, participants were asked to place a plastic stent in the PD and a plastic stent in the CBD. Finally, participants were asked to extract a single stone from the common bile duct using an extraction basket. A coffee bean was used as a stone. For each exercise time was recorded, with a time limit of 10 minutes per assignment for logistical reasons. After 10 minutes the procedure was scored as failed. Participants were not made aware of the time limit at the start of the assignment and they were encouraged to complete the exercises to best of their ability without a competitive intent.

Data analysis

All statistical analyses were performed using SPSS 21.0 software (IBM Corp: Armonk, NY). Descriptive statistics were used for all measures. Assuming that the experts require less time to fulfil the assignments compared to novices, variations in outcomes between groups were compared using a Kruskal-Wallis test. A separate analysis between the four groups was performed using a Mann-Whitney U Test. Data are presented as median and range. A p-value of less than 0.05 was considered significant.

RESULTS

Participants

In total, 46 participants were included in the study, 11 novices, 5 intermediates, 8 experienced ERCPists and 22 ERCP experts, they originated from 20 different countries from all continents. The percentage of female participants was 21.7% and all ERCP experts turned out to be male. The mean number of years of endoscopic experience was 23.32 (range 15 – 34) for experts and 1.6 years for novices (range 0.1 – 5.0). Novices claimed 100% familiarity with previous use of endoscopy simulators, experts reported 77.3%. All participants completed the exercises and filled out the evaluation form. Figure 4 displays the study design and baseline characteristics can be found in Table 1.

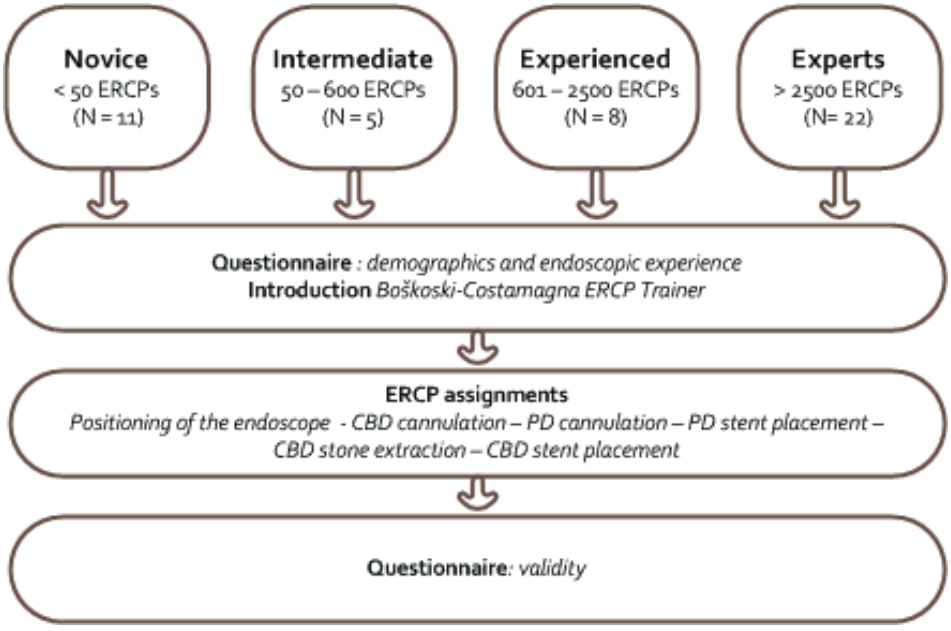

Figure 4. Study design.

Table 1. Baseline characteristics.

	Novices	Intermediate	Experienced	Experts	Total
No. participants	11	5	8	22	46
Male (%)	27.3	60	100	100	78.3
Mean age (y)	32.3	38.4	46.5	52.0	45.0
Academic hospital (%)	45.5	100	87.5	95.5	82.6
Endoscopic experience (y)	1.63	7.2	15.5	23.3	15.1
Simulator familiarity (%)	100	80	62.5	77.3	80.4

Novice, 10 fellows and 1 gastroenterologist; intermediate, 3 gastroenterologist, 1 fellow and 1 surgeon; experienced, 7 gastroenterologists and 1 surgeon; experts, 20 gastroenterologists and 2 surgeons.

Face validity

The ERCP experts rated the Boŝkoski-Costamagna ERCP Trainer 7.12 on a 10-point Likert scale for overall realism. Table 2 details the experts' average ratings of various components of the simulator. Table 3 demonstrates the perceived opinion of the ERCP-specific components, as judged by experts. In general, most of the experts rated the more complex procedural aspects of the Boŝkoski-Costamagna ERCP Trainer as very realistic. Biliary plastic stent placement scored 7.99 on a ten-point Likert scale, pancreatic plastic stent placement 7.80 and removal of a common bile duct stone 7.42.

Table 2. Expert opinion on the Boŝkoski-Costamagna ERCP Trainer.

Component	Average rating* N=22
Overall realism	7.12
Overall difficulty	6.86
Simulator setup	7.50
Anatomical representation	7.18
Endoscopic control	7.70
Haptic feedback	7.32
Endoscopic image presentation	7.82
Radiologic image presentation	6.41

*Scores are based on a 10-point Likert Scale (1= very unrealistic, 10= very realistic)

Table 3. Expert opinion on the Boŝkoski-Costamagna ERCP Trainer – ERCP Procedures.

Component		**Average rating* N=22**
Biliary plastic stent placement	Overall	7.99
	Anatomical representation	8.23
	Endoscopic control	8.24
	Haptic feedback	7.64
Pancreatic plastic stent placement	Overall	7.80
	Anatomical representation	7.90
	Endoscopic control	8.10
	Haptic feedback	7.52
Stone removal	Overall	7.42
	Anatomical representation	7.59
	Endoscopic control	7.64
	Haptic feedback	7.05

**Scores are based on a 10-point Likert Scale (1= very unrealistic, 10= very realistic)*

Construct validity

Construct validity of the Boŝkoski-Costamagna ERCP Trainer was evaluated by comparing the procedure time and attempts at success per assignment across the four groups. Data output regarding the construct validity is presented in tables 4 and 5. All assignments were completed faster by the experts (p=0.000), experienced (p=0.000) and intermediate (p=0.052) than by the novices (Table 3). Novices (N=11) completed the procedure in a mean time of 21.09 (min:sec), intermediates (N=5) in 10.58, experienced (N=8) in 06.42, and experts (N=22) in 06.05. Unintentional CBD cannulation occurred with a median of 4.6 in novices, 0.8 for intermediates, 2.0 for experienced, and 1.4 unintended CBD cannulations for experts(p=0.028). Unintended PD cannulation occurred less frequent, median of 0.4 for novices, zero unintended cannulations for intermediates and experienced, and 0.2 for experts (p=0.449). There were no statistical differences between novices and experts in the number of attempts per assignment (p=0.985). We performed a separate analysis between the four groups using a Mann-Whitney U test. No statistical significant differences were seen between the intermediate, experienced and experts, they performed all assignments faster than the novices (Table 4).

Table 4. ERCP assignments overview in procedural time.

		Novice N=11	Intermediate N=5	Experienced N=8	Expert N=22	P-value*
Positioning endoscope	Mean	01:07	00:26	00:11	00:14	0.000
	Median	00:59	00:15	00:10	00:12	
	Range	00:25 - 02:31	00:09 - 01:08	00:08 - 00:20	00:06 - 00:40	
CBD cannulation	Mean	02:03	01:36	00:48	00:39	0.000
	Median	02:05	00:52	00:45	00:40	
	Range	00:37 - 04:05	00:28 - 03:24	00:11 - 01:14	00:05 - 01:31	
PD cannulation	Mean	05:47	01:55	01:09	01:06	0.013
	Median	06:27	01:17	01:13	00:27	
	Range	00:12 - 10:00	00:13 - 06:18	00:05 - 03:58	00:06 - 05:17	
PD stent placement	Mean	03:35	00:43	00:45	00:39	0.000
	Median	06:53	00:47	00:48	00:38	
	Range	01:15 - 10:00	00:30 - 00:49	00:26 - 01:12	00:13 - 01:27	
CBD stone extraction	Mean	05:11	03:05	02:31	01:25	0.044
	Median	03:55	01:46	02:41	01:06	
	Range	01:38 - 10:00	00:47 - 10:00	00:32 - 04:24	00:37 - 03:32	
CBD stent placement	Mean	04:21	03:11	01:15	01:25	0.000
	Median	03:42	01:56	01:08	01:06	
	Range	01:14 - 10:00	01:03 - 08:38	00:51 - 01:48	00:37 - 03:32	
Total procedure time	Mean	21:09	10:58	06:42	06:05	0.000
	Median	20:21	10:20	06:33	05:39	
	Range	07:16 - 34:07	04:20 - 28:49	04:32 - 09:10	02:32 - 12:02	

Procedural time in mm:ss, *Kruskal-Wallis Test

Table 5. Differences between groups.

		Novice vs. Intermediate	Novice vs. Experienced	Novice vs. Experts	Intermediate vs. Experienced	Intermediate vs. Expert	Experienced vs. Expert
Positioning endoscope	Chi-square	6.500	0.000	6.000	10.000	33.000	75.000
	Asymp.sign.	0.013	0.000	0.000	0.171	0.186	0.565
CBD Cannulation	Chi-square	17.000	12.000	17.000	12.000	25.000	70.000
	Asymp.sign.	0.267	0.007	0.000	0.284	0.064	0.420
PD Cannulation	Chi-square	12.000	15.000	42.000	14.000	42.000	80.500
	Asymp.sign.	0.090	0.016	0.002	0.435	0.447	0.730
PD stent placement	Chi-square	0.000	0.000	2.500	17.500	43.500	67.500
	Asymp.sign.	0.002	0.000	0.000	0.724	0.485	0.344
CBD Stone extraction	Chi-square	11.500	26.000	50.000	17.000	54.000	68.000
	Asymp.sign.	0.069	0.152	0.006	0.724	0.976	0.368
CBD Stent placement	Chi-square	18.000	3.000	22.000	8.000	27.000	80.000
	Asymp.sign.	0.320	0.000	0.000	0.093	0.086	0.730
Total procedure time	Chi-square	10.000	2.000	6.000	18.000	40.000	66.500
	Asymp.sign.	0.052	0.000	0.000	0.833	0.377	0.320

Mann-Whitney U Test, two tailed test, exact significance

Didactic/Training value

Expert opinion was that the Boŝkoski-Costamagna ERCP Trainer is a useful tool in the basic training of novice endoscopist (3.91 on a four-point Likert scale) and that the ERCP trainer should be incorporated into the training of novice endoscopists (3.86 on a 4-point scale). The expertise gained on this simulator should be applicable in a clinical curriculum (3.59 on a four-point scale). Most experts agreed that there is a limited role for the simulator in the training of experienced ERCP performing endoscopists (rated 1.86 on a four-point scale).

DISCUSSION

This study reports the first formal validation of the Boškoski-Costamagna mechanical ERCP Trainer and demonstrates good construct and face validity. We demonstrate the results of endoscopists originating from all over the world, classified in four different expertise levels based on ERCP lifetime experience. The data reveal that the simulator is able to discriminate between different levels of expertise. Both experienced and expert endoscopists demonstrated superior performance on all parts of the ERCP procedure compared to novices.

All experts agree that the Boškoski-Costamagna ERCP Trainer seems to offer a satisfactory representation of clinical ERCP and that the expertise gained on the simulator should be transferrable to a clinical curriculum The tactile feedback of the simulator was evaluated positively, even though the mechanical ERCP simulator is constructed from plastic and rubber components. The specific strengths of the simulator are the high levels of realism of the more complex ERCP interventions, such as stent placement and stone extraction. This means that this novel ERCP simulator provides us with a platform to train inexperienced endoscopists in these complex procedures until they feel comfortable and perform up to a certain standard before exposing them to actual patient procedures. Our data do not support the use of this simulator in training endoscopists who already have a more experienced performance level.

A recent systematic review by our study group[10] presented an overview of the current available simulators and their known potential in training novices. Only six simulators have previously been described in the literature[18,19,21,24-26]. A comparison validation study of three of the available simulators was performed by Sedlack et al.[27] They included the Erlangen Endo Trainer, a bio simulation model, the live porcine model and the GI Mentor II, a virtual reality simulator. The study describes the potential value of all the simulators in training novice endoscopists, but they all have certain advantages and disadvantages. In terms of realism, bio simulation models and live porcine models scored higher than mechanical and virtual reality simulators. However, major drawbacks of these types of

simulators include costs and organizational difficulties due to the ethical incidentals. The X-Vision ERCP training simulator and the ERCP mechanical simulator have not been included in the study of Sedlack et al., both mechanical simulators[21,22]. The X-vision ERCP trainer has been validated, but no studies have been published on the implementation of the model in a training setting. The ERCP Mechanical Simulator has proven its training value in novice trainees[28].

There were some limitations in our study. It would have been ideal to include only naive trainees in the group with novices, we included five novices without any experience and six novices with less than 50 performed ERCPs. There is bias in terms of exposure and experience. However, with the current ASGE guidelines in mind, defining ERCP competence after at least 200 cases[5], our novices are all in their very early learning curve. Another limitation might be the use of procedure times for the various ERCP assignments as a proxy for competence. Time as a surrogate marker for outcome is not ideal. However, in many simulation validation studies it is unavoidable to use procedure times. This is an accepted method where participants are not made aware of the time element and encouraged not to give their fastest but to give their best performance[21, 29-32].

We believe that compared to the previously described simulators, the Boškoski-Costamagna ERCP Trainer has added value. It has the advantage that a real endoscope and real accessories are used, providing novice endoscopists with the opportunity to learn how to handle the movements of the endoscope and experience the haptic feedback of their actions. Fluoroscopy image is created with the use of a simple camera, without the need for specific x-ray equipment. The total set-up creates the idea of a standard endoscopy unit. The Boškoski-Costamagna ERCP Trainer is light enough to be transported, is easy to set up, and is not restricted to a specific environment. Despite the mechanical aspect of the model, its realism was scored satisfactory by experts. Experts believe that the Boškoski-Costamagna ERCP Trainer will improve trainee performance in the early training setting.

CONCLUSION

The Boškoski-Costamagna ERCP Trainer demonstrates good face and construct validity as a novel simulator for basic ERCP training. Experts generally agree on the didactic strength and added value of this simulator in the training curriculum of novice endoscopists.

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4

Face validity of a synthetic papilla designed for biliary sphincterotomy training

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Endoscopy International Open, 2019

ABSTRACT

Background: ERCP is considered one of the most technically demanding endoscopic procedures. Still, limited data are available on simulators in ERCP training. Recently, the Boškoski-Costamagna ERCP Trainer was validated as a realistic training model by our study group. As an extension to this model, a novel synthetic papilla has been designed allowing to train biliary sphincterotomy. We aimed to determine the face validity of this synthetic papilla and its didactic value for training sphincterotomy.

Methods: Expert participants, each with more a than 2500 ERCPs lifetime experience, were invited to perform a biliary sphincterotomy and fill out a questionnaire on the realism of the procedure and the didactic value.

Results: A total of 40 ERCP experts were included, originating from 16 different countries. Experts' opinion on realism of performing a biliary sphincterotomy was rated with a median of 7 on a ten-point Likert scale, resemblance of the performed manoeuvres 8and tactile feedback 7. When asked if the cutting was perceived as realistic, experts rated 6 and the cutting result was rated 8. The potential as a training tool of the cutting papilla in training novices was rated 4 on a four-point scale, and there was a high agreement among the experts to include the papilla in the training of novices (4).

Conclusion: This is the first synthetic papilla available for trainingsphincterotomy on the Boškoski-Costamagna ERCP Trainer and it demonstrates good face validity. ERCP experts highly agree on its didactic value and added value in the training curriculum of novice endoscopists.

INTRODUCTION

Endoscopic Retrograde Cholangiopancreatography (ERCP) is one of the most technically demanding and high risk procedures in gastrointestinal endoscopy. Traditionally, trainees learned endoscopy by hands-on training in clinical setting on real patients under the supervision of an experienced endoscopist. In the last decades, simulators have gained an important role in creating sufficient hands-on training, without compromising patient safety, and to create a safe learning environment for trainees[1]. Despite the fact that ERCP seems to be an ideal platform for simulation-based training, limited data are available on simulators in training ERCP. Recently, our study group has validated a novel mechanical ERCP simulator, the Boškoski-Costamagna ERCP Trainer[2]. This simulator enables novice trainees to practice cannulation, stent placement in both common bile duct (CBD) and pancreatic duct (PD) and CBD stone extraction. So far, this simulator was not equipped with a papilla that could be used to train endoscopic sphincterotomy.

Endoscopic sphincterotomy was first reported in 1974 and is one of the key therapeutic interventions during ERCP[3]. At the same time, it is also considered one of the more risky parts of the procedure. This is because of its technical difficulty and its associated risk of bleeding, perforation and post-ERCP pancreatitis[4,5]. These complications are most often a result of an incorrect performed sphincterotomy and frequently associated with trainees or inexperienced endoscopists[5]. First experience in sphincterotomy is usually acquired through practice during live cases in an “on-the-job” setting. It goes without saying that this is not the ideal situation to train for such a complex procedure for both trainees and trainers alike, let alone the patient. Ideally, such training requires a simulated setting that resembles the real thing as close as possible without jeopardizing patient safety and preferably the possibility to break down the procedure in steps that can be repeated as many times as necessary in order to gain proficiency. Currently, only a handful of training models are available for training ERCP and not every model is equipped with the possibility to train sphincterotomy. Available training models include in vivo and ex vivo training simulators, mechanical simulators and virtual reality simulators[6-12]. Each training model shows its own prominent features, but have all important limitations, including ethical and practical concerns, differences in anatomy of the papilla, and lack of realism and tactile feedback. Up until now, no optimal training model for training sphincterotomy has been designed yet. A novel synthetic papilla has recently been developed and produced by Cook Medical (Cook Medical, Limerick, Ireland) for the Boškoski-Costamagna ERCP Trainer in order to train sphincterotomy. This is a single-use synthetic papilla that can be easily replaced for repeated attempts at sphincterotomy. Validity assessment of a simulator can be performed on various levels. One of the most commonly used forms of validation is face validity. Face validity is evaluated by a defined group of subjects who are asked to judge the degree of resemblance

between a training model and the real activity. The aim of this study was to evaluate the extent to which the novel papilla simulates real-life endoscopic biliary sphincterotomy, and to assess the didactic value or potential of the papilla for sphincterotomy training.

MATERIALS AND METHODS

Synthetic papilla

The synthetic papilla is a newly developed insertable component in the previously described mechanical ERCP simulator, the Boškoski-Costamagna ERCP Trainer (Cook Medical, Limerick, Ireland)[2]. It can be used to perform sphincterotomy. This novel synthetic papilla is made out of rubber and metal filaments and can be easily manually inserted into the Boškoski-Costamagna ERCP Trainer (Figures 1 and 2). It is a single-use disposable papilla, with a specific alloy allowing for electrical conduction and cutting of the material with all commercially available sphincterotomes and needle knives.

Figure 1. The synthetic papilla. **a**. Front view of the papilla. **b**. Close-up of the papilla, demonstrating the rubber with incorporated metal filaments.

Figure 2. The Boškoski-Costamagna ERCP Trainer. (Source: Cook Medical, Bloomington, Indiana).

Participants

We included participants with a broad experience in ERCP based on lifetime endoscopic experience. Expressing experience levels in ERCP remains debatable, currently there is no consensus in the literature. In our previous study[2] we attempted to define four groups of participants according to the most reported numbers in the literature[13-15]. We set the bar for the definition of ERCP experts on 2500 ERCPs lifetime to reassure a group with an irrefutable reputation and broad experience in performing sphincterotomy.

Sphincterotomy simulation setting

All participants performed a simulator session during the course of the UEG Week in 2016 in Vienna, Austria. Experts were asked to perform a single biliary sphincterotomy and to fill out a questionnaire on demographics, medical experience, and endoscopy experience, including the numbers of ERCP procedures performed annually and estimated lifetime numbers. We asked the participants to perform a sphincterotomy using a standard sphincterotome (Omnitome, Cook Medical, Limerick, Ireland) Following this assignment, they were asked to rate their appreciation of the realism of the cutting papilla. Appreciation was expressed on a 10-point Likert scale[16], varying from very unrealistic (1) to very realistic (10). Questions were asked about the realism of performing sphincterotomy, anatomical representation, difficulty, the actual cutting and the achieved cutting result. Furthermore, experts were asked to evaluate the didactic value of the cutting papilla on a 4-point Likert scale, varying from strongly disagree (1) to strongly agree (4).

Data analysis

Statistical analyses were performed using IMB SPSS Statistics, Version 24.0. Armonk, NY: IBM Corp. Descriptive statistics were used for all measures. Data are presented as median and interquartile range. Inter-rater agreement and reliability were evaluated by computing the intraclass correlation coefficient (ICC) in a two-way mixed model.

RESULTS

Participants

In total, 40 ERCP experts participated in this study originating from 16 different countries worldwide. Of the participants, 37 were gastroenterologists and the remaining three participants (7.5 %) were surgeons. All participants were male, with a mean age of 49.6 years (standard deviation 9). Mean number of years in practice as an endoscopist was 20.9 (interquartile range 11). All participants completed the assignment and filled out the questionnaire. Baseline characteristics can be found in Table 1.

Table 1. Expert baseline characteristics

Characteristics	
Male, n (%)	40 (100%)
Age, years[a]	49.6 (9)
Number of countries	16
Profession, n (%)	
Gastroenterologist	37 (92.5)
Surgeon	3 (7.5)
Endoscopic experience, years[b]	20.9 (11)

a Data are expressed as mean and standard deviation
b Data are expressed as median and interquartile range

Face validity

The experts rated the anatomical representation of the synthetic papilla 8 on a 10-point Likert scale. Adequacy to position the endoscope in front of the papilla scored 9. Table 2 shows the experts' ratings on the papilla and its performance. The realism of performing a biliary sphincterotomy scored 7 on a 10-point Likert scale. Resemblance of maneuvers compared to real life scored 8 by the experts and the associated tactile feedback scored 7 on a 10-point scale. The experts scored the cutting as realistic with a 6 and the cutting result was rated 8 on a 10-point scale. The Intraclass Correlation Coefficient demonstrated strong agreement between the experts (ICC = 0.917), with a 95% CI of 0.796 to 0.983.

Table 2. Expert opinion on the novel synthetic papilla.

	Expert opinion N=40
Resemblance to the real papilla	8 (4)
Position in front of the papilla	9 (1)
Realism of performing sphincterotomy	7 (1)
Making the exact manoeuvres as in real life	8 (1)
Realism of haptic feedback	7 (3)
Cutting is perceived as expected	6 (3)
Cutting result	8 (1)

Data are expressed as median and interquartile range

Didactic/Training value

Experts rated the papilla as a useful tool in basic training of novice endoscopists (4 on a 4-point scale; interquartile range [IQR] 0) and they unanimously agreed that the synthetic papilla should be incorporated in a training curriculum (4 on a 4-point scale; IQR 0). The experts' opinion was that the expertise gained with the synthetic papilla is transferrable

into the clinical setting (4 on a 4-point scale; IQR 1). The role of the synthetic papilla in training more experienced ERCPist was rated to be limited according to the experts (rated 2 on a 4-point scale; IQR 3). The ICC for the average of the 40 experts was 0.983 with a 95% CI of 0.951 to 0.998, indicating an excellent level of interrater agreement and reliability.

DISCUSSION

Performing a sphincterotomy is one of the key elements in ERCP and is considered a challenging and high-risk procedure. Yet, what and how ample training of endoscopists in order to perform safe sphincterotomies should look like is a much debated topic. The most obvious reason why current training practice is considered suboptimal is the lack of a suitable, representative and safe simulator training environment. Here we report the first results and validation of a synthetic papilla that can be used for training sphincterotomy in the Boškoski-Costamagna ERCP Trainer. The data of the current study demonstrate good face validity and ERCP experts from all over the world highly agree on the didactic value and added value of this papilla in the training curriculum of novice endoscopists.

Recently, we presented the Boškoski-Costamagna ERCP Trainer, a mechanical simulator for training ERCP[2]. Experts agreed on the didactic strength of the simulator and the added value of this simulator in the training curriculum of novice endoscopists. An important limitation of this model was the inability to train sphincterotomy. Currently, most endoscopists are being trained, including their first attempts with the procedure, in real-life patients. This is not a desirable situation because there is little to no room for mistakes, not to put patients at risk. Furthermore, clinical training opportunities are limited by the available patients that require a papillotomy and the time and availability of an experienced endoscopist to train the novice ERCPist appropriately. The optimal learning environment is a setting where the procedure can be repeatedly simulated step-by-step in the most realistic way possible with room for mistakes, thus enabling trainees to train inexhaustible to gain technical skills and confidence before being exposed to such a procedure in real-life patient.

Despite the potential of currently available training models[6-12], all these simulators have certain limitations and an optimal model for training sphincterotomy has not been developed yet. In terms of realism, bio simulation models and live porcine models are superior[8, 17]. Live anesthetized pig models have been shown to be adaptable to all procedural aspects of ERCP, including sphincterotomy. In a study by Sedlack et al.[48] participants followed a two-day training course and showed an increase in confidence scores, especially in the complex procedures such as needle-knife pre-cut sphincterotomy[18].

The Erlangen ERCP model[7], an ex vivo tissue model, has been scored as one of the most realistic and useful available training models[17]. Major drawbacks of both in vivo and ex vivo tissue models include important differences between human and porcine anatomy (e.g. location of papilla) and, importantly, for training purpose of sphincterotomy the papilla of the live porcine model can only be used once. The complete set-up requires a lot of preparation and is therefore probably only used in workshops and not in daily training. Additionally, costs and organizational difficulties due to the ethical considerations make this type of simulator setup difficult to incorporate in a training curriculum. Known mechanical trainers for training ERCP include the ERCP Mechanical simulator and X-Vision ERCP Training System[10,11]. Training sphincterotomy on the X-Vision ERCP Training System[11] was carried out using an organic papilla. No details have been provided on the biomaterials that were used. The ERCP Mechanical simulator (EMS)[10] consists of a disposable papilla constructed of foam, held in place by electrical contacts with conducting gel providing electrical conductivity. Studies validating the use of the EMS for training sphincterotomy are lacking. Computer modules for training endoscopic sphincterotomy are available on the Simbionix GI Mentor, with the possibility to train possible complications as well (e.g. bleeding, perforation). Though, the model has received low scores for realism caused by the major lack of tactile feedback and control of handling real equipment[13].

All experts agreed that the novel synthetic papilla well mimics the human papilla for training biliary sphincterotomy. They were satisfied with the realism of performing a sphincterotomy, mainly with the opportunity to practice the exact manoeuvres needed to correctly perform the procedure. The tactile feedback of the synthetic papilla was evaluated positively, despite the fact that the papilla is constructed out of rubber. This probably also explains why the cutting effect was rated only 6 as it is not the same as cutting living tissue. The obvious advantage of this synthetic papilla is that it is easily replaced by a new one after it has been cut thereby offering the possibility to repeatedly train the procedure. Importantly, its use is not impeded by ethical concerns given the mechanical origin of the simulator and papilla. The expert opinion on the possibility to use the synthetic papilla as a training tool was considered of great value in our study and all agreed that the synthetic papilla is a useful tool in training novice endoscopists in performing a sphincterotomy. Experts also agreed that the expertise gained on the papilla should be directly transferrable into a clinical curriculum.

Despite the enthusiasm of experts for the synthetic papilla as a training tool for biliary sphincterotomy, some limitations remain including the absence of simulation of potential complications such as bleeding and perforation. Also, due to the mechanical nature

of the simulator there is no peristalsis and therefore endoscopic control and positioning still differs from to the real-life situation.

Notwithstanding these limitations, we believe that this novel synthetic papilla offers added value over currently available simulator options for training sphincterotomy. It has the advantage that a real endoscope with real accessories are used in a validated mechanical ERCP Trainer model providing novice endoscopists with a safe opportunity to learn how to execute the necessary movements and actions under the supervision of an experienced endoscopists in order to perform a real sphincterotomy with the ability to train the various steps of the procedure as many times as desired.

This novel synthetic papilla is a validated tool for training biliary sphincterotomy on the Boškoski-Costamagna ERCP Trainer. We have demonstrated good face validity, meaning that this papilla can be used to perform sphincterotomies that resemble the real-life situation. ERCP experts highly agree on the didactic value and added value of this papilla in the training curriculum of novice endoscopists.

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5

Impact of ERCP simulator training on the early ERCP learning curves of novice trainees. A multicenter trial.

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Submitted

ABSTRACT

Background and study aim: Simulator-based training has been extensively studied in training gastroduodenoscopy and colonoscopy and shown to significantly improve learning curves of novices. Data on simulator-based training in ERCP are scarce. We aimed to determine the impact of two-days intensive hands-on simulator training on the course of the learning curve of novice trainees.

Methods: We conducted a prospective multicenter trial using a validated mechanical ERCP simulator (Boškoski-Costamagna ERCP Trainer). Six trainees were allocated to the simulation course program (SG). Each of these trainees were paired to an endoscopy trainee starting regular ERCP training at the same center but without be exposed to a simulation course program (control group; CG). The course included lectures, live ERCP demonstrations, and hands-on ERCP training to educate trainees in basic techniques related to cannulation, stent placement, stone extraction and stricture management. After the course, both SG and CG started with their formal ERCP training in their respective centers. The Rotterdam Assessment Form for ERCP was used to register each performed ERCP. Simple moving average was applied to create learning curves based on successful common bile duct (CBD) cannulation. Outcomes were plotted against a historical cohort (HC).

Results: Thirteen trainees were included, six trainees in the SG and seven trainees in the CG with a total of 717 ERCPs. Mean successful ERCP cannulation rate was higher for the simulator group at baseline compared to both CG and HC, 64% versus 43% and 42% respectively. Differences become less explicit after 40 ERCPs, but persist until a median of 75 ERCPs.

Conclusions: We demonstrate that a two-day hands-on simulator-based ERCP training course exerts a positive effect on the learning curves of ERCP trainees and should be considered an integral part of the training curricula for ERCP to develop skills prior to patient-based training.

INTRODUCTION

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a technically challenging procedure with significantly higher complication rates compared to standard endoscopic procedures[1,2]. The outcome of ERCP is highly operator dependent. Complications are more likely to occur when an ERCP is performed by an inexperienced endoscopist[3]. Extensive training and procedural exposure is required to gain both technical and cognitive competency in ERCP.

To date, novice ERCPist are trained in a clinical setting through supervised, hands-on training in real patients. Advantages of the current training system include, amongst others, the opportunity to gain immediate feedback by an experienced endoscopist. However, this approach does have distinct disadvantages. This type of training is an example of learning by 'trial and error' and potentially increases the risk of complications and patient discomfort. Additionally, it adds time and costs to each procedure affecting total capacity and financial resources[4]. Trainees operate in a stressful environment which may be less suited to process feedback appropriately with the risk of being exposed to an overload of new information. The optimal methodology to acquire competence in ERCP is an ongoing topic of debate. Historically, it was assumed that competence is gained when a minimum number of ERCP procedures is performed, with guidelines recommending threshold numbers, varying from 100 to 200 ERCP procedures at which time a trainee should reach a 80% CBD cannulation success rate[5]. In a study of Verma et al.[6], however, it was shown that a CBD cannulation rate of more than 80% was consistently achieved only after 400 supervised procedures. As a result of this study there has been a shift to a more individualized approach, considering that individual trainees develop endoscopic skills at a different pace[7]. The specific role of simulators in training ERCP have not been defined yet. The outcome of simulator-based training on competence in gastroduodenoscopy and colonoscopy have been extensively studied, demonstrating that novices gain significant experience by training on simulators before they are exposed to real patients[8,9]. The improvement of performance seems most prominent in the early phase of the training. For example, a study by Koch et al. evaluating simulator training in colonoscopy demonstrated that there was no further improvement after 60 procedures[10]. Data on simulator training for training ERCP is scarce. Previously, our study group validated a novel mechanical ERCP trainer, the Boskoski-Costamagna ERCP trainer[11,12].

For this study our primary aim was to assess whether a two-days intensive hands-on training including the use of the Boškoski-Costamagna ERCP Trainer in novice ERCP trainees at the start of patient-based training, results in an acceleration and improve-

ment of their learning curve. Our secondary aim was to establish to what extent this advantage would last.

MATERIALS AND METHODS

Study design

This was a prospective multicenter trial conducted in seven tertiary referral centers in five countries (supplementary table 1). A total of 13 advanced endoscopy trainees participated in this study. Allocation of participants was not strictly random, but was based on registration to a two-day ERCP simulator training course in Rome, Italy. Participation in the course was allowed for endoscopists at the beginning of their ERCP career. The simulator course participants (SG, simulator group) were paired with a starting advanced endoscopy trainee at their respective institution to form a control group (CG, control group). At study onset, all subjects completed a questionnaire to determine their demographics, baseline endoscopic experience, ERCP specific experience, and simulator familiarity.

Simulator

The Boškoski-Costamagna ERCP Trainer (Cook Medical, Limerick, Ireland) was used in this study. This is a mechanical simulator and consists of a metal framework with the esophagus, stomach, and duodenum constructed from plastic. The simulator has been designed to train novice endoscopists on correct positioning of the endoscope, assuming that a successful ERCP is largely dependent upon the ability to achieve an optimal position of the endoscope in front of the papilla. The simulator enables use of a real duodenoscope and commercially available accessories. A small video camera provides simulated fluoroscopy. The simulator has been previously described in detail in a validation study[11].

Two-day ERCP training program

The two-day ERCP simulator training course is hosted in the European Endoscopy Training Centre (EETC) at the Gemelli University Hospital, Rome, Italy, and a comparable training setting has been set up at the Eastern Hepatobiliary Hospital, Second Military Medical University, Shanghai, China. The course includes lectures, live ERCP demonstrations, and hands-on ERCP training to teach trainees the basic techniques related to cannulation, stent placement, stone extraction and stricture management. The program starts with a lecture on the basics of cannulation and sphincterotomy techniques, followed by a two-hour session of live demonstrations focusing on the position of the endoscope and cannulation techniques. In the afternoon trainees follow hands-on training on the simulator for at least 3.5 hours. The second day starts with a lecture on

the prevention of biliopancreatic complications followed by live demonstration with additional lectures on stent and stricture management. Subsequently, the trainees are again exposed to hands-on training for at least 2.5 hours. During these hands-on training sessions trainees are able to extensively practice the various techniques under the supervision of experienced endoscopists. The course content was delivered by the EETC faculty and the visiting faculty. The group comprised a maximum of ten trainees and at least one or two ERCP practitioners of the visiting faculty were present. Five Boškoski-Costamagna ERCP Trainers were available for hands-on training. Two trainees were allocated per simulator. Both trainees alternated in their role as assistant and endoscopist. ERCP training was performed using a standard therapeutic duodenoscope (PENTAX Medical, Hoya Corp., Tokyo, Japan) and commercially available accessories from Cook Medical, Limerick, Ireland.

Rotterdam Assessment form for ERCP

Both simulator and control groups started to their formal ERCP training in a real life setting in patients at their own departments. The Rotterdam Assessment Form for ERCP (RAF-E) was used to register and score each performed ERCP. In 2014 Ekkelenkamp et al.[13] demonstrated that this self-assessment tool allows both trainees and trainers to gain insight in procedural quality in ERCP procedures by means of proposed ERCP quality indicators[14]. The tool was used in a second study to evaluate the learning curves of novice trainees[15]. The RAF-E form is largely based on previously validated assessment tools. All ERCPs performed in this study were part of routine clinical care performed at the participating centers. Participants completed a RAF-E form after each procedure.

Historical cohort

Results in terms of successful biliary cannulation rates of both SG and CG were plotted against a historical cohort (HC) of 15 ERCP trainees. In 2014, Ekkelenkamp et al., from the same research group, published the results of a prospective study evaluating the ERCP learning curves of 15 novice trainees in the Netherlands[15]. A total of 1541 ERCPs were included in the study. The trainees followed their regular training program, without previous ERCP simulator training, and documented each performed ERCP using the RAF-E.

Outcome measure

The main outcome measure was successful common bile duct cannulation rate.

Statistical analysis

Statistical analyses were performed using SPSS 25.0 software (IBM Corp: Armonk, NY, USA). Baseline characteristics, group averages and standard deviations were presented

mean, median with standard deviation or interquartile range, respectively. A two-sided value of less than 0.05 was considered significant. Graphs were created with standard software. Simple moving average technique was used to analyze the ERCP learning curves of the trainees based on successful cannulation rates. The moving average technique depicts data points by creating a series of averages of different subsets of the complete data set, we applied the technique with a moving average order of 10 ERCPs.

RESULTS

A total of thirteen trainees (9 male) from six countries were included in this study. The study group (SG) consisted of six trainees. The remaining seven trainees were assigned to the control group (CG). The mean age of the trainees was 32 years. Five (38.5%) trainees had been trained previously on a simulator (gastroduodenoscopy or colonoscopy simulator training), two were assigned to the SG and three trainees to the CG. Ten trainees had no previous ERCP experience, two trainees had a maximum of ten previously performed ERCPs (in each group one trainee), and one trainee had performed a maximum of twenty procedures and was included in CG. The SG performed around 30 procedures per person during the two-day training course. Overall, the group of trainees performed a total of 717 ERCPs at their own institutions. The median number of ERCP procedures per trainee performed during the study period was 24 procedures with a broad range of 9 to 153 procedures. The median number of ERCPs in the simulator training group was significantly higher than in the conventional training group (56 versus 22 procedures, p=0.002). The overall percentage of ERCPs performed in patients with a native major papilla was 52.4% and did not differ significantly between groups. A statistically significant difference between groups was seen in ERCP difficulty degree (p=0.001), with more difficult ERCPs in the SG. The baseline characteristics are outlined in Table 1.

Moving average curve

The simple moving average of SG versus CG and HC is plotted in Figure 1. The X- signifies the cumulative ERCP procedure number and the Y- represents the percentage of successful CBD cannulation in patient-based ERCP. Mean successful ERCP cannulation rate was higher for the simulator group at baseline (moving average after the first 10 ERCPs) compared to both CG and HC, 64% versus 43% and 42%, respectively. After 40 ERCPs the differences in successful CBD cannulation become less explicit between the SG and both the CG and HC, but persisted until a median of 75 ERCPs. At this point. a successful CBD cannulation rate of 82% is seen in both the SG and control group. From this point on the available data were too limited to detect statistical difference between the learning curve. The historical cohort did not cross the line of the SG and shows a successful cannulation rate of 68% after 75 procedures.

Table 1. Baseline characteristics.

	Simulator Group	Conventional Group	Total	P
Trainees	6	7	13	
Male, n (%)	5 (83.3)	4 (57.1)	9 (69.2)	0.190
Age in years, mean (SD)	33.0 (1.0)	31.2 (2.5)	32.0 (2.1)	
Simulator familiarity (%)	2 (33.3)	3 (42.9)	5 (38.5)	0.436
Patient-based ERCP procedures performed, n (%)	383 (53.3)	334 (46.5)	717	0.002
Median number of ERCP procedures, n (range)	56 (13-140)	22 (9-153)	24 (9-153)	
Indication				0.089
``Reaching and intubating papilla, n (%)	16 (4.2)	20 (6.0)	36 (5.0)	
Complete stone extraction CBD, n (%)	120 (31.3)	99 (29.6)	219 (30.5)	
Endoprothesis – stenosis CBD, n (%)	121 (31.6)	91 (27.2)	212 (29.6)	
Metal stent – stenosis CBD, n (%)	73 (19.1)	64 (19.2)	137 (19.1)	
Endoprothesis bile leakage, n (%)	13 (3.4)	6 (1.8)	19 (2.6)	
Therapy chronic pancreatitis, n (%)	7 (1.8)	17 (5.1)	24 (3.3)	
Other, n (%)	33 8.6)	37 (11.1)	70 (9.8)	
Difficulty degree, n (%)				0.001
1	187 (48.8)	211 (63.2)	398 (55.5)	
2	161 (42.0)	102 (30.5)	263 (36.7)	
3	35 (9.1)	21 (6.3)	56 (7.8)	
Native papillary anatomy, n (%)				0.067
Yes	211 (55.1)	165 (49.4)	376 (52.4)	
No	172 (44.9)	169 (50.6)	341 (47.6)	
Previous ERCP failure, n (%)				0.336
Yes	41 (10.7)	42 (12.6)	83 (11.6)	
No	262 (68.4)	211 (63.2)	473 (66.0)	
Not applicable	80 (20.9)	81 (24.3)	161 (22.5)	
ASA Score, n (%)				0.000
ASA 1	58 (15.8)	60 (21.6)	118 (18.3)	
ASA 2	198 (54.1)	176 (63.3)	374 (58.1)	
ASA 3	99 (27.0)	38 (13.7)	137 (21.3)	
ASA 4	8 (2.2)	4 (1.4)	12 (1.9)	
ASA 5	3 (0.8)	0 (0)	3 (0.5)	

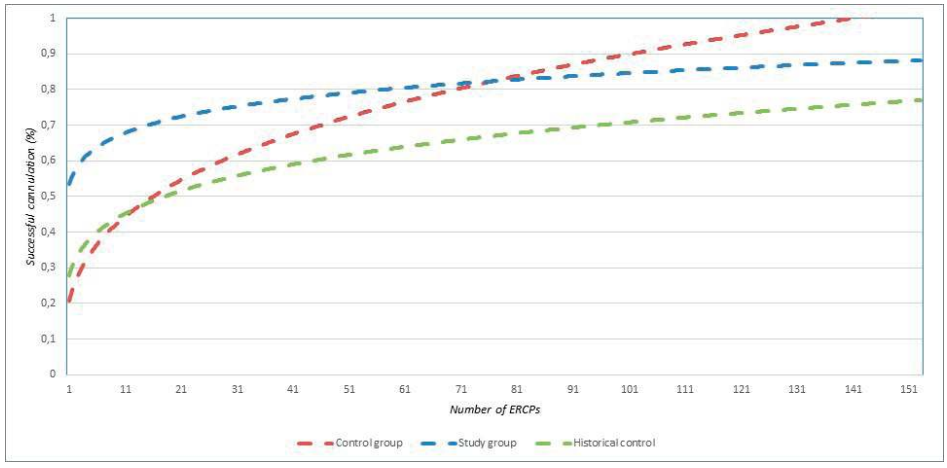

Figure 1. Moving average curve for successful CBD cannulation in patient-based ERCP.

Table 2. Degrees of difficulty of endoscopic retrograde cholangiopancreatography (ERCP) procedures, based on the classification of Schutz & Abbott.

Degree of Difficulty	Biliary procedures	Pancreatic procedures
Grade 1	Diagnostic cholangiography Biliary cytology Stone extraction <10 mm Dilatation of stenosis/ stent placement/nasobiliary drain in extrahepatic strictures	Diagnostic pancreaticography, pancreatic cytology
Grade 2	Stone extraction >10 mm Dilatation of stenosis/ stent placement/nasobiliary drain in hilar tumors or benign intrahepatic strictures	Cannulation of minor papilla
Grade 3	Billroth II anatomy Intrahepatic stone extraction Stone extraction with litotripsy	Therapeutic pancreatic procedures including pseudocyst drainage

DISCUSSION

In this prospective study, we demonstrate that novice ERCP trainees gain significant experience by training on the mechanical ERCP simulator before they are exposed to real patients. The two-day hands-on training course had a positive effect on the performance of trainees compared to the control group. The beneficial effect of simulation-based ERCP training on patient-based performance lasted up to around 75 ERCPs.

Despite growing awareness that procedural numbers are an inadequate means to define competence in ERCP, it is still the predominant methodology used to define the competence of trainees in most training curricula. Several studies have demonstrated that trainees reach competency at various points in training and that training guidelines

underestimate the number of ERCPs necessary to achieve competence[15,16]. A recent published review by Voiosu et al.[17] provides an overview of the current studies concerning trainee competence in ERCP. Importantly, most trainees do not reach predefined competence thresholds supporting the idea that a more individualized approach is necessary. The role of simulator-based training in ERCP has not been defined yet, but the essence of simulation-based training is to provide the trainee with the opportunities to understand the anatomy and to become familiar with both endoscope and accessories at their own pace without comprising patient safety. Simulation-based training creates a unique and safe learning environment to teach trainees the basic skills of ERCP and to provide the trainer with insights into the learning curve of the trainee with the opportunity to timely intervene. According to our study results, compared to on-the-job learning, a two days hands-on course in a stress free simulated training environment has a positive impact on the subsequent learning curve when performing real-life ERCP procedures with a beneficial effect that lasts up to around 75 procedures. The effect of simulator-based training is observed immediately from the beginning of patient-based ERCP performance when measuring successful cannulation in the first ten procedures with a successful cannulation rate of 64% in SG compared to 43% in the CG. Compared to the historical cohort CG demonstrates a steeper learning curve potentially indicating that training options have improved over the last years. Our data correspond with previous simulator training studies in endoscopy, mostly in the field of training colonoscopy, demonstrating a significant benefit of simulator training in the early learning curve[9].

Limited data available for simulator training in ERCP concern mainly the ERCP mechanical simulator (EMS Trainer) demonstrating that trainees who underwent simulator-based training achieved higher success rates with selective and deep cannulation of the CBD compared to the control group in the first months of training[18-20.] A potentially valuable addition to the Boškoski-Costamagna ERCP Trainer is the synthetic papilla, which can be used to train sphincterotomy using commercially available sphincterotomes and needle knives. The papilla has been validated in a previous study by our study group[12], but was not yet available for training during the study period.

Some limitations of our study need to be considered when interpreting our results. The number of participating trainees was limited. Results are representative for the trainees with no or very little real-life ERCP exposure. It cannot be inferred how these results translate to trainees with limited but more extensive (e.g. 50-100 procedure) experience. Dropout of participants who did not continue ERCP training, either due to insufficient training resources at their respective facilities or the fact that there was a shift in priorities during their specialty training, prohibit to draw conclusions beyond 75 procedures. This is not a formal randomized controlled trial but a paired controlled cohort study

with inclusion of the participants of the intervention group based on their specific interest to attendant an ERCP training course which may have introduced selection bias. Although the two-day ERCP simulator training course was structured and equal for all participants, the real life training at the respective institutions was not and was left to the discretion of the local team. Potential bias in this regard was attempted to be partly overcome by including a control trainee from the same training center.

This study however provides ample rationale that simulator training in the early learning phase trainees has a beneficial effect and should be considered to have a formal role in ERCP training curricula. Simulator training provides trainees with the opportunity to perform the procedure multiple times without risks at their own pace before performing the procedure on a real patient. It may be inferred that apart from potentially decreasing complication risks and patients discomfort, also less time is spend per patient in the early phase of training thereby increasing procedural capacity. It is out believe that based on our results further research is warranted to determine the optimal duration and extent of simulator training, the optimal simulator to be used and finally how such training should be implemented in the training curricula.

In conclusion, we demonstrate a positive effect of simulator-based training during a two-day hands-on training course in the early learning curves of ERCP trainees prior to patient-based training. Simulator-training should be considered an integral part the training curricula for ERCP.

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SUPPLEMENTARY DATA

Supplementary file 1: List of participating advanced endoscopy training centers

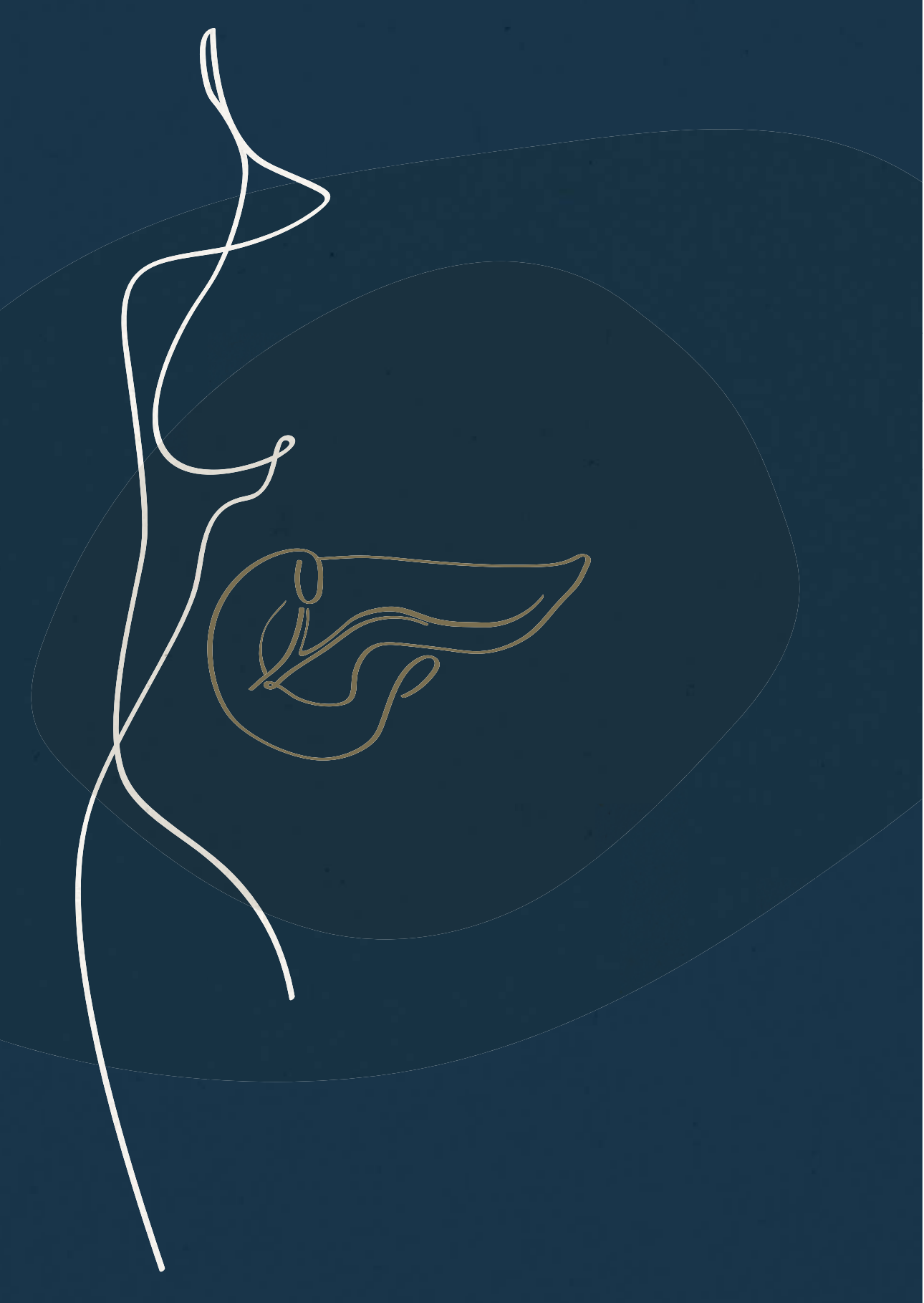
Erasmus University Medical Center	Rotterdam, The Netherlands
Academic Medical Center	Amsterdam, The Netherlands
Helsinki University Hospital	Helsinki, Finland
Turku University Hospital	Turku, Finland
Nottingham University Hospitals	Nottingham, United Kingdom
Eastern Hepatobiliary Surgery Hospital	Shanghai, China
Leuven University Hospital	Leuven, Belgium

Supplementary file 2. Rotterdam Assessment Form for ERCP (RAF-E form)
Trainee:
Hospital:
Date:

1. ASA Classification:	☐ I	A normal healthy patient
	☐ II	A patient with mild systemic disease
	☐ III	A patient with severe systemic disease
	☐ IV	A patient with severe systemic disease that is a constant threat to life
	☐ V	A moribund patient who is not expected to survive without the operation
2. ERCP Performed by:	☐	Started by the trainee
	☐	Completed by the trainee
	☐	Performed by supervisor
3. Intention for ERCP:	☐	Intubation and reaching the papilla
	☐	Complete biliary stone extraction
	☐	Plastic stenting of a bile duct stricture
	☐	Metal stenting of a bile duct stricture
	☐	Bile duct drainage in a biliary leak
	☐	Therapy for chronic pancreatitis
	☐	Other, please specify:
4. Virgin papilla1:	☐	Yes
	☐	No
5. Previous ERCP failure:	☐	Yes
	☐	No
6. ERCP difficulty degree2:	☐	Schutz 1
	☐	Schutz 2
	☐	Schutz 3
7. Papilla reached:	☐	Yes
	☐	No
If no, mechanical obstruction:	☐	Yes
	☐	No
8. CBD Cannulation3:	☐	Success
	☐	Failure
	☐	Not applicable

9. PD Cannulation4:	☐	Success
	☐	Failure
	☐	Not applicable
10. Unintentional PD Cannulation:	☐	Not applicable
	☐	Contrast
	☐	Not applicable
	☐	Guidewire
	☐	Catheter
11. Sphincterotomy:	☐	Success
	☐	Failure
	☐	Not applicable
12. Precut:	☐	Success
	☐	Failure
	☐	Not applicable
13. Stone extraction:	☐	Success
	☐	Failure
	☐	Not applicable
14. Stent Placement:	☐	Success
	☐	Failure
	☐	Not applicable
15. PD Endotherapy:	☐	Success
	☐	Failure
	☐	Not applicable
16. Procedural intention accomplished:	☐	Yes
	☐	No

* 1 Virgin papilla: no previous precut or sphincterotomy
* 2 Schutz's classification
* 3 CBD = Common Bile Duct
* 4 PD = Pancreatic Duct



PART III

ERCP in the Netherlands

6

Implementation of mandatory ERCP registration in the Netherlands and compliance with European Society of Gastrointestinal Endoscopy performance measures: A multicenter database study

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Endoscopy, 2021

ABSTRACT

Background and study aims: In 2018, the European Society of Gastrointestinal Endoscopy (ESGE) and United European Gastroenterology (UEG) published quality performance measures for endoscopic retrograde cholangiopancreatography (ERCP). Since January 2016, all endoscopists in the Netherlands have been required to register all ERCP procedures in a nationwide quality registry. This study aimed to evaluate the procedural success rates of ERCP after the implementation of mandatory national registration and to compare these with the ESGE quality performance measures.

Patients and methods: This study was conducted with data from a multicenter endoscopy database. Data from 2019 and 2020 were analyzed. The primary outcome was ERCP procedural outcome. ESGE performance measures that could be evaluated were the percentage of successful bile duct cannulations in patients with virgin papillary anatomy, successful stent placement for a biliary obstruction located below the liver hilum and complete removal of bile duct stones (<10mm).

Results: In total, 5295 ERCPs, performed in 11 centers were included for analysis. Overall procedural success was 89.1%. Successful biliary cannulation in patients with a virgin papilla was 90.3% in non-academic and 92.4% in academic centers. Successful stent placement in patients with a biliary obstruction located below the liver hilum was 97.0% in non-academic and 98.2% in academic centers, and successful bile duct stone extraction (<10 mm) was 97.9% in both non-academic and academic centers.

Conclusion: Quality of ERCPs performed meets five of the six evaluated ESGE performance measures. The 95% target for successful biliary cannulation in patients with virgin papillary anatomy in academic centers was not met. Mandatory registration provides valuable insight in ERCP performance rates.

INTRODUCTION

In recent years, quality assurance of endoscopic retrograde cholangiopancreatography (ERCP) procedures has increasingly gained interest from healthcare professionals and patient organizations. This is not without reason, as ERCP nowadays is primarily a therapeutic minimally invasive procedure associated with potentially severe complications[1-3]. Significant training and experience is required to maximize procedural success and minimize complication risks[4].

In 2018, the European Society of Gastrointestinal Endoscopy (ESGE) and the United European Gastroenterology (UEG) set up an initiative and published a list of key quality performance measures for ERCP and endoscopic ultrasound (EUS)[5]. These performance measures are intended to set a minimum standard for quality and the outcome of ERCP and EUS. Both societies encourage healthcare professionals to implement these performance targets on a national basis. Quality assurance in ERCP has also gained significant awareness in the Netherlands. Since January 2016 endoscopists in the Netherlands are required to register several procedural steps and outcomes of all ERCP procedures in a mandatory nationwide quality registry, using the Rotterdam Assessment Form for ERCP (RAF-E), a self-assessment registry tool that provides insight into ERCP performance[6]. One of the reasons of this mandatory registry was the finding of Ekkelenkamp et al. in 2014 that the overall procedural success rate of ERCP, using the RAF-E, was only 85.8%[7]. Interestingly, since the implementation of the mandatory quality registry it was seen that fewer endoscopists perform more ERCPs (unpublished finding) which is likely beneficial with regard to procedural success and quality outcomes.

The current study aimed to evaluate the procedural success of ERCP after the implementation of the mandatory nationwide registry and to determine whether performance measures, according to the ESGE standards, were met.

METHODS

Database and data collection

Data was retrieved from a prospectively maintained gastrointestinal (GI) endoscopy database (Trans.IT database, Rotterdam, the Netherlands). All centers participating in the database use a uniform structured tool to report endoscopy findings and all endoscopy reports are then uploaded into the database. The database has recently been described in detail elsewhere[8]. In short, this anonymized multicenter database was initiated in 2012 and currently collects GI endoscopy data from 19 Dutch hospitals (three academic and 16 non-academic hospitals), distributed over 9 of the 12 provinces in the Netherlands. The database also automatically creates a RAF-E form based on findings in the

ERCP report and uploads this to the mandatory national registry. The RAF-E includes several items, such as, amongst others, the indication for performing the ERCP, a priori ERCP difficulty degree (Schutz score), presence of a virgin papillary anatomy, outcome of common bile duct cannulation and procedural success9. Some endoscopy centers decided to use the Trans.IT database as an intermediary to report ERCPs to the national registry. Other centers report directly to the website of the national registry in which case a RAF-E form is not created in the Trans.IT database. In the current study, 11 of 19 centers use the Trans.IT database to create a RAF-E form. Therefore, data from 11 centers (two academic, nine non-academic, distributed over 8 of the 12 provinces in the Netherlands, were available for analysis. Registration of procedural intention and procedural outcome were used as an indicator for completeness of data, with only the years in which at least 90% of the performed ERCPs were completely registered considered for inclusion. This was achieved from 2019 onwards. All ERCP reports of procedures in the Trans.IT database performed between January 2019 to December 2020 from the 11 centers were analyzed. ERCP reports were included if the indication and procedural outcome of the procedure were in fact registered. ERCP procedures for patients aged younger than 16 years were excluded.

Outcomes and definitions

The primary outcome was the overall procedural outcome, defined as ‘’success’’ or ‘’failure’’ of ERCP, which was identical to the primary outcome measure described in the prospective voluntary evaluation by Ekkelenkamp et al.[7]. The ESGE performance measures that could be analyzed based on outcome findings in the database were: (a) the percentage of successful bile duct cannulations in patients with virgin papillary anatomy (and a biliary indication); (b) the percentage of successful stent placements for a biliary obstruction located below the liver hilum; and (c) complete removal of bile duct stones (stone size <10mm). The outcomes of academic centers were compared with outcomes of non-academic centers.

The ESGE performance measures that could not be analyzed were the percentage of patients with adequate administration of prophylactic antibiotics before ERCP (when indicated) and the rate of post-ERCP pancreatitis, since these data are not included in the nationwide ERCP registry.

Additionally, we evaluated success of cannulation in patients with a virgin papilla in relation to the type of sedation used and to the American Society of Anesthesiologists (ASA) classification. The type of sedation was categorized into either propofol sedation or general anesthesia in one group, or conscious sedation with midazolam and fentanyl in a second group. ASA classifications were grouped into ASA class 1-2 and ASA class 3-4.

Statistical analysis

The statistical analysis was based on descriptive analyses, using frequencies (%) for categorical variables, and mean (standard deviation [SD]) for normally distributed continuous variables or median (interquartile range [IQ]) for non-normally distributed continuous variables. Categorical variables were analyzed using Chi-square tests and continuous variables were analyzed using the Mann-Whitney U test. A two-sided p-value of <0.05 was considered statistically significant. All data were exported in comma-separated value files (CSV) from the Trans.IT database and imported into SPSS software for statistical analysis (statistical Product and Service solutions, SPSS 25.0 software, IBM Corp: Armonk, NY).

Ethical considerations

Collecting patient data in the Trans.IT database has been approved by the privacy officer of the Erasmus Medical Center in accordance to the Dutch Personal Data Protection Act. All patient data is anonymously stored in a secure environment and therefore exempt from formal ethical approval. All included hospitals provided written consent for participation.

RESULTS

From January 2019 to December 2020, a total of 5671 ERCP procedures were registered by 57 endoscopists in 11 centers (2064 in an academic and 3607 in a nonacademic setting). The median number of ERCPs per endoscopists was 95 in this period (IQR 23–129). Not all endoscopists performed ERCPs during the full study period either because of retirement or starting as a newly registered gastroenterologist. The median number of ERCPS per month per endoscopist, corrected for months of participation, was 4.7 (IQR 3.5–6.3). Of the 5671 ERCPs, 21 ERCPs (0.4 %) were excluded because patients were under 16 years of age, 173 (3.1 %) because the indication was not registered, and 182 (3.2 %) because the procedural outcome was not registered. Therefore, 5295 ERCPs (93.4%) were available for analysis.The overall procedural success rate was 89.1%. Table 1 shows procedural success according to indication and degree of difficulty as per the classification on the RAF-E form. The ESGE target standards for performance measures and the study outcomes overall and per degree of difficulty are shown in table 2.

Successful biliary cannulation in patients with a virgin papilla was achieved in 90.3% of ERCPs in nonacademic centers (ESGE target standard 90 %) and in 92.4% of ERCPs in academic centers (ESGE target standard 95%). Successful stent placement in patients with a biliary obstruction located below the liver hilum was achieved in 97.0% of ERCPs in nonacademic centers (ESGE target standard 95%) and 98.2% of ERCPs in academic centers (ESGE target standard 95%). Successful extraction of bile duct stones smaller than 10mm was achieved in 97.9% in both nonacademic centers (ESGE target standard 90%) and in academic centers (ESGE target standard 95%).

Table 1. Procedural success rates for the different indications and degrees of difficulty.

	Voluntary registry		Mandatory registry (2019 - 2020)	
	n (%)	Procedural success, % (n)	n (%)	Procedural success, % (n)
Indication				
Complete stone extraction CBD	4388 (51.2)	85.2 (3740)	2439 (46.1)	98.5 (2183)
Endoprosthesis - stenosis CBD	1829 (21.3)	86.2 (1576)	1021 (19.3)	90.2 (921)
Metal stent - stenosis CBD	545 (6.4)	87.3 (476)	669 (12.6)	87.4 (585)
Endoprosthesis - bile leakage	292 (3.4)	87.7 (256)	174 (3.3)	93.7 (163)
Therapy chronic pancreatitis	186 (2.2)	78.5 (146)	243 (4.6)	83.5 (203)
Other	1335 (15.6)	88.0 (1175)	749 (14.1)	88.8 (665)
Total procedures	8575 (100)	85.8 (7360)	5295 (100)	89.1 (4720)
Difficulty degree				
1	5676 (66.3)	4999 (88.1)	3162 (60.8)	91.2 (2885)
2	1989 (23.2)	1676 (84.3)	1444 (27.8)	87.5 (1263)
3	890 (10.4)	669 (75.2)	595 (11.4)	82.5 (491)

CBD, common bile duct.
*as reported by Ekkelenkamp et al. (2014)[6]

Table 2: Target standards for the ESGE performance measures and outcomes for the different degrees of difficulty in academic and nonacademic centers.

ESGE Performance measure	n	Target standard %	Overall Success % (n)	Schutz 1 Success, % (n)	Schutz 2 Success, % (n)	Schutz 3 Success, % (n)
Successful biliary cannulation in patients with a virgin papilla						
Non-academic (N=9)	2007	90	90.3 (1813)	91.2 (1291)	90.9 (430)	72.1 (62)
Academic (N=2)	473	95	92.4 (437)	92.0 (275)	93.0 (120)	92.7 (38)
Appropriate stent placement biliary obstruction, after successful biliary cannulation						
Non-academic (N=9)	694	95	97.0 (673)	99.1 (453)	93.2 (178)	93.1 (27)
Academic (N=2)	791	95	98.2 (777)	98.4 (421)	97.8 (310)	100 (36)
Bile duct stone extraction, <10 mm						
Non-academic (N=9)	1313	90	97.9 (1286)	97.9 (1286)	-	-
Academic (N=2)	190	95	97.9 (186)	97.9 (186)	-	-

Fig. 1 shows the individual endoscopist cannulation rates in patients with a virgin papilla and the number of ERCPs performed in the study period. The rates of successful cannulation in patients with a virgin papilla were not significantly different between ERCPs performed with the patient under general anesthesia or propofol sedation and those under conscious sedation, both for patients with an ASA class of 1 or 2 and those with an ASA class of 3 or 4 (Table3).

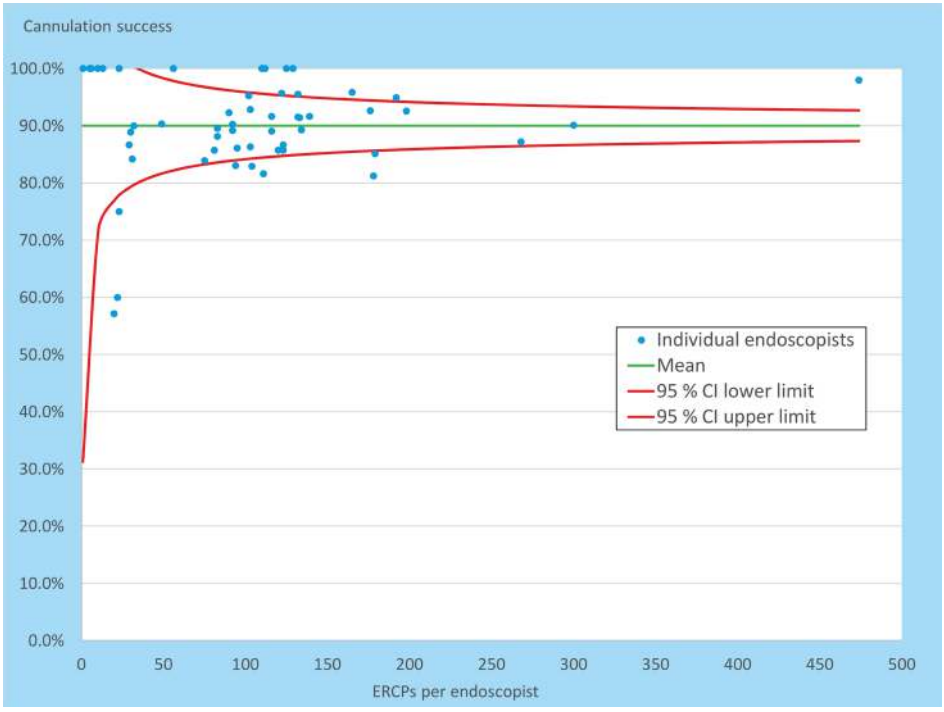

Figure 1. Individual endoscopist cannulation rates for patients with a virgin papilla and number of endoscopic retrograde cholangiopancreatographies (ERCPs) performed.
CI, confidence interval.

Table 3. Cannulation outcomes in patients with a virgin papilla for the different sedation types and ASA classifications.

	N	Common bile duct cannulation success, % (n)
ASA Classification 1 or 2		
Propofol	928	92.0 (854)
Midazolam + Fentanyl	526	92.6 (487)
ASA Classification 3 or 4		
Propofol	667	88.3 (589)
Midazolam + Fentanyl	141	89.4 (126)

ASA, American Society of Anesthesiologists.

DISCUSSION

In this study, we evaluated whether the ERCP outcome data of 11 Dutch hospitals collected within a mandatory ERCP registration database met the quality performance targets, as defined by the ESGE. We found an overall procedural success rate of 89.1% and five of the six ESGE target standards that could be assessed from the database were met. Successful bile duct cannulation in patients with virgin papillary anatomy was not

met in the academic centers, with a rate of 92.4% compared with the required 95%. The target standards were met for successful bile duct cannulation in patients with virgin papilla in nonacademic centers, successful stent placements for an obstruction located below the liver hilum in academic and nonacademic centers, and successful removal of bile duct stones in academic and nonacademic centers. This mandatory registry permits valuable insights into the performance of Dutch gastroenterologists and provides source information to help improve the overall quality of ERCPs.

This is the first study that has reported on the procedural outcomes of ERCP in the Netherlands since the implementation of the nationwide mandatory quality registry in 2016. A previous study by Ekkelenkamp et al. that was based on voluntary registration, including approximately 50% of all ERCP procedures performed in the Netherlands in 2014, reported an overall procedural success rate of 85.8%[7]. In the current study, the overall procedural success rate was higher at 89.1%. Although a direct comparison is difficult to make, it is at least reassuring that, despite mandatory registration, results have numerically improved. It is therefore tempting to speculate that as a consequence of the implementation of the mandatory registry, endoscopists performing ERCPs are more conscious and critical about their own performance. This may be reflected by the observation that, compared with the study of Ekkelenkamp, currently fewer endoscopists perform more ERCPs in the majority of Dutch centers.

We aimed to compare our results with the ESGE quality performance measures, which were published in order to improve the outcome and quality of endoscopy. The current study is the first to investigate whether the ESGE quality performance measures for ERCP procedures are being met in daily clinical practice. The results show that monitoring of the ESGE quality performance measures is not only feasible but also provides valuable insight into the performance level of individual endoscopists, centers, and ultimately a country.

Our results for successful biliary stenting and stone extraction were comparable to an Austrian nationwide benchmarking program, in which 28 of 140 ERCP sites participated. Biliary stenting was successful in 97.8% vs. 97.0%–98.2% in our study and stone extraction in 98.6% vs. 97.9% in our study[10]. In the current study, the target standard of successful biliary cannulation in patients with a virgin papilla in academic centers was not met, with 92.4% compared with the 95% target. In this regard, it is important to take into consideration that the ESGE has stated that the quality of the evidence used to develop the target measure for biliary cannulation was graded as low. Further evaluation is needed as to whether the target standard of 95% for expert centers is realistic, taking into consideration that potentially more primarily failed and difficult ERCPs are

referred to academic centers, for which sometimes more advanced selective cannulation techniques are required.

Compared with our study, the successful cannulation rate in patients with a virgin papilla was found to be lower in a study from the UK (84% vs. 90.3%–92.4%)[11]. A nationwide study from Sweden[12] and a multicenter study from Norway, including 11 hospitals[13], reported common bile duct cannulation rates of 92% and 91.1%, respectively, but these studies did not report selectively on cannulation rates in patients with a virgin papilla. The ERCP outcome data for the nine nonacademic centers in the current study are in line with a study from the USA that reported on ERCP outcomes from eight community hospitals[2].

A notable finding in our study was the low cannulation rate in nonacademic centers for cases with a Schutz 3 difficulty score (72.1%). It should be noted however that this finding is based on only 62 procedures and that more evidence is needed to establish whether this observation holds true. However, we believe this is an excellent example of the strength of a national registry, giving the opportunity to detect these trends and making it possible to intervene on both a personal and national level. Further actions, such as additional training of endoscopists in nonacademic centers or maybe centralizing the more difficult ERCP cases in academic centers, should be explored. The funnel plot provided in Fig. 1 is another example of the strength of a national registry and shows how the national registry permits the identification of low performing endoscopists who may benefit from additional training in ERCP. An additional finding of our study was that cannulation rates in patients with a virgin papilla were similar whether the ERCP was performed with the patient under general anesthesia or propofol sedation, or under conscious sedation with midazolam and fentanyl, regardless of the ASA classification. A prospective nationwide study from Sweden that reported on the impact of sedation types on cannulation rates in patients with a virgin papilla, in a total of 31001 ERCP procedures, found a statistically significant difference based on the type of sedation, with a cannulation success rate of 89.0% for propofol sedation vs. 86.7% for midazolam sedation, although this small difference seems to carry limited clinical relevance[14].

The Trans.IT database was chosen for this project because it currently offers more transparency than the national database, which is a key strength of this study. The national registry only registers procedures that are submitted to the registry and does not record how many ERCPs are actually performed in each center. The Trans.IT database includes all ERCP procedures performed in a center and an overview of the quantity of data registered for each procedure. This allowed us to control for the completeness of data for all ERCP procedures performed within a certain time period, which is not possible with

the national database. We attempted to minimize bias by analyzing only the time period in which at least 90% of the performed ERCPs were completely registered. As such, the outcomes of our study are a reliable representation of everyday clinical practice. This is however a Dutch study, which makes it potentially difficult to generalize our results. For example, in the Netherlands, it is common practice that gastroenterologists perform endoscopic procedures, such as ERCP, in combination with direct patient care management in both an inpatient and outpatient setting. The median number of 95 ERCPs per endoscopist during the study period may suggest that further concentration of ERCP procedures should be considered, as other studies have shown that endoscopists may benefit from higher yearly volumes of ERCPs to achieve core skills[15].

The limitations of this study that need to be addressed are firstly the fact that this is not a strictly nationwide report. Although the 11 centers included in the current study are distributed over eight of the 12 provinces in the Netherlands and represent both academic and nonacademic centers, it is not certain that the outcomes from these 11 centers is representative of the whole of the Netherlands. Nonetheless, more than 5000 ERCPs were included, which amounts to approximately 12.5% of the total number of ERCPs performed in the Netherlands in this period. Second, not all centers participating in the Trans.IT database could be included, because eight of the 19 participating hospitals registered ERCPs in the Trans.IT database without using the RAF-E form. Third, not all years during which the reporting of ERCPs was mandatory were included. Owing to start-up problems and the time required to train endoscopists to correctly register ERCPs during the first years of the national registry, a sizeable percentage of ERCPs were not registered completely (registration rates for procedural indications and outcomes of 63.1% and 56.0%, respectively, in 2017 vs. 95.4% and 93.7%, respectively, in 2019). Registration problems occurred not only in the Trans. IT database but were seen also on a nationwide level in the national registry. We believe that including these years with low registration rates could have potentially induced bias and therefore we decided to exclude these years from the analysis. A correct registration in these years would have allowed us to perform a time-trend analysis and to assess whether procedural success increased each year during mandatory registration. Finally, not all ESGE quality performance measures could be evaluated because the RAF-E form that is currently used does not include information on antibiotic prophylaxis or post-ERCP pancreatitis.

In conclusion, the Dutch national mandatory centralized registry of ERCP reporting offers the opportunity to evaluate and improve the quality of ERCP. Comparison with the ESGE quality performance measures is feasible and showed that the overall quality of ERCP in Dutch ERCP centers is high. Five out of six ESGE quality performance measures

were achieved successfully, but the 95% target for successful biliary cannulation of a virgin papilla in academic centers was not met.

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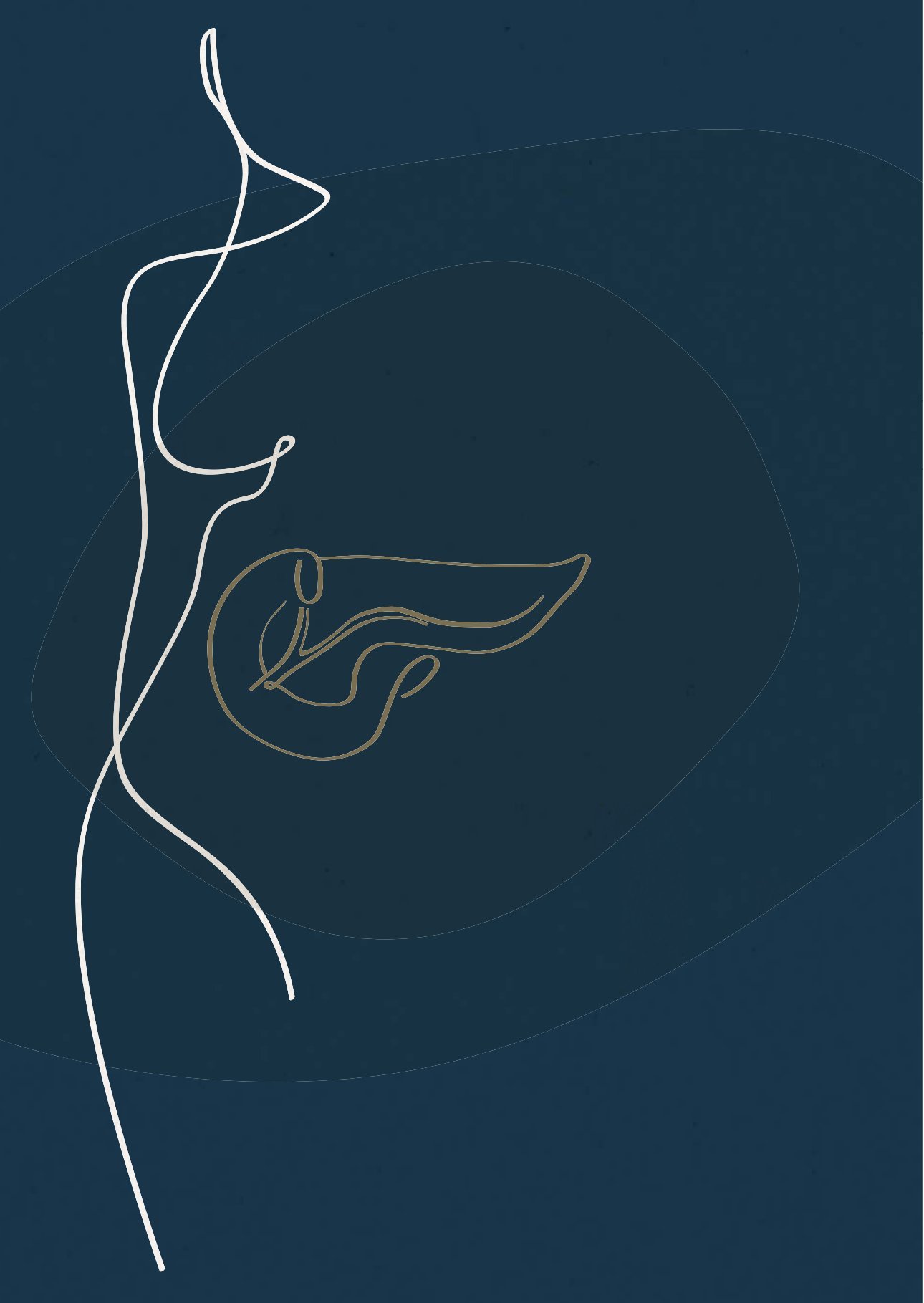

PART IV

Advanced endoscopic procedures

7

Preliminary report on the safety and utility of a novel automated mechanical endoscopic tissue resection tool for endoscopic necrosectomy: a case series

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Endoscopy International Open, 2020

ABSTRACT

Background and study aims: Endoscopic drainage of walled-off necrosis and subsequent endoscopic necrosectomy has been shown to be an effective step-up management strategy in patients with acute necrotizing pancreatitis. One of the limitations of this endoscopic approach however, is the lack of dedicated and effective instruments to remove necrotic tissue. We aimed to evaluate the technical feasibility, safety and clinical outcome of the EndoRotor a novel automated mechanical endoscopic tissue resection tool, in patients with necrotizing pancreatitis.

Methods: Subjects with infected necrotizing pancreatitis in need for endoscopic necrosectomy after initial cystogastroscopy, were treated using the EndoRotor. Procedures were performed under conscious or propofol sedation by six experienced endoscopists. Technical feasibly, safety, clinical outcome were evaluated and scored. Operator experience was assessed by means of a short questionnaire

Results: Twelve patients with a median age of 60.6 years, underwent a total of 27 procedures for removal of infected pancreatic necrosis using the EndoRotor. Of these, nine patients were treated de novo. Three patients had already underwent unsuccessful endoscopic necrosectomy procedures using conventional tools. The mean size of the walled-off cavities was 117.5 ± 51.9 mm. An average of two procedures (range 1-7) per patient was required to achieve complete removal of necrotic tissue with the EndoRotor. No procedure-related adverse events occurred. Endoscopists deemed the device to be easy to use and effective for safe and controlled removal of the necrosis.

Conclusions: Initial experience with the EndoRotor suggests that this device can safely, rapidly and effectively remove necrotic tissue in patients with (infected) walled-off pancreatic necrosis.

INTRODUCTION

Acute pancreatitis (AP) is amongst the most frequent causes of gastrointestinal tract diseases that requires acute hospitalization and its incidence continues to rise[1,2]. Around 20% of patients with acute pancreatitis develop necrotizing pancreatitis with about a third of them progressing to infected necrosis which is associated with mortality rates reported between 15 and 30%[3-5]. Since infected necrosis rarely responds to conservative treatment alone, virtually always some form of invasive and interventional treatment is necessary.

Over recent decades, the treatment of infected necrotizing pancreatitis has changed dramatically. Early open surgery is associated with a very high mortality and is largely avoided nowadays[6]. A shift towards less invasive techniques has become standard of care. Minimally invasive techniques, either by percutaneous drainage if necessary followed by video assisted retroperitoneal drainage or endoscopic ultrasound (EUS)-guided transluminal drainage, if necessary followed by direct endoscopic necrosectomy (DEN) have been shown to improve outcomes for patients with regards to a combined endpoint consisting of mortality, multi-organ failure, external fistula and endo- and exocrine insufficiency[5,7,8]. Several studies have reported on the potential and efficacy of direct endoscopic necrosectomy[9,10].

If signs of infection persevere or worsen after EUS-guided transgastric or transduodenal drainage, the cyst cavity can be entered by a regular forward viewing endoscope to perform DEN. This can be achieved by means of balloon dilation of the transgastric fistula (up to 20 mm) when plastic double pigtail stents were placed initially or directly through the stent opening when a large bore fully covered metal lumen apposing stent was placed. Usually several sessions are required for complete removal of the necrosis, the mean number of DEN sessions varies from 1 to 15 in a meta-analysis by Puli et al.[11] with a weighted mean of 4.09 procedures.

One of the main limitations of endoscopic necrosectomy is the lack of dedicated and effective instruments to remove the necrotic tissue. For this purpose various instruments, originally designed for other indications, are used. These devices, such as lithotripsy baskets, grasping forceps, retrieval nets and polypectomy snares, are able to grasp and hold material but often lack sufficient grip making the procedure cumbersome, time consuming and often marginally effective with only small chunks of necrosis being pulled into the gastrointestinal lumen per pass. Also, opening these devices in areas of necrosis is largely visually uncontrolled as is the amount of tissue that is caught. Pure suction can be helpful to pull out tissue chunks but often results in clogging of the working channel of the endoscope.

The aim of our study was to evaluate the technical feasibility, safety and clinical outcome of the EndoRotor, a novel automated mechanical endoscopic resection system to suck, cut and remove small pieces of tissue in patients with necrotizing pancreatitis.

MATERIALS AND METHODS

This prospective study took place at the department of Gastroenterology and Hepatology of the Erasmus MC, University Medical Center in Rotterdam, a tertiary referral center in the Netherlands and at the Medizinische Klinik II, Sana Klinikum Offenbach in Offenbach, Germany. We recorded data on patient demographics, clinical presentation, etiologies of acute pancreatitis, American Society of Anesthesiologists' (ASA) Physical Status Classification score[12], radiologically defined size of the necrotic collection in a transverse computed axial tomographical image, displaying the largest diameter of the necrotic cavity, procedural details and adverse events during and after endoscopic necrosectomy. All patients with symptomatic WOPN were considered eligible for this study.

The EndoRotor

The EndoRotor (Interscope Medical, Inc., Worcester, Massachusetts, United States) is a novel automated mechanical endoscopic resection system designed for use in the gastrointestinal tract for tissue dissection and resection with a single device. The EndoRotor system can be advanced through the working channel of a therapeutic endoscope with a working channel of at least 3.2mm in diameter. The EndoRotor can be used to suck, cut, and remove small pieces of tissue through the catheter, consisting of a fixed outer cannula with a hollow inner cannula. A motorized, rotating, cutting tool driven by an electronically controlled console performs tissue resection and rotates at either 1000 or 1700 revolutions per minute. The necrotic tissue is sucked into the catheter using negative pressure and cut by the rotating blade from the inner cannula. Tissue is transported to a standard vacuum container. Both the cutting tool and suction are controlled by the endoscopist using two separate foot pedals. During the course of this study the EndoRotor catheter was upgraded to potentially resect necrotic tissue more effectively. All procedures with both versions of the EndoRotor are reported in this study. The originally designed EndoRotor has a 3.0 mm2 opening at the tip, in which the rotator blade is located and teeth on the inner cutter. The novel design is adjusted in order to facilitate the resection of necrotic tissue, the tip has a 50% wider opening of 4.4 mm2, the teeth on the inner cutter are smaller and this design additionally has teeth on the outer cutter. No changes were made in the material or available rotation speed (Figure 1).

Figure 1. The EndoRotor.

Procedure

Procedures were performed as per protocol under conscious or propofol sedation under close monitoring of the anesthesia team and by six senior endoscopists with a broad experience in advanced endoscopic procedures. Initially, all patients underwent EUS-guided transgastric drainage, creating a fistula from the stomach to the adjacent walled-off pancreatic necrosis. The choice of placement of one or more plastic stents or a lumen apposing metal stent (LAMS) was at the discretion of the endoscopist. In some patients a nasocystic irrigation catheter was placed. In the absence of clinical improvement following initial endoscopic transgastric drainage, we proceeded to perform endoscopic necrosectomy. For this a therapeutic gastroscope was advanced into the collection cavity, if necessary after balloon dilation with a CRE-balloon to 18 or 20 mm. The EndoRotor was inserted through the working channel of a therapeutic endoscope and advanced into the collection cavity. Rotation speed of the EndoRotor catheter was recorded as well as changes in setting. Suction was set at between 500 and 620 mmHg, the maximum achievable negative pressure level.

Questionnaire

Endoscopists were asked to rate their experiences with the EndoRotor in a short questionnaire. Appreciation was expressed on a 10-point Likert scale[13], varying from very negative appreciation (1) towards very positive appreciation (10). Questions were asked about the ease of use of the EndoRotor, handling of the device, the safety, and their appreciation on the additional value of the EndoRotor® in the treatment of patients with pancreatic necrosis.

Statistics

All statistical analyses were performed using SPSS 24.0 software (IBM Corp., Armonk, NY, United States). Data were expressed as mean ± standard deviation, median, and range.

RESULTS

Patient characteristics

Twelve patients with a mean age of 60.6 ± 11.4 years underwent endoscopic necrosectomy using the EndoRotor. Of these 12 patients, nine patients were male (75%). Two patients (16.7%) had a class IV score on the ASA physical status classification system. Four patients (33.3%) scored ASA class III, five patients (41.7%) scored class II and one patient scored ASA class I (8.3%). Nine patients were diagnosed with acute necrotizing pancreatitis, which had developed into infected walled-off pancreatic necrosis. The time from the onset of acute complicated pancreatitis to necrosectomy was a median of 48 days (range 13 to 368). Three patients were initially drained because of mechanical complaints from large fluid collections. As a result of these procedures, the necrotic debris became infected necessitating necrosectomy. The mean necrotic collection size was 117.5 ±51.9 mm. The etiology of the acute pancreatitis was biliary in four patients (33.3%), alcoholic in three patients (25%), ERCP with sphincterotomy (one patient; 8.3%), and in four patients (33.3%), the etiology was unknown.

Transgastric endoscopic drainage was performed in all patients; eight patients (66.6%) received two or three plastic stents, and four patients (33.3%) received a lumen apposing metal stent to achieve transluminal drainage of necrotic debris. In all patients, an aspirate of the WOPN was obtained and sent for gram staining and culture. Culture-proven infected necrosis was present in ten out of 12 patients (83.3%). The predominant microorganisms found were *Streptococcus* species. Three patients (25%) were previously treated unsuccessfully with conventional instruments before being treated with the EndoRotor. Patient characteristics are included in table 1. Figure 2 illustrates a typical case of infected walled-off pancreatic necrosis and the steps during DEN.

Table 1. Patient characteristics.

Patient	Age, years	Sex	Etiology	Infected necrosis by culture	Size of the collection, mm	Stent placement	Previous necrosectomy*
1	56	Female	Biliary	Yes	100	3 Pigtails	2
2	65	Male	Unknown	Yes	167	2 Pigtails	3
3	68	Male	Unknown	Yes	182	LAMS	1
4	43	Male	Biliary	Yes	141	2 Pigtails	0
5	67	Male	Biliary	Yes	130	2 Pigtails	0
6	71	Male	Biliary	Yes	78	LAMS	0
7	76	Female	Alcoholic	Yes	124	2 Pigtails	0
8	58	Male	Iatrogenic	Yes	220	3 Pigtails	0
9	51	Male	Alcoholic	Yes	84	LAMS	0
10	67	Female	Unknown	Yes	45	LAMS	0
11	66	Male	Unknown	Unknown	100	2 Pigtails	0
12	39	Male	Alcoholic	Yes	90	1 Pigtail	0

LAMS, lumen apposing metal stent.
*Number of endoscopic necrosectomy procedures previously performed with conventional instruments.

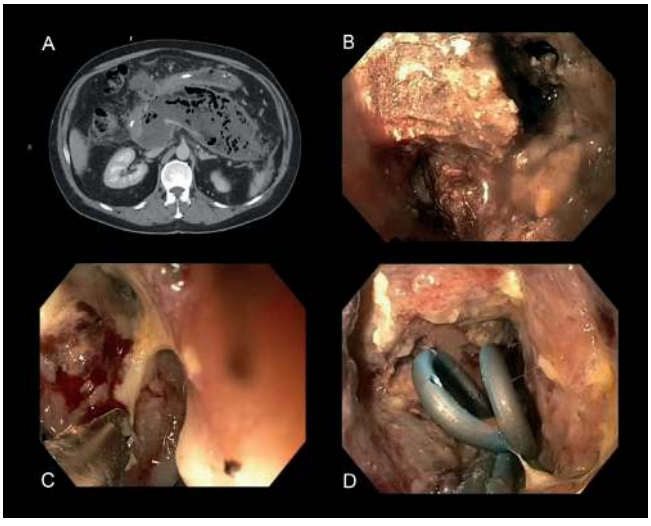

Figure 2. Typical case of infected walled-off pancreatic necrosis (WOPN). A Pre-intervention computed tomography scan illustrating WOPN with air bubbles. B Endoscopic view of necrosis after direct access into the cavity. C Necrosectomy using the EndoRotor. D Post-necrosectomy result.

Endoscopic procedure

In the 12 patients described, a total of 27 endoscopic necrosectomy procedures were performed using the EndoRotor to achieve complete removal of necrotic tissue. The median procedure time was 38 minutes (IQR 28.9). To achieve complete removal of

pancreatic necrosis, the median number of required procedures was two per patient (range 1 to 7). The first version of the EndoRotor was used in 19 procedures, the median procedure time was 45.8 minutes (IQR 28.1), with a median number of required procedures of 2.0 (range 1 to 7). The second version was used in eight procedures with a median procedure duration of 33 minutes (IQR 31.3), the median number of required procedures was 1.5 (range 1 to 3) to achieve complete removal of necrotic tissue.

Adverse events

No adverse events occurred during the necrosectomy procedures or within the next 24 hours. Three patients (27.2%) experienced adverse events within the course of their infected pancreatic necrosis. One patient died eight days after the last endoscopic necrosectomy as a result of ongoing multi-organ failure caused by massive collections of infected pancreatic necrosis which despite multiple sessions could not be completely removed. One patient eventually died three months after discharge due to an underlying pancreatic carcinoma after have undergone two successful endoscopic necrosectomy procedures for infected necrotizing obstructive pancreatitis using the EndoRotor. In one patient a gastrointestinal bleed occurred two days after the procedure necessitating coiling of the splenic artery. During the procedure there was no evidence of bleeding or damage to any exposed vessel.

Questionnaire

Endoscopists rated the EndoRotor easy in its use (mean 10-point Likert scale score 8.3, range 8 to 9) and an effective tool to remove necrotic tissue (mean 10-point Likert scale score 8.3, range 8 to 9). They were especially satisfied by the ability to manage the removal of necrotic tissue in a controlled way (mean 10-point Likert scale score 8.6, range 8 to 9). The risk to cause complications was estimated low (mean 10-point Likert scale score 1.9, range 1 to 2). Overall, the device was judged to be of substantial additional value in the management of pancreatic necrosis (mean 10-point Likert-scale score 8.6, range 8 to 9) and respondents were very willing to use the device in subsequent cases with necrotizing pancreatitis (mean 10-point Likert-scale score 9.3, range 9 to 10).

DISCUSSION

Direct endoscopic necrosectomy has proven to be safe and effective in the treatment of patients with infected pancreatic necrosis, however, up until now no dedicated instruments were available for threating these patients. Recently, we published our preliminary experience with the EndoRotor[14]. This multicenter prospective cohort study describes the results in the first twelve patients with infected pancreatic necrosis who underwent a combined total of 27 DEN procedures using the EndoRotor. We have dem-

onstrated the efficacy of the EndoRotor and good clinical outcome, without any directly device related adverse events.

For years, open necrosectomy has been considered as the gold standard treatment for management of pancreatic necrosis, however, it was accompanied by high morbidity and mortality rates[6]. Carter et al.[15] demonstrated a new minimal invasive approach in 2000 indicating that adequate necrosectomy can be achieved by either percutaneous or endoscopic techniques. These results encouraged several research groups to further investigate minimal invasive techniques, with the first randomized controlled trial published in 2010 by Van Santvoort et al.[5] confirming the benefit of a minimal invasive approach versus open necrosectomy in terms of major complications or death[6, 15-17]. The potential and efficacy of endoscopic necrosectomy in terms of overall outcome is undisputed, but the proper tools available for adequate endoscopic debridement remain missing. Several alternative options have been described as additional treatment after initial endoscopic debridement to optimize clinical results, such as the use of a high-flow-waterjet system[18-22], the use of hydrogen peroxide[23, 24] and a vacuum-assisted closure system[25-27]. These techniques seem promising, but to date, only small case series are published.

All 12 patients in this study underwent minimal invasive DEN using the EndoRotor. Of these 12 patients, three patients were treated after initial failure using conventional instruments. During the procedures, the rotation speed of the EndoRotor catheter was set at 1000 or 1700 revolutions per minute at the discretion of the treating endoscopist, with suction set at 620 mmHg negative pressure, the maximum achievable level. For optimal removal of tissue, the angle of the device relative to the necrotic tissue plane is important. The cutter opening should be directed to face the necrosis with direct contact. The high vacuum setting alone was not always able to suck in all the tissue, the best results were reached by 'trapping' the necrotic tissue between the cavity wall and the cutter opening of the catheter. This resulted in relatively fast and highly effective removal of necrotic tissue. There was no need for "blind" grabbing into the necrosis as is often unavoidable with snare-based instruments. The tip of the EndoRotor cutter remains visible at all times making it a very safe and controlled procedure.

A median number of two procedures was required to achieve complete removal of necrotic tissue in this series. Several studies have reported on the mean number of interventions necessary to completely remove the necrotic tissue using conventional instruments, with a weighted mean of four endoscopic necrosectomy procedures per patient[11,28]. Two large studies, published by Papachristou et al.[29] and Seifert et al., described a mean of four and even six procedures respectively, with a maximum of 10 and

even 35 endoscopic procedures. A more recently published study by Van Brunschot et al.[30] showed that 41% of patients undergoing transluminal endoscopic necrosectomy required at least three procedures to achieve complete removal. Our study was not powered to detect a difference in the number of procedures compared to historical series or between the two technical iterations of the EndoRotor. Nevertheless, taking into consideration the large sizes of the necrotic collections in our series, the current data suggest that this device and in particular the adapted design of the EndoRotor is even more effective to achieve complete clearance of the pancreatic necrosis in terms of the number of procedures needed and the time spent.

Despite the reduction in overall mortality over the last years, acute necrotizing pancreatitis is still associated with high morbidity and mortality rates[3-5]. In patients treated endoscopically a complication rate of 36% was reported in a recently published meta-analysis, with bleeding as the most prevalent complication (22%)[30]. In the current study, no device related complications occurred during the procedures or within the first 24 hours. One patient died as a result of ongoing organ failure eight days after the last necrosectomy procedure, the necrotic cavity was very comprehensive and complete removal of necrotic tissue was therefore not achieved. There was this other patient that died as a result of pancreatic carcinoma, which became apparent two months after successful endoscopic treatment of pancreatic necrosis using the EndoRotor, in the absence of complications. One patient suffered from a gastrointestinal bleed occurring two days after the necrosectomy necessitating coiling of the splenic artery. During the necrosectomy no bleeding or damage to any exposed vessel was observed. We believe that the bleeding was a direct result of ongoing inflammation within the remaining necrosis leading to pseudoaneurysm formation and eventually bleeding. Based on our experience, we believe that the risk of bleeding using this device is low, due to the fact that removal of necrosis occurs under direct endoscopic vision in a very controlled way.

The general opinion of the endoscopists on the use of the EndoRotor for pancreatic necrosectomy was encouraging in the way that this novel tool was judged to be easy to use, effective, having a low risk of complications, and being of additional value in the treatment of patients with acute necrotizing pancreatitis. A limitation of the current study is the number of patients that were included. This was partly compensated by the fact that in total 27 necrosectomy procedures were carried out. This study was set up as a prospective cohort study testing initial feasibility and safety. These results should be confirmed by others and in comparative series.

The EndoRotor is the first instrument specifically designed to facilitate easy, safe, and rapid removal of necrotic tissue in patients with (infected) walled-off pancreatic necrosis

under direct endoscopic vision. Its unique design overcomes some of the inherent problems and shortcomings that are associated with conventional instruments currently used for endoscopic necrosectomy. Prospective comparative evaluation of the EndoRotor in a larger series of patients is required to confirm these favorable observations and to further evaluate its safety profile and clinical efficacy.

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Pancreatoscopy-guided electrohydraulic lithotripsy for the treatment of obstructive pancreatic duct stones; a prospective consecutive case series (PELstone study)

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Accepted for publication at Gastrointestinal Endoscopy, 2021

ABSTRACT

Background and Aims: 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 ($P < .001$). The most common adverse event was acute pancreatitis, all mild and treated conservatively (n = 7).

Conclusions: Pancreatoscopy-guided EHL is a promising treatment for symptomatic CCP patients with obstructive PD stones.

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 (Supplementary Table 2). 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-molecularweight 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 duodeno- Q5 scope (ED34-i10T2; Pentax Medical, 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 Sum-

mary [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[15,16]. 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 $P < .05$ 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 (Fig. 1), and therefore 34 consecutive patients were included for treatment of PD stones in the head and/or neck of the pancreas with pancreatoscopyguided EHL. Patient demographics at baseline are presented in Table 1. At baseline, 18 patients (53%) used daily opiate medic ation.

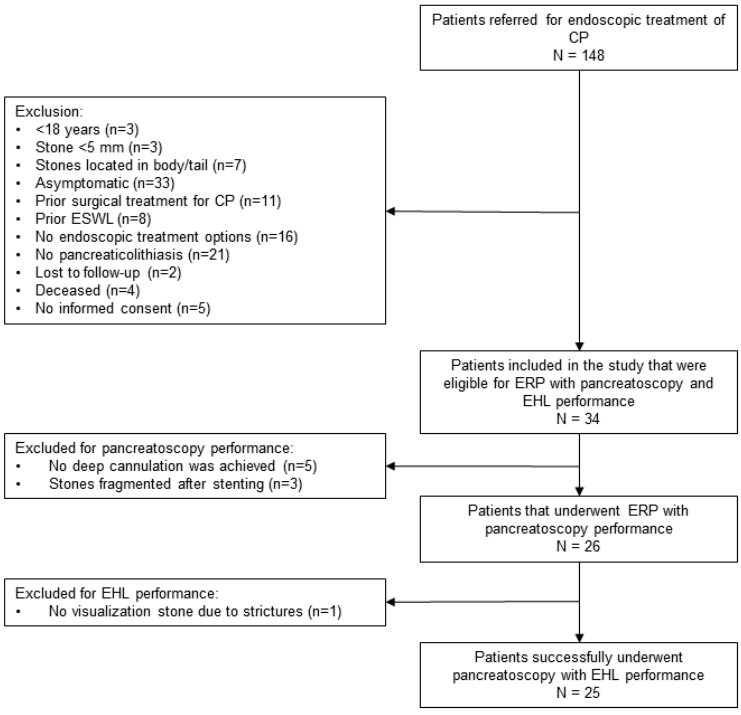

Figure 1. Flowchart of patient inclusion process.
CP, Chronic pancreatitis; *ESWL*, extracorporeal shock wave lithotripsy; *ERP*, endoscopic retrograde pancreatography; *EHL*, electrohydraulic lithotripsy.

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

Characteristics	N=34
Mean age, y (standard deviation)	56.7 (13.5)
Male gender	21 (62)
Mean body mass index, kg/m^3 (standard deviation)	23.5 ± 4.4
ASA Classification	
II	23 (68)
III	11 (32)
Smoking	
Yes	17 (50)
No	4 (12)
Quit	11 (33)
Unknown	2 (6)
Alcohol	
Yes	9 (27)
No	11 (33)
Quit	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 again 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.

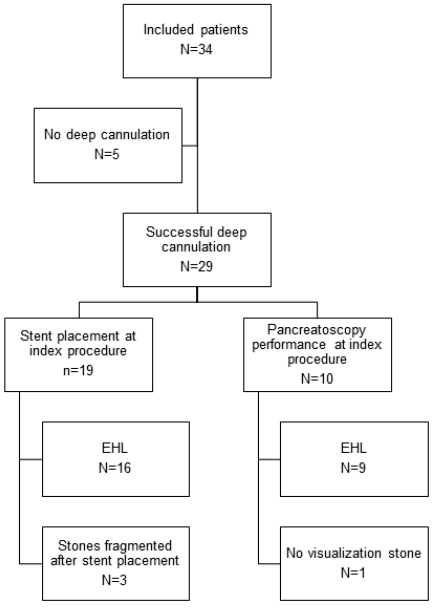

Figure 2. Flowchart of study procedures for all included patients (n = 34).
EHL, Electrohydraulic lithotripsy.

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	
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	8.6 (± 3.3)
EHL	
Number of ERP procedures	2 (1 – 3)
Number of EHL procedures	1 (1 – 2)
Stone clearance	

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

Characteristic	
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)
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)
Postprocedural pain	2 (8)
Cholangitis	1 (4)
NSAID prophylaxis	25 (100)
Time to onset, days	.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 followup, 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 Z .080) and MCS (F-test: P = .164).

Table 3. Izbicki pain scores, opioid usage and quality of life, at baseline and follow-up of the 25 patients that underwent pancreatoscopy and EHL.

		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§	43.3 ± 12.7 (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[6,7,9,17-22]. McCarty et al[23] 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 success 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[23] 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[24].

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. 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[25]. 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 place-

ment 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 confirmor 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

Supplementary table 1. Izbicki pain score system.

Izbicki pain score system		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 4 aspects divided by 4.

Supplementary file 2: Short Form Health-12

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
☐	☐	☐	☐	☐

9

Endoscopic resection of advanced ampullary adenomas: a single-center 14-year retrospective cohort study

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Surgical Endoscopy, 2019

ABSTRACT

Background: Endoscopic ampullectomy has been recognized as a safe and reliable means to resect selective tumors of the ampulla of Vater and is associated with lower morbidity and mortality rates compared to surgical resection. Success rates range from 42 to 92%, with recurrences reported in up to 33%. Studies on endoscopic resection of advanced lesions such as those with intraductal extension of adenoma (IEA) and lateral spreading adenomas (LSA) are limited. We aimed to evaluate the technical success, complications and recurrence of endoscopic resection of ampullary adenomas, including advanced lesions.

Methods: all patients referred to the Erasmus Medical Center for endoscopic resection of an ampullary lesion were retrospectively identified between 2002 and 2016. Endoscopic success was defined as complete excision of the adenoma, irrespective of the number of attempts, in the absence of recurrence.

Results: We included 87 patients with a median age of 65 years. Of these, 56 patients (64%) had an adenoma confined to the ampulla (ACA), 20 patients (23%) an LSA and 11 patients (13%) were treated for an IEA. The median lesion sizes were 24.6mm, 41.4mm, and 16.3mm, respectively (P<0.001). Complications occurred in 22 patients (25.3%), of which hemorrhage was most prevalent (12.6%), followed by perforation (8.1%). Complications were equally divided (P=0.874). The median follow-up duration was 21.1 months (12-45.9) for ACA, 14.7 months (4.2-34.5) for LSA and 5.8 months (3.7-22.0) for IEA (P=0.051). Endoscopic resection was curative in 87.5% of patients with an ACA, 85% in patients with an LSA and in only one patient with an IEA (P <0.001). Recurrence occurred in 10 patients (11.5%) (P=0.733).

Conclusion: Endoscopic ampullectomy is safe and highly successful in selected patients with an adenoma with or without lateral spreading. Outcomes of endoscopic treatment adenomas with an intraductal extension are less favorable and in these cases surgery should be considered.

INTRODUCTION

Lesions of the ampulla of Vater are relatively rare. Adenomas are the most common benign tumors arising from the ampulla even though benign neoplasms account for <10 % of all periampullary neoplasms[1]. The detection of ampullary adenomas has increased over the last years most likely due to the more abundant use of esophagogastroduodenoscopy and ultrasonography[2]. As in colorectal adenomas, ampullary adenomas can undergo malignant transformation, and therefore it is essential to completely remove the lesion[3]. Historically ampullary adenomas have been resected surgically[4,5]. Over the last decades endoscopic ampullectomy (EA) has been recognized as a safe and reliable alternative treatment for selective tumors of the ampulla of Vater[5-7]. Endoscopic ampullectomy has lower morbidity and mortality rates than surgical procedures[3,8]. Success rates after EA have been reported within a wide range from 46 to 92% and are largely based on retrospective, heterogeneous case series. Studies have shown that multiple procedures may be required to completely remove adenomatous tissue, in particular for larger lesions[9-14]. It is difficult to compare the outcomes of the various studies due to the lack of a consistent definition of 'success' and highly variable follow-up length. Additionally, the success rate also appears to be dependent on the extent of the tumor, i.e. whether it is confined to the ampulla, laterally spreading beyond the ampulla over the duodenal surface or growing intraductally. The overall complication rate of EA is around 15% and mainly consists of bleeding and pancreatitis. Recurrence of adenomas is reported in up to 33% of the cases, despite supposedly complete removal of the tumor at the index procedure[10,12,15]. Despite the increasing number of studies concerning endoscopic resection of ampullary tumors, studies reporting on the outcome of resection of ampullary adenomas with lateral spreading or intraductal extension are limited. There seems to be consensus that every patient with an ampullary tumor should be given a chance of endoscopic resection as long as the tumor appears benign and tumor size is not a contraindication[9,16].

The aim of our study was to evaluate the technical success, complications and recurrence of endoscopic resection ampullary adenomas, in particular lateral spreading ampullary adenomas and those with intraductal extension.

MATERIALS AND METHODS

We conducted a retrospective study in patients referred to the Erasmus MC, University Medical Center Rotterdam (Rotterdam, the Netherlands) for endoscopic resection of an ampullary adenoma over a 14-year period (between January 2002 and November 2016). All 107 cases were identified using an electronic endoscopic database reporting system (ENDOBASE, Olympus, Hamburg)) searching for the terms 'papillary resection', 'papillectomy', 'ampullectomy', 'adenoma', and 'spreading'. Additionally, a search was done

in the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) to search for patients diagnosed with an ampullary adenoma at our institution.

We identified 87 patients with ampullary tumors that were histologically confirmed to be adenomas. Pathology slides were not re-examined. Additional inclusion criteria included adenomas of both major papilla and minor papilla, without invasive cancer on biopsy, and adenomas with substantial intraductal extension and adenomas with a lateral spreading growth pattern. A lateral spreading adenoma was defined as an adenoma of ≥10 mm in diameter that extends laterally along the surface of the gastrointestinal tract[17]. Patients with FAP were included in our study. Non-adenomatous tumors of the ampulla of Vater (neuroendocrine neoplasms, carcinomas) were excluded. Data that was extracted from the electronic patient records included patient demographics, clinical presentation, laboratory results, diagnostic findings, details on the endoscopic resection, follow-up, and morbidity and mortality.

The decision to perform endoscopic ultrasound (EUS) prior to endoscopic retrograde cholangiopancreatography (ERCP) was at the discretion of the treating physician and endoscopist. In early years not always performed, but EUS evaluation has become part of routine work-up during the last years. Endoscopic resection was performed using a side-viewing therapeutic duodenoscope. Procedures were done under either conscious sedation, anesthesia administered propofol sedation or general anesthesia. Rectal NSAID's were administered during the procedure since 2010 to reduce the risk of pancreatitis. The technique of EA is not standardized and dependent on local anatomy, extension and characteristics of the adenoma and personal preference of the endoscopist. For snare resection, "ENDO CUT Q'' mode was used with standard settings for polypectomy: effect 3, cut duration 1, cutting interval 6 (VIO200D, ERBE, Tübingen, Germany), and standard materials were used, among which an oval snare (Acusnare, Cook Medical) and a stiff hexagonal snare (Captivator, Boston Scientific, USA). In general, in cases without intraductal extension the first step is cannulation of the pancreatic duct to fill the duct (partially) with diluted methylene blue to facilitate cannulation of the pancreatic duct after resection. In bulky or smaller adenomas in which en bloc resection is attempted the caudal and lateral parts of the lesion are lifted with saline. This step is done carefully since "over-lifting" can lead to a more difficult resection of the ampulla itself. After resection the specimen is retrieved with either the snare or a Roth-net and sent for pathological examination. At this stage procedural bleeds are most likely to occur and these can be treated endoscopically with either adrenalin injection, a coag-grasper or clips. Visible residual adenomatous tissue is either resected with the snare or treated with argon plasma coagulation (APC). The final step of the procedure is cannulation of the pancreatic duct and placement of a 4 or 5 french unflanged single pigtail endoprothesis. A plain abdominal film was obtained

within two weeks after the resection to check for spontaneous stent migration. If no spontaneous migration had occurred the stent was removed at gastroscopy. Lateral spreading lesions were removed in a piecemeal fashion with continuous lifting with gelofusine, methylene blue and diluted epinephrine (5 ml 1:10000 in 500 ml gelofusine). In most instances resection was started at the most caudal part of the lesion and the ampullary region itself was resected last. Resected pieces of the adenoma were positioned in either bulb or stomach and retrieved at the end of the procedure. In case of intraductal extension, a biliary and/or pancreatic sphincterotomy was performed to facilitate removal of intraductal tissue after a balloon sweep of the duct.

The surveillance protocol after treatment consists of a repeat examination after 1 to 6 month (depending on the initial success of treatment) followed by repeat examinations every 3-6 months for two years, and yearly thereafter for a total period of five years. Median follow-up time was calculated in months from the initial endoscopic ampullectomy up to the most recent endoscopic examination or surgical intervention. Endoscopic success was defined as complete excision of the adenoma, disregarding the number of sessions needed, and the absence of recurrence over the total follow up period. It was decided to use endoscopic success as an alternative for curative resection, because a R0 resection is often not acquired and in a number of cases complete removal is achieved in more than one session.

All statistical analyses were performed using SPSS 21.0 software (IBM Corp: Armonk, NY, United States of America). Data were expressed as mean ± standard deviation, median, and range. Statistical analysis included the chi-square test, Fisher's exact test and Kruskall Wallis Test with P values <0.05 regarded as significant. Survival analysis was demonstrated using the Kaplan–Meier method.

RESULTS

Patient demographics and tumor characteristics

A total of 110 patients were treated endoscopically for suspected adenomas of the ampulla of Vater during the 14-year study period. Twenty-three cases were excluded from the study, because they did not met the inclusion criteria (carcinoma [n=11], non-availability of the resection specimen [n=7], specimen showing signs of inflammation without dysplasia [n=3], ganglioneuroma [n=1], neuroendocrine tumor [n=1]). Eventually, 87 patients were included, 60 patients (69%) with low grade dysplasia (LGD) and 27 patients (31%) with high grade dysplasia (HGD). Based on the anatomical extension of the adenoma, the 87 patients were divided into three groups: 56 patients had an adenoma confined to the ampulla (ACA), 20 patients had a lateral spreading ampullary adenoma

(LSA), and 11 patients had an adenoma with intraductal extension (IEA). A study overview is depicted in Figure 1. Figure 2 illustrates advanced ampullary adenomas. Patients demographics are listed in Table 1. A total of 45 men and 42 women with a mean age of 65 years (range 32-89 years) were included. In 18 patients (20.7%) the adenoma was found incidentally or during endoscopic examination in case of FAP. The remaining patients had symptoms for which medical investigations were initiated: abdominal pain in 34 patients (39.1%), anemia in 16 patients (18.4%), weight loss in six patients (6.9%), jaundice in four patients (4.6%) and pancreatitis in three patients (3.4%). No statistical differences were observed among groups. Tumor characteristics are listed in Table 2. Seventy-one (81.6%) patients underwent biopsy before endoscopic ampullectomy: no dysplasia was seen in three patients (3.4%), 44 patients (50.6%) had LGD and 24 patients (27.6%) had HGD. Post-ampullectomy histological diagnosis confirmed LGD in 60 patients (69%) and HGD in 27 patients (31%). The average tumor size was 27.7mm (SD ±15.9). Lateral spreading adenoma were significantly larger (41.4 mm, SD ±12.9, p<0.001).

Table 1. Demographics and clinical presentation.

	Adenoma confined to the ampulla	Lateral spreading adenoma	Intraductal extending adenoma	Total	P
No. of patients, n (%)	56 (64.4%)	20 (23.0%)	11 (12.6%)	87	
Male, n (%)	29 (51.8%)	9 (43.9%)	7 (63.6%)	45 (51.7%)	0.610
Mean age, years1	63.0 (13.3)	64.6 (11.7)	74.7 (10.7)	64.9 (13.1)	0.017
FAP, n (%)	7 (12.5%)	5 (25%)	0	12 (13.8%)	0.139
Presentation, n(%)					
Incidental	5 (8.9%)	2 (10%)	0	7 (8.0%)	0.859*
FAP follow up	7 (12.5%)	4 (20%)	0	11 (12.6%)	0.334*
Biliary-pancreatic symptoms	9 (16.1%)	1 (5%)	2 (18.1%)	12 (13.8%)	0.377*
Abnormal laboratory results	5 (8.9%)	2 (10%)	2 (18.1%)	9 (10.3%)	0.497*
Nonspecific symptoms	29 (51.8%)	11(55%)	6 (54.5%)	46 (52.9%)	0.948
Clinical symptoms, n (%) **					
Asymptomatic	16 (28.6%)	7 (35%)	2 (18.2%)	25 (28.7%)	0.698
Jaundice	2 (3.6%)	0	2 (18.2%)	4 (4.6%)	0.108*
Abdominal pain	22 (39.3%)	6 (30%)	6 (54.5%)	34 (39.1%)	0.290
GI Bleeding	6 (10.7%)	1 (5.0%)	0	7 (8.0%)	0.595*
Anemia	8 (14.3%)	7 (35%)	1 (9.1%)	16 (18.4%)	0.126*
Pancreatitis	3 (5.4%)	0	0	3 (3.4%)	0.700
Cholangitis	2 (3.6%)	0	1 (9.1%)	3 (3.4%)	0.439*
Cholecystitis	2 (3.6%)	0	0	2 (2.3%)	1.000*
Weight loss	4 (7.1%)	1 (5.0%)	1 (9.1%)	6 (6.9%)	1.000*

* Fisher's Exact test (Exact Sig.(2-sided))

** Some patients had multiple complaints at clinical presentation

Data are expressed as mean and standard deviation

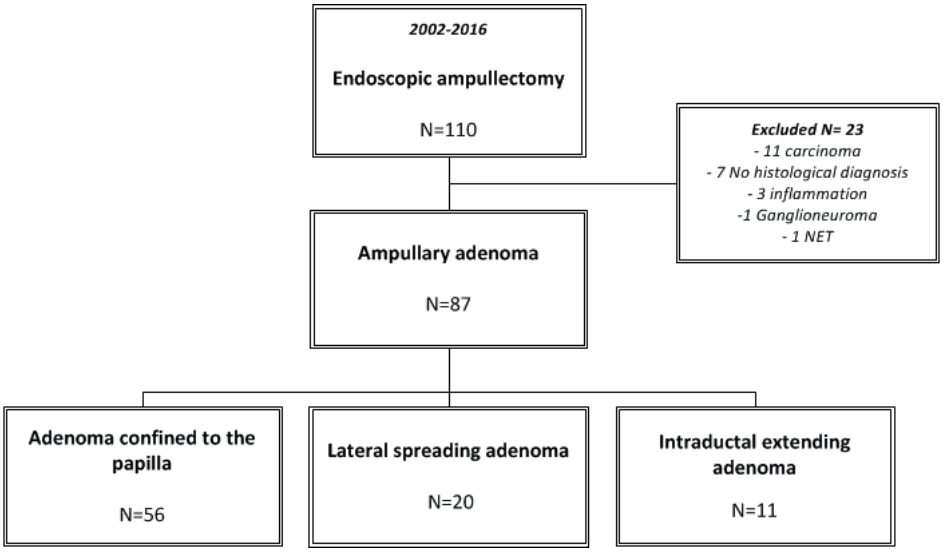

Figure 1. Study overview.

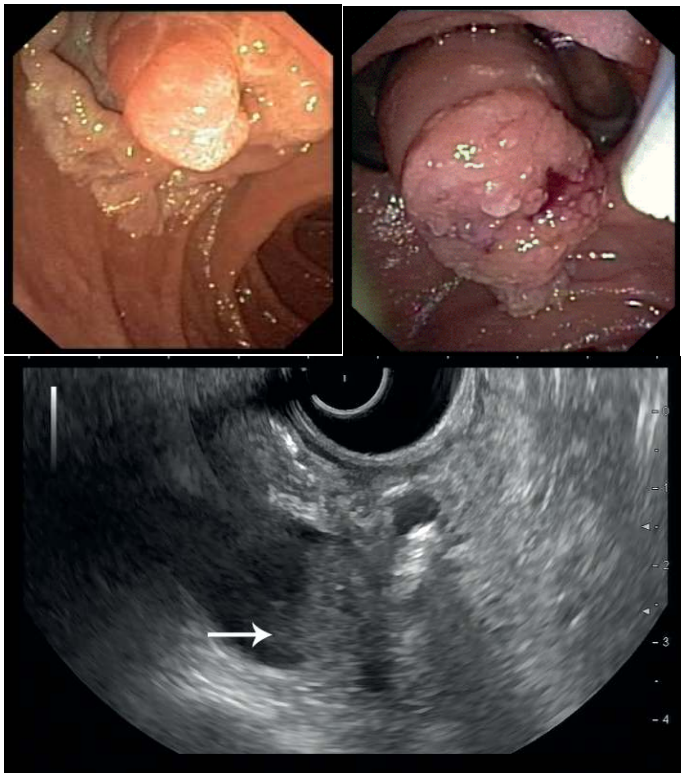

Figure 2. Overview of advanced ampullary adenomas. A LSA. B Intraductal extended adenoma with extension in the common bile duct. C Radial EUS image of the intraductal extended adenoma depicted in B.

Table 2. Tumor characteristics.

	Adenoma confined to the ampulla N=56	Lateral spreading adenoma N=20	Intraductal extending adenoma N=11	Total N=87	P
Pre-resection biopsy, n (%)	45 (80.4%)	16 (80%)	10 (90.9%)	71 (81.6%)	0.841*
No dysplasia	3 (5.4%)	0	0	3 (3.4%)	0.737*
LGD	28 (50%)	11 (55%)	5 (45.5%)	44 (50.6%)	0.737*
HGD	14 (25%)	5 (25%)	5 (45.5%)	24 (27.6%)	0.737*
EUS assessment, n (%)	47 (83.9%)	13 (65%)	11 (100%)	71 (81.6%)	0.047*
Type of resection, n (%)					
En Bloc	37 (66.1%)	1 (5.0%)	3 (27.3%)	41 (47.1%)	<0.001
Piecemeal	18 (32.1%)	16 (80%)	8 (72.7%)	42 (48.3%)	<0.001
Tumor size, in mm[a]	24.6 (15.1)	41.4 (12.9)	16.3 (4.3)	27.7 (15.9)	<0.001
Histology resection specimen, n (%)					
LGD	39 (69.6%)	13 (65.0%)	8 (72.7%)	60 (69.0%)	0.835
HGD	17 (30.4%)	7 (35.0%)	3 (27.3%)	27 (31.0%)	0.835

* Fisher's Exact test [Exact Sig.(2-sided)]

[a] Data are expressed as mean and standard deviation

Endoscopic ampullectomy

Overall, success resection with absence of recurrence was achieved in 67 patients (77%); 87.5% for ACA, 85% for lateral spreading adenoma, and only 9.1% in case of intraductal extension (P <0.001). Multiple procedures were required to successfully remove the adenoma in three patients with an ACA, seven patients with LSA and one patient with an IEA. En bloc resection was achieved in 37 patients with an ACA (66.1%). Post-ampullectomy argon plasma coagulation application (APC) to treat remnant adenomatous tissue was applied in 58 patients (66.7%). Endoscopic ampullectomy was complemented with placement of a pancreatic duct stent in 60 patients (68.9%). Eight patients (9.2%) were referred for surgery after failed endoscopic resection, of whom six with intraductal extension. Of these latter patients the final histopathological diagnosis was LGD (n=3), HGD (n=2) and invasive carcinoma (n=1).

Complications

Complications occurred in 22 patients (25.3%). The most common complication was post procedural hemorrhage (12.6%). Five patients required transfusions and seven patients underwent endoscopic management (adrenaline injection and/or hemoclip placement). In one patient bleeding was controlled by coiling the gastroduodenal artery. (Retro)peritoneal perforation occurred in seven patients (8.1%). One patient developed a pneumothorax for which a thorax drain was placed. All other patients were treated with antibiotics only. Acute pancreatitis developed in three patients (3.4%), mild in two

patients and severe in one patient. All three patients suffering from post-ERCP pancreatitis successfully underwent pancreatic duct stent placement. Cholangitis occurred in only one patient, treated with antibiotics. There was no procedure related mortality. No stenosis of the papilla of Vater was observed in our cohort. There were no statistical significant differences in the occurrence of complications between groups. Endoscopic success rates and complications are shown in Table 3.

Table 3. Endoscopic success and post-procedural complications.

	Adenoma confined to the ampulla N=56	Lateral spreading adenoma N=20	Intraductal extending adenoma N=11	Total N=87	P
Endoscopic success, n (%)	49 (87.5%)	17 (85.0%)	1 (9.1%)	67 (77.0%)	<0.001*
Referral to surgery after failed ER, n (%)	1 (1.8%)	1 (5%)	6 (54.5%)	8 (9.2%)	<0.001*
Complications, n (%)	15 (26.8%)	4 (20.0%)	4 (36.4%)	23 (26.4%)	0.630
Bleeding	8 (14.3%)	2 (10.0%)	1 (9.1%)	11 (12.6%)	0.823
Perforation	3(5.4%)	2 (10.0%)	2 (18.2%)	7 (8.1%)	0.337
Pancreatitis	3 (5.4%)	0	0	3 (3.4%)	0.423
Cholangitis	1 (1.8%)	0	0	1 (1.1%)	0.756
Papillary stenosis	0	0	0	0	-

*Fisher's Exact test [Exact Sig. (2-sided)]

Follow-up and recurrence

The median follow-up period was 18.6 months (IQR 7.6 to 39.5 months); 21.1 months in ACA, 14.7 months in LSA and 5.8 months in IEA. Recurrence was observed in ten patients (10.7%). Five patients with ACA showed recurrence (8.9%), of the 20 patients treated for an LSA, four patients showed recurrence (20%). In the IEA only 11 patients were endoscopically treated, six patients were referred for surgery and in two patients it was decided to discontinue follow-up because of other medical conditions. Of the remaining three patients, one developed recurrence of the IEA. In only one patient with ACA (1.8%) surgical resection because of recurrence was required. LSA patients with recurrence were all treated endoscopically. The IEA patient with recurrence was also referred for surgery. After two years of follow-up, 93% of patients with an ACA were free from recurrence and 90% of patients with an LSA, as depicted in Figure 3. Details are listed in Table 4.

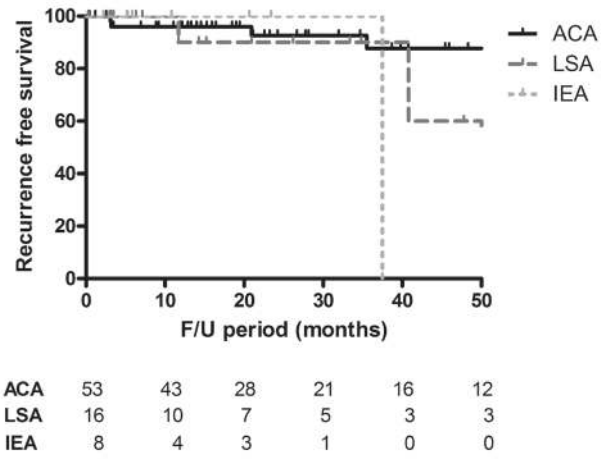

Figure 3. Recurrence-free survival according to endoscopic resection and extension of the adenoma.

Table 4. Follow-up and recurrence.

	Adenoma confined to the ampulla N=56	Lateral spreading adenoma N=20	Intraductal extending adenoma N=11	Total N=87	P
Follow-up, months[a]	21.1 (12.0 - 45.9)	14.7 (4.2 - 34.5)	5.8 (3.7 – 22.0)	18.6 (7.6 - 39.5)	0.051
Recurrence, n (%)	5 (8.9%)	4 (20%)	1 (9.1%)	10 (11.5%)	0.305*
Time to recurrence, months[a]	9.2 (4.2 – 25.7)	21.8 (5.2 – 79.8)	21	13.1 (4.6 – 33.1)	0.733
Recurrence free survival after 24 months	93%	90%	0%	-	-

* Fisher's Exact test [Exact Sig.(2-sided)]
Data are expressed as median and interquartile range

DISCUSSION

This is a retrospective single center cohort study describing the endoscopic management and outcome of patients with (advanced) ampullary adenomas. Since the first large cohort study in 1993 by Binmoeller et al.[11] various reports have been published showing promising results of the endoscopic treatment of ampullary adenomas as an alternative for surgical resection[9,12,13,18-21]. Our data show that endoscopic ampullectomy is indeed a safe and effective treatment, also in patients with lateral spreading adenomas. In patients with intraductal extension however, surgical resection should be considered as primary treatment.

Currently, guidelines on the endoscopic or surgical management of ampullary adenomas are lacking. Literature data suggest that surgery is indicated for patients with larger

lesions, for cases when no skilled interventional endoscopists with experience in ampullectomy are available and, obviously, in lesions suspected for malignancy and potential lymph node invasion[18,22]. Surgical options include transduodenal ampullectomy and pancreaticoduodenectomy, but are associated with high morbidity and mortality rates. Morbidity rates vary from 4 to even 68% of patients who underwent pancreaticoduodenectomy and mortality is reported up to 7%[23,24]. With the introduction of endoscopic ampullectomy in 1983 by Suzuki et al.[25] treatment has shifted towards minimal invasive endoscopic resection as an alternative to surgery and this shift has been accelerated due to technical improvements in endoscopy over the last decades.

The study by Binmoeller et al.[11] included 25 patients with ampullary adenomas that were endoscopically treated, demonstrating lower morbidity and mortality rates than surgical intervention with a success rate of 75%. To date, outcome data of endoscopic ampullectomy are largely based on retrospective case series in which success is reported in the range of 46% to 92%[9-14]. This wide range is explained by differences in selection criteria, tumor size, extent of the tumor, and probably of key importance, the experience of the endoscopist. In our study, the overall success rate of endoscopic resection was 77%. Categorization of adenomas based on the extent of the tumor however, showed a significant difference in success rates. The success rate in patients with an adenoma confined to the ampulla and patients with a lateral spreading adenoma is excellent, 87.5% and 85% respectively. In contrast however, the endoscopic management of patients with an intraductal extending adenoma was much less favorable with complete removal of the adenoma in one out of 11 patients only. Extension into the biliary duct or pancreatic duct of an ampullary adenoma has been historically regarded as a contraindication of endoscopic management[12,13,19,26]. Therefore, studies evaluating the endoscopic management of IEAs are rare and mostly based on small groups. Bohnacker et al.[20] reported a success rate of 46% in 31 patients endoscopically treated for an IEA. The authors could not identify criteria predicting a successful resection and postulate that limited intraductal involvement allows for a reasonable attempt of endoscopic management, provided by experienced endoscopists. Cheng et al.[10] treated two patients with IEA endoscopically of which one was lost to follow-up and one showed no recurrence at one-year follow-up. The optimal treatment strategy in patients with ampullary adenomas with intraductal extension remains elusive. Ideally, after appropriate ampullary resection and sphincterotomy, the intraductal extension of the adenomatous lesion is exposed, visually inspected and removed. The role of radiofrequency ablation to treat intraductal extension of ampullary adenomas is currently under investigation and shows some promise[27,28]. Needless to state that adequate follow-up is pivotal importance in order to timely revert to surgical resection not losing out on an opportunity for curative treatment.

Even though various studies have confirmed a decrease in procedure-related complications for endoscopic management of ampullary adenomas in comparison to surgical resection, complication rates are described up to 33% and remain an important concern[10,12,15]. Catalano et al.[12] performed a large study combining the results of endoscopic ampullectomy from four pancreaticobiliary endoscopy centers, including 103 patients with a success rate of 80% and a complication rate of 10%. In 2013 Onkendi et al.[8] published the results of a large comparative study of the outcomes of operative and endoscopic resection showing post-endoscopic complications in 29% of treated patients. Procedure-related complications in our cohort, including mainly bleeding, perforations and pancreatitis, occurred in 25.3% of patients with no statistical between groups.

Post EA bleeding was seen most often in our cohort (12.6%), with literature data indicating a median risk of 8.5% of cases[29]. Most patients were treated endoscopically, but one patient required coiling of the gastroduodenal artery to control the bleed. Although the intraductal extending adenomas and adenomas with a lateral growth pattern are reported to be associated with a higher bleeding risk[15,20,30], we did not observe this in our series.

Post-ERCP pancreatitis is the most common complication after EA, with an incidence reported between 8 to 19%[10,12,20,30,31]. Pancreatic stent placement during the procedure may reduce the risk of this complication[9,20,32,33], as well as administration of nonsteroidal inflammatory drugs (NSAIDs)34. Previous studies reported a success rate of pancreatic stent placement in patients with an ampullary adenoma of 4% to 92%[11,12,35]. In the present study, pancreatic stent placement was successful in 69% of patients. Post-ERCP pancreatitis was diagnosed in only 3.4% of patients. Administration of rectal NSAIDs has become standard practice at our unit since 2010, in accordance with the ESGE guideline[36]. All three patients that suffered from post-ERCP pancreatitis in our series had undergone prophylactic pancreatic duct stent placement.

Perforation occurred in seven patients (8.1%). There were no statistical differences among groups (P=0.337), however, as expected, our data indicate that perforation occurred more in the advanced adenoma groups. The incidence of perforation is higher in our cohort compared to previous series, however patients were successfully managed with conservative treatment. Papillary stenosis is a known late complication of EA with an incidence of 2.9% to 8%. No cases of papillary stenosis were reported in our cohort.

The median follow-up of patients with an ampullary adenoma treated endoscopically reported in literature ranges from 9 to 66 months with recurrence described up to 33% of cases[10,12,19,20]. In our study, the median follow-up duration was 18.6 months. No clear

guidance regarding the appropriate length of endoscopic follow-up is available, but several studies indicate a period of at least two years[9-12]. In the present study, recurrence occurred in 11.5% of patients after a median of 13.1 months (IQR 4.6 – 33.1), but in one case recurrence was found 55 months after initial therapy.

There are several potential limitations to our study. The retrospective nature makes this study prone to selection and recall bias. However, due to the rarity of this condition a prospective study is unlikely to be carried out. Also, the number of patients in the advanced adenoma groups was small making statistical comparisons between groups of limited value.

In conclusion, this single-center retrospective cohort study confirms that endoscopic ampullectomy can be a safe and successful treatment modality for patients with an ampullary adenoma confined to the ampulla, but also for patients with a lateral spreading papillary adenoma. Meticulous endoscopic follow-up to detect and treat recurrence is pivotal. In case of intraductal extension of adenomatous tissue, endoscopic success rates are reduced to such a level that surgical resection should be considered.

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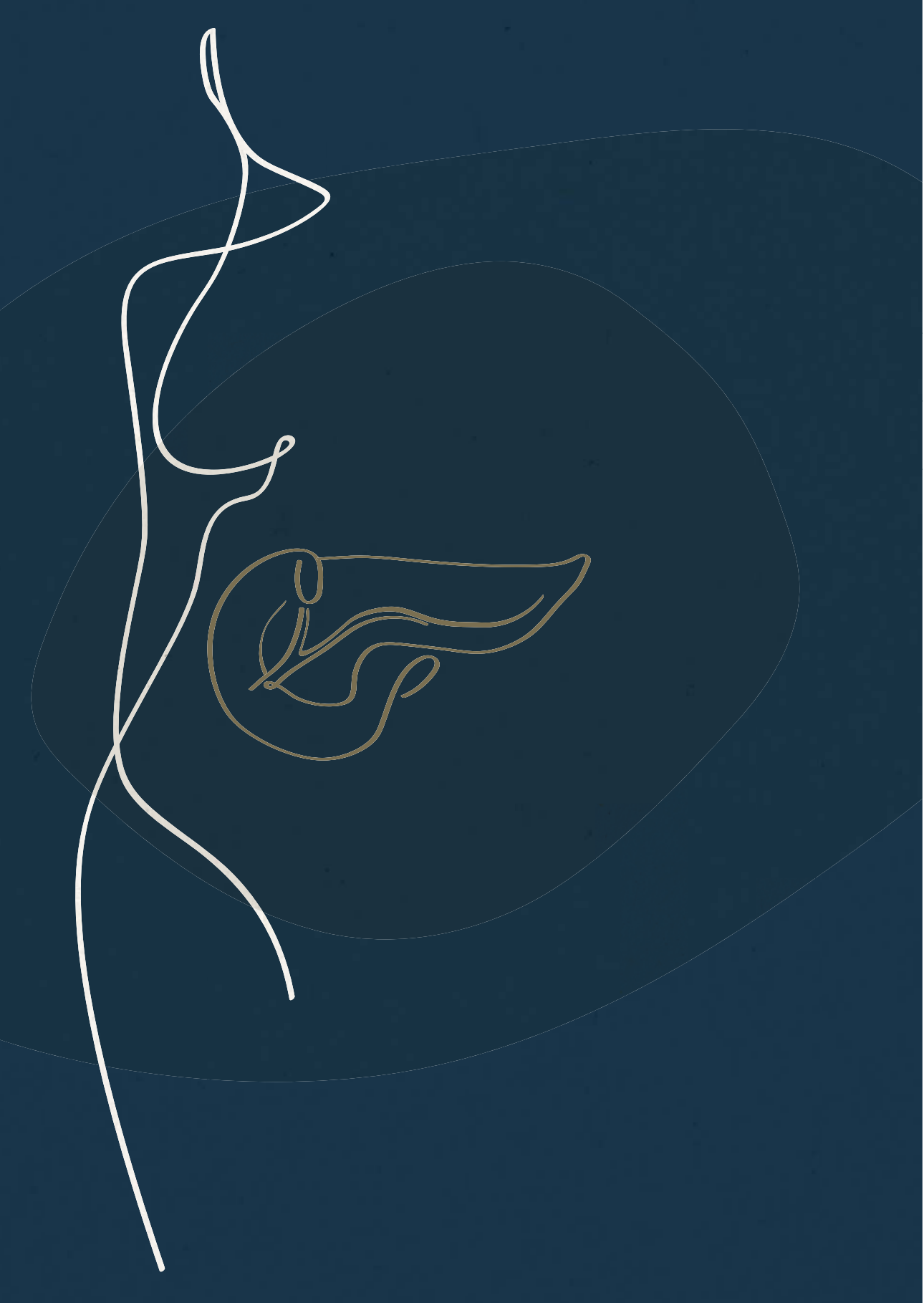

PART V

General discussion, summary and appendices

10

General conclusions and future perspectives

GENERAL CONCLUSIONS

This thesis explored how to improve medical therapy for patients with a disease of hepatopancreatobiliary and duodenal tract. First, it provided insight in simulation-based training in gastrointestinal endoscopy, specifically in training endoscopic retrograde cholangiopancreatoscopy (ERCP). Then, we evaluated procedural success of ERCP performance in the Netherlands after implementation of a mandatory nationwide registry in 2016. In the last part of this thesis, we focused on the outcome of more advanced endoscopic procedures. Firstly, we evaluated if a novel mechanical endoscopic tissue resection tool was sufficient and safe in removing necrotic tissue in patients with walled-off pancreatic necrosis. Secondly, we performed a study to evaluate endoscopic pancreatoscopy-guided intraductal lithotripsy as first line treatment in patients with chronic pancreatitis and obstructive main pancreatic duct stones. Finally, in the last study of this thesis, we explored the success of endoscopic resection of advanced adenomas of the ampulla of Vater. In this final chapter we summarize and discuss our findings and provide recommendations and possible directions for future research.

Simulator training in gastrointestinal endoscopy

Simulation-based training in gastrointestinal endoscopy has earned its place in training novices, facilitating a safe environment to apply theory and gain experience in skills and procedures[1]. Simulation-based training has been integrated in the training curricula for teaching endoscopy, and studies have demonstrated that simulation-based training is associated with better performance of the trainee and improved patient outcomes[2]. In **Chapter 2**, we presented a review of current available simulators for training endoscopy. Numerous simulators have been developed since the 1960s for training endoscopic procedures. Training models are available as mechanical simulators, live animal models, ex vivo models and virtual reality (VR) computer simulators. Our overview demonstrates that simulation-based training is mainly developed in training gastroduodenoscopy and colonoscopy and that simulators have proven their value in training novice endoscopists in the first steps of their endoscopic career. Strikingly however, training options for therapeutic interventions are lacking, even the more standardized therapeutic procedures such as standard polypectomy. This limits the options for the more experienced endoscopists to train common therapeutic interventions such as polypectomy and bleeding scenarios. Another important conclusion of our review is the lack of (validated) simulators in the field of ERCP. In 1968, the first report on retrograde opacification and successful cannulation of the main pancreatic duct was published in the Annals of Surgery[3]. Ever since, the technique has evolved from a primarily diagnostic tool to a therapeutic tool. As for the development of the procedure itself, the training options and requirements have also drastically changed over the years, unfortunately, simulation-based training

is still underdeveloped for training ERCP despite the overwhelming positive results in other fields of endoscopic procedures[2]. Previous studies have demonstrated that the process of developing competence in ERCP is complex[4, 5]. Apart from the additional knowledge of pancreatobiliary pathologies and the understanding of the indications and contraindications of the procedure, the trainee has to work with a side-viewing endoscope instead of a forward viewing endoscope and various dedicated instruments. A lot of this information can be transferred by books, live ERCP demonstrations, but ultimately learning ERCP is done by extensive hands-on training. For these reasons, and the fact that ERCP is associated with serious complications in particular when done by an inexperienced operator, the concept of simulation-based training is ideally suited for training ERCP. Therefore, in **Chapter 3**, the Boškoski-Costamagna mechanical ERCP Trainer, was validated. We were able to demonstrate good face and construct validity of the simulator. This means that the simulator simulates ERCP to a favorable degree of realism according to experts, despite the mechanical nature of the simulator, and secondly, that the simulator is able to distinguish between different levels of competency. Our data do not support the use of the simulator in training more experienced endoscopists in performing ERCP. This implicates that this simulator is of additional value in training novices the basic principles of ERCP. Previous studies concerning simulation-based training in gastrointestinal procedures have demonstrated that simulator-based training is mainly limited to train endoscopists at the start of their career[2, 6]. In **Chapter 4**, we investigated an extension of the Boškoski-Costamagna mechanical ERCP Trainer, a papilla constructed out of rubber for training endoscopic sphincterotomy. Endoscopic sphincterotomy is one of the key therapeutic interventions of ERCP and one of the many reasons ERCP is considered a complex and risky procedure. Forty ERCP experts (>2500 lifetime ERCPs) were asked to perform a biliary sphincterotomy and rate the novel papilla on realism and didactic value in training novice endoscopists. They agreed that the papilla mimics the human papilla, mainly the maneuvers that need to be performed to perform a biliary sphincterotomy and that the experience gained on the papilla should be directly transferrable to the training of novices in a clinical curriculum. The absolute advantage of this papilla is that a real endoscope with real accessories are used, compared to previously published training options for sphincterotomy[7-10]. The simulator unfortunately, is not able to mimic complications such as bleeding or perforation. Although simulation based-training might never be exactly comparable to the human anatomy and tactile feedback, it enables the trainee to acquire knowledge, skills and behavioral experiences in a low-risk environment. We therefore do believe that this simulator is of additional value in the training curricula of ERCP trainees, as supported by the experts in our study. However, what the specific role of the simulator in training curricula should be, is open for discussion. At first, providing trainees with the possibility to use a simulator does not equal proper training. In 2004, Mahmood et al. [11], dem-

onstrated that simulation-based training has no effect on endoscopic skill-acquisition when delivered without feedback from experienced trainers. On top of that, methods to measure ERCP competence are lacking and poorly defined. The current guidelines recommend at least 100 to 200 procedures to gain competence[12]. Additionally, guidelines demand a 80-90% successful common bile duct (CBD) cannulation rate for trainees at the end of training as a surrogate marker for competence. Interestingly, in 2007, Verma et al.[13] demonstrated that a 80% successful unsupervised CBD cannulation rate was only achieved after 400 procedures. This emphasizes even more that trainees learn at their own pace and need a more individualized approach to train and develop their ERCP skills. Based on our study results we believe that simulation-based training can play an important role to achieve such goal. To further explore the role and added value of simulation-based training, we designed a prospective study to determine the impact of a two-day hands-on training course in ERCP trainees at their beginning of training. The effect of this two-day training course was outlined in **Chapter 5**. Six trainees were allocated to the simulation course program (SG) which contained lectures, live ERCP demonstrations, and hands-on training to provide the trainees with basic techniques related to cannulation, stent placement, stone extraction, and stricture management. A match control group was created consisting of seven starting endoscopy trainees at their local training center. Our data demonstrate a higher mean successful CBD cannulation rate for the SG at baseline (64% versus 43%). The differences in favor of the SG persist until a median of 75 ERCPs, however the number of participating trainees was very low at that point during the study which makes it very difficult to generalize the results. Nevertheless, our data support the high value of simulator-based training in ERCP and warrant further research to determine the extent of simulator training versus no simulator training, the duration of the training, the specific role for simulator training in ERCP, and the implementation in training curricula.

Mandatory ERCP registration in the Netherlands

As we discussed in the introduction of this thesis, healthcare quality and monitoring is a growing topic of interest. In **Chapter 6** we performed a prospective registration study to provide insight into the procedural success of ERCP after registration of the structured procedural reporting became mandatory in the Netherlands in 2016. In 2018, the European Society of Gastrointestinal Endoscopy (ESGE) published a list of key quality performance measures, intending to set a minimum standard for quality in ERCP, and we used this performance targets to evaluate the ERCP performance in the Netherlands[14]. We included eleven Dutch hospitals, both academic and non-academic hospitals, with a total number of 5671 ERCPs over a two year period, which amounts to approximately 12.5% of the total number of ERCPs performed in this period in the Netherlands. Our study revealed that the overall procedural success rate was 89.1%. Beforehand we hypothesized

that in view of its mandatory nature, the current overall procedural success rate would be lower than the 86% procedural success rate in a voluntary registration as published by Ekkelenkamp et al.[15], who performed a comparable study in the Netherlands. A direct comparison should be interpreted with great cautions, but this might reflect the positive effect of the mandatory registration. A likely explanation for this result is that poor ERCP performers are more conscious about their performance and have stopped performing some more complex procedures or have quit doing ERCP, a phenomenon that we even observed during the voluntary registration. The latter explanation is supported by our observation that compared to the earlier study fewer endoscopists perform more ERCPs in the majority of Dutch Centers. When then moved from overall procedural success to more specific performance measures, we evaluated the results of successful biliary cannulation, successful biliary stent placement and successful extraction of bile duct stones, according to the ESGE target standards. ESGE target standards were met for all parameters, except for successful biliary cannulation in patients with naive papillary anatomy in academic centers (92.4% of the targeted 95%). Whether this target standard is realistic for all institutions remains debatable, due to the fact that more failed and difficult ERCPs are referred to (academic) specialty centers, for which sometimes more advanced selective cannulation techniques are required. Our results imply that a nationwide registry offers the opportunity to evaluate and improve the quality of ERCP and that ERCP performance in the Netherlands is of high quality.

Advanced endoscopic procedures

The final section of this thesis focused on advanced endoscopic procedures of the hepatopancreatobiliary and duodenal tract. In recent years, endoscopic techniques have made numerous advancements, providing many possibilities to endoscopically treat advanced gastrointestinal diseases, obviating the need for surgical intervention with in most cases higher morbidity and mortality rates compared to minimally invasive endoscopic interventions. As presented in **Chapter 7**, we evaluated a novel endoscopic resection tool to facilitate endoscopic necrosectomy in patients with acute infected necrotizing pancreatitis, the EndoRotor. Necrotizing pancreatitis is the most dreadful complication of acute pancreatitis and knows a mortality rate of 15%, and around 30% in case of infected necrosis[16-18]. Intervention is generally required for infected necrotizing pancreatitis, and a major focus of innovation is to find a suitable tool to effectively remove pancreatic necrosis endoscopically, because current available tools are designed for other indications and lack effectiveness for this purpose. We used the novel EndoRotor tool in twelve patients, who underwent a combined total of 27 procedures. In our cohort, complete removal of necrotic tissue was achieved with a median number of two procedures. Studies evaluating conventional tools demonstrated a median number of three to six procedures[19-22]. Endoscopic necrosectomy is accompanied by high com-

plication rates, especially a high bleeding risk[22], but in our cohort no procedure related adverse events occurred. This finding is in line with another trial evaluating the safety of the EndoRotor during necrosectomy in 30 patients[23], of which the formal peer reviewed publication is awaited.

Chapter 8 demonstrates the results of a study in which we investigated the role of pancreatoscopy-guided electrohydraulic lithotripsy (EHL) for obstructive main pancreatic duct stones in patients with chronic calcifying pancreatitis (CCP). Several studies demonstrated the potential of pancreatoscopy-guided EHL as a treatment modality in patients with CCP, but mainly after previous failed extracorporeal shock wave lithotripsy (ESWL)[24-33]. These findings have raised the question if pancreatoscopy-guided EHL could possibly be used as first-line therapy obviating the need for ESWL. We prospectively investigated this hypothesis in a consecutive cohort of 36 patients. We were able to demonstrate a technical success rate of 70.6%. During the study period we experienced that the technical success was mainly limited by the inability to achieve deep cannulation of the pancreatic duct (PD). In case ductal access could be secured the technical success rate increased to 92.3%, with complete stone removal in 80% of patients. Clinical success was achieved in 72% of patients with >50% decrease in pain scores or reduction in opioid usage at six months of follow-up. These findings imply that pancreatoscopy-guided EHL holds promise as a first line treatment of PD stones with the constraint however that its success is highly dependent on achieving successful cannulation of the PD. Therefore, one may suggest that for logistical planning of the treatment of these patients it is approached as a two-step procedure starting with an ERP to secure ductal access (i.e. by stent placement) and a subsequent ERP to perform pancreatoscopy-guided EHL. The question raises what is the benefit of pancreatoscopy-guided EHL compared to ESWL, since studies demonstrated that in up to 38% of cases ESWL is the sole treatment obviating the need for PD cannulation and stone fragment removal. The main advantage of pancreatoscopy and EHL seems however that it has the potential to be available much more wide spread and that its performance is not bound to an (external) ESWL facility but is in the hands of the ERCPist him/herself. Future prospective studies in this population are indicated to further explore the role of pancreatoscopy-guided EHL in comparison to ESWL and/or surgical treatment.

In **Chapter 9**, we investigated the technical success and complications of endoscopic resection of ampullary adenomas. Tumors of the ampulla of Vater are increasingly diagnosed due to better accuracy of endoscopic detection technologies. The success rate of endoscopic resection appears to be dependent on the growth pattern of the adenoma. The adenoma can either be confined to the ampulla (ACA), laterally spreading beyond the ampulla (LSA) and/or growing intraductally (IEA). We retrospectively analyzed 87

patients, 56 with an ACA, 20 with a LSA and eleven patients with an IEA. Overall successful endoscopic ampullectomy, without recurrence, was achieved in 77% of patients in our cohort, albeit with a significant difference between the three types of adenomas. Endoscopic resection of intraductally growing adenomas was only successful in 9.1% of patients and 54.5% were referred for surgical intervention. This is in contrast to a curative endoscopic resection in 87.5% of patients with ACA, and 85% of patients with LSA. Procedure-related complications were seen in 26.4%, mainly post procedural hemorrhage (12.6%) and retroperitoneal perforation (8.1%). Overall recurrence was seen in ten patients (11.5%), in two patients surgical resection because of recurrence was required (one ACA and one IEA). Our data indicate that endoscopic ampullectomy can be a safe and successful treatment even in patients with a laterally spreading adenoma, but that in patients with an intraductally spreading adenoma surgery remains the safest option. Comparable results are described in literature[34-36]. The recently updated guideline by the ESGE on the endoscopic management of ampullary tumors stated that endoscopic treatment of ampullary adenomas is recommended in patients without intraductal extension[37].

RECOMMENDATIONS AND FUTURE PERSPECTIVES

This thesis focused on various aspects of advanced endoscopic procedures with the mutual goal to improve treatment for patients with a disease of the pancreatobiliary and duodenal tract. Efforts should be made to continuously improve healthcare quality at various levels. At first, improving health care starts with proper training of the operators intended to perform these procedures. Based on previous research and the results presented in this thesis, we are convinced that ERCP simulators should be incorporated in the pre-patient training curricula of novices in training for ERCP. This does not only creates a safe environment for trainees with the opportunity to extensively train the procedure in a relative short period of time, thereby overcoming decreasing patient burden and potential complications. The specific role of simulation-based training in ERCP, and to determine at what level trainees are ready to start with real-life ERCPs in patients, should be further explored. Based on the current available data, we recommend to evaluate trainees according to their personal learning curve, both during simulation-based training as well as patient-based training, providing the trainee a direct feedback mechanism and the trainer with solid information for evaluate whether the trainee has reached a certain level of competence to make the transfer to real life patients and a next level of procedural complexity. Secondly, efforts should be made to continuously improve ERCP simulators to mimic real life, to maximize the learning benefits.

Teaching endoscopic procedures to novices and reaching a certain level of competence is challenging, but maintaining endoscopic proficiency is of equal importance and

can be difficult as well. We believe that ERCPists should receive regular feedback on their procedural outcome in comparison to accepted performance standards and the performance of their peers. For this the establishment of a nationwide mandatory ERCP registry in 2016 was an important milestone. Nevertheless, we also expose the fact that even after 5 years we still encountered many registration issues in the nationwide registry during our research which renders the data to be incomplete. Efforts should be made to improve the registry not only to monitor on a nationwide level, but also to provide individual ERCPists the opportunity to evaluate their own performance by direct feedback.

The current thesis provides new information and techniques for three advanced endoscopic treatment modalities. As illustrated by data presented in this thesis, endoscopic options in treatment of diseases of the pancreatobiliary and duodenal tract increase rapidly, obviating the need for surgical interventions. Results are promising. Our data however are based on limited number of patients and mostly single center. To truly evaluate long-term outcome and adverse events preferably in comparison to surgical and or radiological options, additional studies are warranted, preferably with a multi-center randomized controlled setting. One should realize that these procedures are technically demanding and we recommend to perform these procedures in expert centers with sufficient exposure and experience.

The results of this thesis shed light on various aspects of improvement of health care for patients with a disease of the pancreatobiliary and duodenal tract, and provide leads for further research to optimize both training and treatment strategies for advanced endoscopic procedures, with a specific interest in ERCP.

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11

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Dit proefschrift heeft tot doel de medische behandelingsopties voor patiënten met een pancreatobiliaire aandoening of aandoening van het duodenum te verbeteren. Het eerste deel van het proefschrift geeft inzicht in het gebruik van simulatoren voor training in het verrichten van gastro-intestinale endoscopie. In dit proefschrift hebben we specifiek onderzoek gedaan naar het gebruik van een mechanische simulator voor het trainen van Endoscopische Retrograde Cholangio- en Pancreaticografie (ERCP). In het tweede deel van dit proefschrift evalueerden we het succes van de in Nederland uitgevoerde ERCPs nadat het in 2016 landelijk verplicht werd elke verrichte ERCP te registreren. In het laatste deel van dit proefschrift hebben we ons gericht op de uitkomst van meer geavanceerde endoscopische procedures. We hebben onderzocht of een nieuw mechanisch instrument geschikt en veilig was voor het verwijderen van necrotisch weefsel bij patiënten met een acuut necrotiserende pancreatitis. Tevens hebben we een studie verricht bij patiënten met chronische pancreatitis gecompliceerd door obstruerende stenen in de ductus pancreaticus, waarbij we onderzocht hebben of deze obstruerende stenen endoscopisch konden worden verwijderd als eerstelijnsbehandeling middels pancreatoscopy-geleide intraductale lithotripsie (EHL). De laatste studie van dit proefschrift beschrijft een retrospectief onderzoek naar het endoscopisch verwijderen van adenomen van de Papil van Vater. In het laatste hoofdstuk van mijn proefschrift, **Hoofdstuk 11**, hebben we de belangrijkste bevindingen samengevat en geven we aanbevelingen voor toekomstig onderzoek.

Simulator training

De afgelopen decennia heeft het gebruik van simulatoren voor het aanleren van gastrointestinaal endoscopische procedures zijn plek verdiend binnen het curriculum voor medisch specialisten in opleiding (AIOS). Het doel van simulatietraining is het nabootsen van de werkelijkheid zodat de AIOS in een veilige omgeving de geleerde theorie kan toepassen en ervaring op kan doen met de technische mogelijkheden van de verschillende endoscopische procedures[1]. Diverse studies hebben aangetoond dat simulatietraining geassocieerd is met betere prestaties van de AIOS en tevens gepaard gaat met een betere uitkomst voor de patiënt[2]. In **Hoofdstuk 2** presenteren we een overzicht van de huidig beschikbare simulatoren voor het trainen van vaardigheden binnen de gastrointestinale endoscopie. Sinds de jaren 60 zijn er tal van simulatoren ontwikkeld voor het trainen van endoscopische procedures. Diverse modellen zijn beschikbaar, mechanische simulatoren, levende dieren, ex-vivo modellen en virtual reality computersimulatoren. Uit onze review komt naar voren dat er voornamelijk simulatoren ontwikkeld zijn voor het trainen van gastroduodenoscopie en colonoscopie en dat deze simulatoren hun waarde hebben bewezen bij het opleiden van beginnende AIOS. Opvallend is dat

het trainen van endoscopische therapeutische interventies op een simulator nog niet mogelijk is, zelfs voor de meer gestandaardiseerde therapeutische procedures als poliepectomie. Dit beperkt ook de mogelijkheden voor de meer ervaren medisch specialist om therapeutische interventies als poliepectomie en bloedingsscenario's te trainen. Een tweede belangrijke conclusie van onze review is het ontbreken van (gevalideerde) simulatoren voor het trainen van vaardigheden in ERCP. De eerste data over succesvolle canulatie van de ductus choledochus (CBD) werden al gepubliceerd in 1968 in het tijdschrift Annals of Surgery[3]. Sindsdien is de techniek sterk geëvolueerd van een primair diagnostische ingreep naar een therapeutische behandelingsmodaliteit. Los van de ontwikkelingen rondom de procedure zijn ook de opleidingsopties en -vereisten in de loop der jaren drastisch veranderd. Echter is het gebruik van simulatoren voor het aanleren van het verrichten van een ERCP helaas nog steeds onderontwikkeld, ondanks de overwegend positieve resultaten bij het gebruik van simulatoren voor andere endoscopische procedures[2]. Eerder verrichte studies hebben aangetoond dat het proces van competentie-ontwikkeling in ERCP zeer complex is[4,5]. Naast de kennis die de AIOS dient te hebben van de diverse pancreatobiliaire aandoeningen en de indicaties en contraindicaties van het uitvoeren van een ERCP, dient de AIOS ook te werken met een zijwaarts kijkende endoscoop in plaats van een voorwaarts kijkende endoscoop zoals bij gastroduodenoscopie en colonoscopie. De zijwaarts kijkende endoscoop maakt gebruik van andere instrumenten specifiek geschikt voor ERCP. Veel van deze informatie over de procedure kan worden verkregen via boeken, workshops en live ERCP demonstraties, maar uiteindelijk zal het leren van de vaardigheden voor ERCP plaatsvinden middels uitgebreide praktijkgerichte training. Op basis van deze gegevens en het feit dat het uitvoeren van ERCP gepaard kan gaan met ernstige complicaties, vooral wanneer de ERCP wordt uitgevoerd door een onervaren arts, is het concept training op basis van simulatie bij uitstek geschikt voor het trainen van ERCP. In **Hoofdstuk 3** werd de Boškoski-Costamagna mechanische ERCP Trainer gevalideerd. In deze studie hebben we aangetoond dat de Boškoski-Costamagna mechanische ERCP Trainer een valide instrument is voor het nabootsen van ERCP op basis van goede indruksvaliditeit (face validity) en constructvaliditeit (construct validity). Indruksvaliditeit geeft aan in hoeverre experts op het gebied van ERCP (>2500 verrichte ERCPSs) de indruk hebben dat de simulator geschikt is voor het trainen van ERCP aan de hand van het oefenen op de simulator en een vragenlijst. De experts kwamen tot de conclusie dat de simulator de realiteit in gunstige mate simuleert, ondanks het mechanische karakter. Constructvaliditeit geeft aan of de simulator in staat is om het competentieniveau van verschillende gebruikers met wisselende endoscopische ervaring van elkaar te onderscheiden. De simulator is daarmee in staat om verbetering van beginnende AIOS vast te leggen na herhaaldelijke oefening, we hebben dit getest door vier verschillende groepen te creëren op basis van ERCP ervaring variërend van geen ervaring tot endoscopisten met meer dan 2500 verrichte ERCPs

gedurende zijn of haar carrière. Onze uitkomsten ondersteunen echter niet het gebruik van de simulator bij meer ervaren endoscopisten. Dit suggereert dat de simulator voornamelijk ingezet kan worden bij het trainen van ERCP basis vaardigheden aan de beginnende AIOS. Onze conclusie wordt ondersteund door data van eerder uitgevoerde studies waarbij is aangetoond dat het effect van simulator training voornamelijk beperkt is tot het trainen van AIOS aan het begin van hun endoscopische carrière[2,6]. In **Hoofdstuk 4** onderzochten we een replica van de Papil van Vater gemaakt van rubber voor het trainen in de uitvoering van endoscopische sphincterotomie als uitbreiding van de Boškoski-Costamagna mechanische ERCP Trainer. Het verrichten van een sphincterotomie is één van de belangrijkste therapeutische interventies bij ERCP en één van de vele redenen waarom ERCP als een complexe en risicovolle procedure wordt beschouwd. Veertig ERCP experts (>2500 verrichte ERCPs) werden gevraagd om een biliaire sphincterotomie uit te voeren op de simulator. Gevraagd werd de papil te beoordelen ten opzichte van de realiteit en de waarde van de papil in te schatten als didactisch middel voor het aanleren van een biliaire sphincterotomy. De experts waren het erover eens dat de synthetische papil de menselijke papil nabootst, met name ten aanzien van de endoscopische bewegingen die moeten worden uitgevoerd om een biliaire sphincterotomie uit te voeren. Daarbij vonden de experts dat de ervaring die opgedaan werd tijdens het gebruik van de simulator direct overdraagbaar is naar de opleiding van beginnende endoscopisten. Het absolute voordeel van het gebruik van deze synthetische papil is dat er gebruik wordt gemaakt van een echte endoscoop met echte accessoires in tegenstelling tot eerder gepubliceerde trainingsmogelijkheden voor sfincterotomie[7-10]. De simulator is helaas niet in staat complicaties zoals bloedingen of perforaties na te bootsen. We zijn ons ervan bewust dat het gebruik van een simulator nooit direct vergelijkbaar kan zijn met de menselijke anatomie en de tactiele feedback van het weefsel, maar het stelt de AIOS wel in staat kennis, vaardigheden en ervaring op te doen in een niet stressvolle omgeving zonder kans op complicaties. Wij zijn dan ook van mening dat deze simulator van meerwaarde is binnen het opleidingsplan van de AIOS Maag-, Darm- en Leverziekten voor het uitoefenen van ERCP, onze mening wordt ondersteund door de experts uit ons onderzoek. De specifieke rol van de simulator binnen het curriculum voor de AIOS dient nog uitgezocht te worden. Het aanbieden van een simulator geeft geen garantie voor een adequate training. In 2004 toonden Mahmood en collega's aan dat het gebruik van een endoscopische simulator niet effectief is als er geen directe feedback is van een ervaren endoscopist[11]. Bovendien ontbreken methoden om competentie-ontwikkeling te meten en zijn de competentie vereisten slecht gedefinieerd. De huidige richtlijnen gebruiken canulatie van de ductus choledochus als surrogaatmarker voor certificatie en adviseren ten minste 100 tot 200 procedures te verrichten alvorens competent te worden verklaard, daarbij adviseert de richtlijn dat de AIOS aan het eind van de opleiding in 80-90% van de verrichte ERCPs succesvolle canulatie van de CBD dient te bereiken[12].

Interessant is dat Verma en collega's in 2007 aantoonden dat een succespercentage van meer dan 80% zonder supervisie pas bereikt werd na 400 verrichte ERCPs[13]. Dit benadrukt nog meer dat AIOS in hun eigen tempo leren en dat AIOS een meer gepersonaliseerde benadering nodig hebben voor het aanleren van endoscopische vaardigheden op het gebied van ERCP. Op basis van onze onderzoeksresultaten zijn wij van mening dat training met behulp van simulatoren een belangrijke rol kan spelen om dit doel te bereiken. Om de rol en toegevoegde waarde van simulatietraining voor ERCP verder te onderzoeken, hebben we een prospectief onderzoek opgezet om het effect van een tweedaagse training op een ERCP simulator te evalueren. De studie wordt beschreven in **Hoofdstuk 5** van dit proefschrift. Zes AIOS volgden een tweedaagse cursus die bestond uit presentaties, live ERCP demonstraties en het onder begeleiding trainen op de Boškoski-Costamagna mechanische ERCP simulator. Gedurende de cursus werd informatie gegeven over basis ERCP technieken zoals canuleren, het plaatsen van stents, het verwijderen van galstenen en het behandelen van stricturen. Een controle groep (CG) werd gevormd door de AIOS uit de studiegroep (SG) te koppelen aan een AIOS uit het eigen centrum, de CG bestond uit zeven AIOS. Alle dertien AIOS vulden het Rotterdam Assessment Form for ERCP (RAF-E) in na elke verrichte ERCP in het eigen centrum, waarbij gekeken werd naar het succesvol canuleren van de CBD. De uitkomsten van onze studie tonen aan dat de SG een hoger canulatie succes percentage behaald dan de CG, 64% versus 43% na de eerste 10 ERCPs. Het verschil in het voordeel van de SG houdt aan tot ongeveer 75 ERCPs, helaas was het aantal deelnemers op dat punt van de studie erg laag wat het moeilijk maakt de resultaten goed te generaliseren. Ondanks het beperkt aantal data ondersteunen onze uitkomsten wel degelijk de meerwaarde van gebruik van simulatoren voor het aanleren van ERCP alvorens te starten met ERCP bij patiënten. Verder onderzoek zal moeten beoordelen hoe groot het voordeel is van het gebruik van een simulator, hoe lang de training zal moeten duren, de specifieke rol van de simulator voor het aanleren van ERCP en de rol van de simulator binnen het opleidingsprogramma.

Verplichte ERCP registratie in Nederland

Er is een groeiende interesse in de kwaliteit van de gezondheidszorg en de monitoring van de kwaliteit. In **Hoofdstuk 6** van dit proefschrift hebben we een prospectief registratieonderzoek uitgevoerd om inzicht te krijgen in het procedurele succes van de uitgevoerde ERCPs in Nederland nadat de Inspectie van de Gezondheidszorg in 2016 een registratieplicht voor ERCPs heeft ingesteld. In 2018 publiceerde de European Society of Gastrointestinal Endoscopy (ESGE) een lijst met belangrijke kwaliteitsnormen met als doel een minimumstandaard in te stellen voor de kwaliteit van ERCP[14]. Kwaliteit wordt gemeten aan de hand van verschillende verrichtingen, waaronder het canuleren van de CBD, het plaatsen van een stent in de CBD en het verwijderen van galstenen uit de CBD. Het canuleren van de CBD dient in 90-95% van de ERCPs succesvol te zijn, stentplaat-

sing in de CBD in 95% van de ERCPs en het verwijderen van galstenen uit de CBD in 90-95% van de procedures. De ondergrens geldt voor niet- academische ziekenhuizen en de bovengrens van 95% voor de academische ziekenhuizen. Aan de hand van deze gestelde kwaliteitsnormen hebben wij de ERCP uitkomsten in Nederland geëvalueerd. Wij hebben elf Nederlandse ziekenhuizen geïncludeerd, zowel academische als niet-academische ziekenhuizen, met in totaal 5671 ERCPs over een periode van twee jaar, dit betreft ongeveer 12.5% van het totale aantal ERCPs dat in deze periode in Nederland is uitgevoerd. Uit ons onderzoek bleek dat het algehele succespercentage van de procedure 89.1% was. Dit getal lag hoger dan de door ons vooraf opgestelde hypothese op basis van de studie van Ekkelenkamp en collega's in 2014[15]. Deze studie had een vergelijkbare opgezet, echter op vrijwillige basis voor het invoeren van de registratieplicht. Een succespercentage van 86% werd beschreven. Uiteraard moet een directe vergelijking met voorzichtigheid worden geïnterpreteerd, maar het toegenomen succespercentage kan het positieve effect van een van de verplichte registratie weerspiegelen. Een mogelijke verklaring voor het toegenomen procedurele succes is dat slecht presterende endoscopisten zich meer bewust zijn van hun prestaties en zijn gestopt met het uitvoeren van complexe ERCPs of in het geheel gestopt zijn met het uitvoeren van ERCP, een fenomeen dat tijdens de vrijwillige registratie al werd waargenomen. De laatste verklaring wordt tevens ondersteund door onze observatie dat in vergelijking met studie verricht door Ekkelenkamp en collega's in de meeste Nederlandse centra minder MDL-artsen ERCPs uitvoeren. Vervolgens hebben we ons meer gericht op de specifieke kwaliteitsnormen beschreven in de ESGE richtlijn, zijnde succesvolle canulatie van de CBD, succesvolle stentplaatsing in de CBD en succesvolle extractie van galstenen uit de CBD. De kwaliteitsnormen werden in onze database gehaald voor alle parameters, behalve voor succesvolle canulatie van de ductus choledochus bij patiënten met naïeve anatomie van de Papil van Vater in academische centra (92,4% van de beoogde 95%). Het is discutabel of deze gestelde norm voor alle instellingen realistisch is, omdat meer gefaalde ERCPs en tevens technisch moeilijker uit te voeren ERCPs worden doorverwezen naar (academische) gespecialiseerde centra, waarvoor soms geavanceerdere selectieve canulatietechnieken nodig zijn. Onze resultaten suggeren dat een landelijke registratie de mogelijkheid biedt om de kwaliteit van ERCP te evalueren en zo nodig te verbeteren en dat de uitvoering van ERCP in Nederland van hoge kwaliteit is.

Geavanceerde endoscopische technieken

Het laatste deel van dit proefschrift heeft betrekking op de uitvoering van geavanceerde endoscopische technieken binnen de pancreatobiliaire aandoeningen en de Papil van Vater. De afgelopen jaren zijn er veel nieuwe endoscopische technieken ontwikkeld en kunnen diverse gastro-intestinale aandoeningen endoscopisch worden behandeld. Hierdoor neemt de noodzaak tot chirurgisch ingrijpen af wat vaak gepaard gaat met

hogere morbiditeit en mortaliteit in vergelijking met minimaal invasieve endoscopische ingrepen. In **Hoofdstuk 7** hebben we een nieuw endoscopisch resectie instrument geëvalueerd om endoscopische necrosectomie te vergemakkelijken bij patiënten met acute geïnfecteerde necrotiserende pancreatitis, de EndoRotor. Necrotiserende pancreatitis is de meest gevreesde complicatie van acute pancreatitis en kent een sterftecijfer van 15% en in het geval van geïnfecteerde necrose loopt dit getal op tot ongeveer 30%[16-18]. Het is vrijwel altijd noodzakelijk een interventie te verrichten bij patiënten met geïnfecteerde necrotiserende pancreatitis en een belangrijk speerpunt voor de behandeling van pancreasnecrose is het vinden van een geschikt instrument om de necrose endoscopisch effectief te verwijderen. De huidige beschikbare instrumenten zijn ontworpen voor andere indicaties en zijn voor de verwijdering van necrotisch weefsel niet effectief gebleken. We gebruikten de EndoRotor bij twaalf patiënten, die in totaal 27 procedures ondergingen. In ons cohort werd volledige verwijdering van necrotisch weefsel bereikt met een mediaan van twee procedures. In eerdere studies met conventionele instrumenten werd een mediaan gezien van drie tot zes procedures[19-22]. Endoscopische necrosectomie gaat gepaard met een hoog risico op complicaties, waarbij met name een verhoogd risico op bloeding[22], echter zagen wij in ons cohort geen procedure gerelateerde complicaties. Deze bevinding komt overeen met een andere studie die de veiligheid van de EndoRotor tijdens necrosectomie bij 30 patiënten evalueert[23], waarvan de formele peer-reviewed publicatie binnenkort wordt verwacht.

In **Hoofdstuk 8** presenteren we de resultaten van de PELstone studie, waarbij we hebben gekeken naar de rol van pancreatoscopie-geleide elektrohydraulische lithotripsie (EHL) voor de behandeling van patiënten met chronisch calcificerende pancreatitis (CCP) en obstruerende stenen in de ductus pancreaticus (PD). Bij EHL vindt fragmentatie van de steen plaats onder direct zicht in de PD door middel van schokgolven (lithotripsie), de schokgolven worden gegenereerd door elektrische vonken (elektrohydraulisch). Diverse onderzoeken hebben de potentie aangetoond van pancreatoscopie-geleide EHL als behandelingsoptie bij patiënten met CCP, dit met name na eerder mislukte extracorporale schokgolflithotripsie (ESWL)[24-33]. Ondanks de veelbelovende resultaten van de eerder verrichte studies werd de rol van pancreatoscopie-geleide EHL nog niet beschreven als eerstelijnsbehandeling bij patiënten met CCP. Wij hebben dit prospectief onderzocht in een cohort van 36 patiënten. Wij toonden aan dat de procedure technisch succesvol was in 70.6% van de patiënten. Een belangrijke bevinding gedurende de studieperiode was dat het technisch succes voornamelijk werd beperkt door het onvermogen tot het bereiken van diepe canulatie van de PD. Echter in het geval dat het de endoscopist lukte om de PD te canuleren, steeg het technisch succespercentage van 70.6% naar 92.3% met volledige verwijdering van de obstruerende steen bij 80% van de patiënten. De procedure werd als klinisch succesvol gezien indien er een afname was van >50% van

pijnscores of een afname van opiaatgebruik na zes maanden follow-up, dit werd bij 72% van de patiënten bereikt. De resultaten van onze studie suggereren dat pancreatoscopie-geleide EHL veelbelovend is als eerstelijnsbehandeling van PD stenen, echter het succes is in hoge mate afhankelijk van het bereiken van succesvolle canulatie van de PD. Op basis van de ervaringen tijdens de studieperiode zouden wij de behandeling van deze patiënten opdelen in twee tempi, in eerste instantie ERCP om toegang tot de PD te verkrijgen en middels stentplaatsing de toegang te zekeren en als tweede stap behandeling van de obstruerende steen middels pancreatoscopie-geleide EHL. Uiteraard roept dit de vraag op wat het voordeel dan is van pancreatoscopie-geleide EHL in vergelijking met ESWL, aangezien in eerdere studies werd aangetoond dat bij 38% van de patiënten enkel ESWL nodig was voor het verwijderen van obstructieve stenen in de ductus pancreaticus zonder noodzaak tot aanvullende ERCP met canulatie van de PD en extractie van steenfragmenten. Het belangrijkste voordeel van pancreatoscopie-geleide EHL lijkt echter dat het de potentie heeft om veel breder beschikbaar te zijn en dat de prestaties niet gebonden zijn aan een (externe) ESWL-faciliteit, maar in handen zijn van de MDL-arts zelf. Toekomstige prospectieve studies in deze populatie zijn geïndiceerd om de rol van pancreatoscopie-geleide EHL verder te onderzoeken in vergelijking met ESWL en/of chirurgische behandeling.

In de laatste studie van dit proefschrift, beschreven in **Hoofdstuk 9**, onderzochten we het technisch succes en de complicaties van het endoscopisch verwijderen van adenomen van de Papil van Vater. Tumoren van de Papil van Vater worden steeds vaker gediagnosticeerd vanwege een betere nauwkeurigheid van endoscopische detectietechnologieën. Het slagingspercentage van endoscopische resectie blijkt afhankelijk te zijn van het groeipatroon van het adenoom. Het adenoom kan zich beperken tot de Papil van Vater (ACA), zich lateraal verspreiden (LSA) en/of intraductaal groeien (IEA). Wij analyseerden retrospectief 87 patiënten, 56 patiënten met een ACA, 20 patiënten met een LSA en elf patiënten met een IEA. Volledig succesvolle endoscopische resectie, zonder recidief, werd bereikt bij 77% van de patiënten in ons cohort, wel was er sprake van een significant verschil tussen de drie verschillende groepen. Endoscopische resectie van intraductaal groeiende adenomen was slechts succesvol bij 9,1% van de patiënten en 54,5% werd dan ook verwezen voor chirurgische resectie. Dit in tegenstelling tot een curatieve endoscopische resectie bij 87.5% van de patiënten met ACA en 85% van de patiënten met LSA. Procedure gerelateerde complicaties werden gezien bij 26.4% van de patiënten, voornamelijk post-procedurele bloeding (12.6%) en retroperitoneale perforatie (8.1%). In het cohort werd een recidief gezien bij tien patiënten (11.5%), bij twee patiënten was chirurgische resectie noodzakelijk vanwege recidief (één ACA en één IEA). Onze gegevens geven aan dat endoscopische resectie een veilige en succesvolle behandeling kan zijn, zelfs bij patiënten met een lateraal groeiend adenoom, maar dat

bij patiënten met een intraductaal groeiend adenoom chirurgie de veiligste optie blijft. Vergelijkbare resultaten worden beschreven in de literatuur[34-36]. De recent bijgewerkte richtlijn van de ESGE over de endoscopische behandeling van tumoren van de Papil van Vater stelt dat endoscopische behandeling van adenomen van de Papil van Vater wordt aanbevolen bij patiënten zonder intraductale groei[37].

TOEKOMSTPERSPECTIEVEN EN AANBEVELINGEN

Dit proefschrift richtte zich op verschillende aspecten van geavanceerde endoscopische procedures met als gemeenschappelijk doel het verbeteren van de behandeling van patiënten met een pancreatobiliaire aandoening of een adenoom van de Papil van Vater. Er zal continu aandacht moeten zijn om de kwaliteit van de gezondheidszorg op verschillende niveaus te blijven verbeteren. In de eerste plaats begint het verbeteren van de gezondheidszorg bij het optimaliseren van de trainingsmogelijkheden voor de medisch specialisten in opleiding die ERCP in de toekomst zullen gaan verrichten. Op basis van eerder onderzoek en de resultaten gepresenteerd in dit proefschrift, zijn wij ervan overtuigd dat ERCP-simulatoren moeten worden opgenomen in het opleidingsplan van de AIOS in opleiding tot Maag-, Darm- en Leverarts (MDL-arts). Het gebruik van simulatoren creëert behoudens een veilige omgeving ook de mogelijkheid om de procedure in relatief korte tijd herhaaldelijk te trainen waardoor de belasting van de patiënt en tevens de kans op complicaties wordt verminderd. De specifieke rol voor simulatoren bij het trainen van ERCP is nog niet bekend en zal nader onderzocht moeten worden, alsmede het moment waarop de AIOS klaar is voor de overstap van simulatie naar patiënt. Op basis van de huidige beschikbare data adviseren wij AIOS te monitoren op basis van hun persoonlijke leercurve, zowel ten tijde van simulatietraining als tijdens het uitvoeren van ERCPs bij patiënten. Zowel de AIOS als de supervisor krijgen direct feedback waarmee gekeken kan worden of het competentieniveau wordt behaald en of de AIOS klaar is voor de overstap naar de patiënt en daarmee naar een volgend niveau van procedurele complexiteit. Uiteraard zullen er ook inspanningen geleverd moeten worden om ERCP simulatoren te verbeteren zodat ze de realiteit zo goed als mogelijk nabootsen en daarmee de trainingsvoordelen worden geoptimaliseerd.

Het aanleren van endoscopische procedures en het bereiken van een bepaald competentieniveau aan AIOS is een uitdaging, maar het behouden van endoscopische vaardigheden bij de MDL-artsen is van een even groot belang en kan ook een uitdaging zijn. Wij zijn van mening dat MDL-artsen regelmatig feedback moeten krijgen over hun endoscopische resultaten uitgezet tegen richtlijnen en de prestaties van hun collega's. Door de totstandkoming van een landelijke kwaliteitsregistratie voor ERCP in 2016 was de eerste stap gezet, desalniettemin liepen we er in ons onderzoek tegenaan dat zelfs vijf jaar na de implementatie van de verplichte registratie nog veel data ontbreken.

Het systeem zal moeten worden geoptimaliseerd om niet alleen op landelijk niveau te kunnen monitoren, maar ook om de MDL-artsen de mogelijkheid te bieden hun eigen prestaties te evalueren op basis van directe feedback.

Dit proefschrift geeft nieuwe inzichten in het gebruik van drie geavanceerde endoscopische behandelmodaliteiten. De endoscopische opties voor de behandeling van patiënten met gecompliceerde pancreatobiliaire aandoeningen of een aandoening van het duodenum zijn de laatste jaren enorm uitgebreid, waardoor gecompliceerde chirurgische ingrepen vaker overbodig zijn. De resultaten zijn veelbelovend. De onderzoeksresultaten in dit proefschrift zijn gebaseerd op een beperkt aantal patiënten en meestal uitgevoerd in één behandelcentrum. Aanvullende studies zijn nodig om lange termijn uitkomsten en complicaties nog beter in kaart te brengen, bij voorkeur in vergelijking met chirurgische en/of radiologische behandelingsopties. De toekomstige studies dienen bij voorkeur uitgevoerd te worden in een gerandomiseerde, gecontroleerde setting met inclusie van meerdere centra. Men moet zich realiseren dat deze procedures technisch veeleisend zijn en het verdient de voorkeur om deze procedures uit te voeren in deskundige centra met voldoende exposure en ervaring.

Het onderzoeksveld binnen de pancreotobiliaire aandoeningen blijft groeien. Dit proefschrift heeft verschillende aspecten voor het verbeteren van de zorg rondom patiënten met een aandoening van het duodenum of het pancreatobiliaire systeem belicht. Onze resultaten bieden aanknopingspunten voor verder onderzoek om zowel trainings- als behandelstrategieën voor endoscopische procedures te optimaliseren met een specifieke interesse voor het onderzoeksveld binnen de ERCP.

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APPENDICES

LIST OF ABBREVIATIONS

ACA	Adenoma confined to the ampulla
AIOS	Assistent in opleiding tot medisch specialist
ANP	Acute necrotizing pancreatitis
APC	Argon plasma coagulation
ASA	American Society of Anaesthesiologists
ASGE	American Society of Gastrointestinal Endoscopy
CBD	Common bile duct
CCP	Chronic calcifying pancreatitis
CP	Chronic pancreatitis
CSV	Comma-seperated value files
CT	Computed Tomography
DEN	Direct endoscopic necrosectomy
EA	Endoscopic ampullectomy
EASIE	Erlangen Active Simulator for Interventional Endoscopy
EHL	Electrohydraulic lithotripsy
EMR	Endoscopic mucosal resection
EMS	ERCP mechanical simulator
ERCP	Endoscopic retrograde cholangiopancreatography
ERP	Endoscopic retrograde pancreatography
ESD	Endoscopic submucosal dissection
ESGE	European Society of Gastrointestinal Endoscopy
ESWL	Extracorporeal shock wave lithotripsy
EUS	Endoscopic ultrasound
GI	Gastrointestinal
IEA	Intraductal extending adenoma
ITT	Intention to treat
IQR	Interquartile range
FAP	Familial adenomatous polyposis
HGD	High-grade dysplasia
HC	Historical cohort
LGD	Low-grade dysplasia
LL	Laser lithotripsy
LSA	Lateral spreading adenoma
MCS	Mental component summary
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangiopancreatography
NSAID	Nonsteroidal inflammatory drug
OGD	Oesophagogastroduodenoscopy
PCS	Physical component summary

PD	Pancreatic duct
PEP	Post ERCP pancreatitis
PP	Per protocol
QoL	Quality of life
RAF-E	Rotterdam assessment form for ERCP
SD	Standard deviation
SF-12	Short form health survey
UEG	United European Gastroenterology
VAS	Visual analogue score
VR	Virtual reality

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Name PhD Student: Sophia E. van der Wiel
Department: Gastroenterology and Hepatology
Promotor: Prof. dr. M.J. Bruno
Co-promotor: Dr. A. D. Koch

Courses and workshops

	Year	Workload
Endnote workshop, Erasmus MC library, Rotterdam	2015	6 hours
Systematic Literature Retrieval in Pubmed workshop, Erasmus MC, Rotterdam	2015	6 hours
Systematic Literature Retrieval in other databases workshop, Erasmus MC, Rotterdam	2015	6 hours
Basic Introduction on SPSS, Molecular medicine postgraduate school, Rotterdam	2015	24 hours
BROK cursus, Consultatiecentrum Patiëntgebonden Onderzoek, Erasmus MC, Rotterdam	2015	24 hours
English Biomedical Writing and Communication, Erasmus MC, Rotterdam	2016	84 hours
Workshop ''Coachen van toekomstige Erasmusartsen basis'', Erasmus MC, Rotterdam	2016	6 hours
Workshop ''Coachen van toekomstige Erasmusartsen vervolg'', Erasmus MC, Rotterdam	2017	4 hours
Basic Introduction in OpenClinica, Erasmus MC Rotterdam	2017	6 hours
Introduction in GraphPad Prism, Molecular medicine postgraduate school, Rotterdam	2017	10 hours
Integrity in scientific research, Dept. of Medical ethics and Philosophy, Erasmus MC, Rotterdam	2017	16 hours

Oral presentations

	Year	Workload
Expert and construct validity of a novel mechanical ERCP simulator, Digestive disease days, Nederlandse Vereniging voor Gastroenterologie (NVGE), Veldhoven	2017	12 hours
Expert validation of a novel mechanical cutting papilla, Digestive disease days, Nederlandse Vereniging voor Gastroenterologie (NVGE), Veldhoven	2017	12 hours
Poster pitch: Expert validation of a novel mechanical cutting papilla, 25th meeting of the United European Gastroenterology (UEG) week, Barcelona, Spain	2017	12 hours
Endoscopic resection of advanced ampullary adenomas: a single-center 14 year retrospective cohort study, Digestive disease days, Nederlandse Vereniging voor Gastroenterologie (NVGE), Veldhoven	2017	12 hours
A novel tool for fast and effective endoscopic removal of pancreatic necrosis, Digestive disease Days, Nederlandse Vereniging voor Gastroenterologie (NVGE), Veldhoven	2018	12 hours

Poster presentations		
	Year	Workload
Expert and construct validity of a novel mechanical ERCP simulator, Digestive Disease Week, Chicago, Illinois, USA	2017	12 hours
Expert validation of a novel mechanical cutting papilla, 25th meeting of the United European Gastroenterology (UEG) week, Barcelona, Spain	2017	12 hours
Endoscopic resection of advanced ampullary adenomas: a single-center 14 year retrospective cohort study, 25th meeting of the United European Gastroenterology (UEG) week, Barcelona, Spain	2017	12 hours
Endoscopic resection of advanced ampullary adenomas: a single-center 14 year retrospective cohort study, Digestive Disease Week, Washington, USA	2018	12 hours
Expert validation of a novel mechanical cutting papilla, Digestive Disease Week, Washington, USA	2018	12 hours
A novel tool for fast and effective endoscopic removal of pancreatic necrosis, Digestive Disease Week, Washington, USA	2018	12 hours
Pancreatoscopy-guided electrohydraulic lithotripsy for the treatment of obstructive distal main pancreatic duct stones: a prospective consecutive case series (PELstone study), 25th meeting of the United European Gastroenterology (UEG) week	2020	12 hours

Attended (inter)national conferences		
	Year	Workload
Twice Annual Meeting of the Dutch Association of Gastroenterology (NVGE), Veldhoven, The Netherlands	2015	12 hours
Twice Annual Meeting of the Dutch Association of Gastroenterology (NVGE), Veldhoven, The Netherlands	2016	12 hours
Digestive Disease Week, San Diego, Ca, USA	2016	28 hours
United European Gastroenterology Week, Vienna, Austria	2016	28 hours
Twice Annual Meeting of the Dutch Association of Gastroenterology (NVGE), Veldhoven, The Netherlands	2017	12 hours
Digestive Disease Week, Chicago, Illinois, USA	2017	28 hours
Twice Annual Meeting of the Dutch Association of Gastroenterology (NVGE), Veldhoven, The Netherlands	2017	12 hours
United European Gastroenterology Week, Barcelona, Spain	2017	28 hours
Twice Annual Meeting of the Dutch Association of Gastroenterology (NVGE), Veldhoven, the Netherlands, The Netherlands	2018	12 hours
Digestive Disease Week, Washington, USA	2018	28 hours
Pancreasdag, Gouda, The Netherlands	2018	6 hours
Twice Annual Meeting of the Dutch Association of Gastroenterology (NVGE), Veldhoven, the Netherlands, The Netherlands	2019	12 hours

Seminars and Workshops		
	Year	Workload
Lagerhuisdebat hepatitis B/C, Utrecht	2015	3 hours
Casuïstische bespreking NVGE, 2 keer	2017-2018	6 hours
Journal clubs, department of gastroenterology/hepatology, Erasmus MC, Rotterdam	2015-2018	60 hours

Educational activities		
	Year	Workload
Tutoring first year students curriculum Medicine, Erasmus University Rotterdam, Rotterdam, the Netherlands	2015-2018	120 hours

Awards

Poster of Excellence - Expert validation of a novel mechanical cutting papilla, 25th meeting of the United European Gastroenterology (UEG) week, Barcelona, Spain, 2017

Travel Grant - Expert validation of a novel mechanical cutting papilla, 25th meeting of the United European Gastroenterology (UEG) week, Barcelona, Spain, 2017

Memberships

Netherlands Association of Gastroenterology (NVGE)

Koninklijke Nederlandsche Maatschappij tot bevordering der geneeskunst (KNMG)

DANKWOORD

Het dankwoord is misschien wel één van de belangrijkste hoofdstukken van dit proefschrift, want promoveren doe je niet alleen. Dit proefschrift is tot stand gekomen door fijne en intensieve samenwerkingen, goede begeleiding en de steun van collega's, vrienden en familie. Ik wil iedereen die heeft bijgedragen aan dit proefschrift bedanken en onderstaande personen wil ik graag in het bijzonder bedanken.

Beste Prof.dr. Bruno, beste *Marco*, allereerst dank voor het vertrouwen, de steun en waardevolle input tijdens mijn promotie traject. Ik heb van je geleerd wetenschappelijk te schrijven en te denken, voor kwaliteit te gaan en nooit op te geven als een manuscript niet werd geaccepteerd voor publicatie. Ik bewonder je efficiëntie en geduld met ons beginnende wetenschappers en niet minder belangrijk bewonder ik je endoscopische kunsten, wie weet dat ik daar in de toekomst ook nog wat van mag leren!

Beste Dr. Koch, beste *Arjun*, bedankt voor je enthousiasme, kennis en hulp gedurende mijn promotietraject. Ik bewonder je nuchtere blik en geduld. Je hebt me het vertrouwen gegeven en me vrij gelaten tijdens mijn gehele promotieperiode. Je hebt me wetenschappelijk veel geleerd en het is jammer dat ik de endoscopische kunsten niet bij jou af kan kijken tijdens mijn opleiding. Dank voor de fijne begeleiding.

Beste Dr. P.J.F. de Jonge, beste *Pieter-Jan*, geen officiële rol binnen mijn promotie team maar wel een prettige samenwerking in het opzetten van de PELstone studie. Dank voor de hulp in een voor jou hectische periode, waarin ik altijd kon rekenen op snelle en constructieve antwoorden om weer vooruit te kunnen.

De leden van de leescommissie wil ik graag bedanken. *Prof.dr. Spaander*, *prof.dr. van Hooft* en *prof.dr. Vleggaar,* dank voor jullie interesse en tijd in de beoordeling van dit proefschrift. Beste prof.dr. H.J. Metselaar, Prof. dr. P. Fockens en prof.dr. M.G.H. Besselink. Veel dank voor het plaatsnemen in de promotiecommissie. Dear dr. I. Boškoski thank you that you are willing to be a part of my thesis defense committee, all the way from Italy.

Al mijn co-auteurs wil ik bedanken voor de prettige samenwerkingen die tot mooie artikelen hebben geleid. *Pauline*, wat fijn dat jij mijn opvolger was bij de PELstone studie, het is altijd spannend eigen werk over te dragen, maar ik kon alles met een gerust hart achterlaten. Dank voor het harde werken, maar bovenal was het vooral heel leuk om samen te werken! Het wordt nu wel echt tijd om de publicatie officieel te vieren! *Felix*,

wat bracht ons stuk een hoop onrust en wat kan ik anders zeggen dan dat je een enorme volhouder bent. Het resultaat mag er zeker zijn!

Al het onderzoek komt ook met een hoop regelwerk, dit proefschrift had er niet geweest zonder de hulp van Carla. Lieve *Carla*, ik heb heilig ontzag voor je eeuwige geduld en strakke planning, ik keek altijd uit naar een praatje tussen al mijn verzoeken door. Dank! Daarnaast wil ik alle betrokken endoscopisten en verpleegkundigen bedanken voor hun hulp en betrokkenheid bij de verschillende studies.

Beste Dr. van Kouwen, opleider MDL-Ziekten in het Radboud Medisch Centrum, beste *Mariëtte*, dank voor het in mij gestelde vertrouwen om mijn MDL-opleiding te kunnen doorlopen en vooral voor de warme ontvangst in een voor mij nieuwe omgeving. Beste Dr. Scheffer en Dr. Römkens, beste *Bob* en *Tessa*, dank voor de ruimte die jullie mij gaven om mijn vertrouwen en vooral plezier in dit mooie vak weer terug te krijgen tijdens mijn ANIOS tijd en uiteindelijk de steun voor de weg naar een opleidingsplek. Ik kijk er ontzettend naar uit om mijn opleiding bij jullie te vervolgen.

Beste *collega's uit het Amphia*, dank voor alle fantastische borrels, weekendjes en skireis, zonder jullie waren mijn eerste stappen als arts niet hetzelfde geweest. Lieve *Esther, Dianne, Eva, Carlijn* en *Inge* ik vind het enorm waardevol en fijn dat wij elkaar nog steeds zien. Dank aan de stafleden van de Interne Geneeskunde in het Jeroen Bosch Ziekenhuis voor de fijne samenwerking en het fijne leerklimaat gedurende mijn vooropleiding. Daarnaast wil ik alle *MDL-artsen* bedanken in het JBZ, het is elke dag weer een feest om met jullie samen te werken en door jullie opgeleid te worden! Lieve *collega's van de MDL*, dank voor de bijzonder fijne sfeer, collegialiteit en flexibiliteit. *Judith* en *Milou*, samen het MDL pad bewandelen is mij heel dierbaar, maar vooral ook de momenten buiten de muren van het JBZ.

Wat zou promoveren zijn zonder collega's? Mijn tijd in het Erasmus had absoluut niet zo fantastisch geweest zonder mijn collega's. Lieve *labratten* en *dakduiven* dank voor alle borrels, congressen, festivals en legendarische ski-reizen. Ik wist niet waar ik terecht was gekomen de eerste dag dat ik *'het Dak'* betrad, maar het bleek symbool te staan voor hard werken, liters koffie en fijne collega's. Het is nooit meer hetzelfde geweest sinds de dag dat we het dak er letterlijk af zagen gaan. Lieve *dakduifjes*, wat fijn dat wij elkaar ook nog na onze tijd op het Dak zien, weliswaar veel te weinig, maar ik kijk uit naar komende borrels en dinertjes. Lieve *Arjan*, samen begonnen we aan het PhD avontuur en hebben we alles meegemaakt, de mooiste reizen in Amerika, letterlijk strooien met geld op de pistes in Oostenrijk en dansen op festivals, maar ook veel goede gesprekken over ons PhD-traject en sparren over posters en presentaties. Gelukkig gaan

we elkaar de komende jaren nog genoeg tegenkomen! Lieve *Kasper*, het Dak is nooit meer hetzelfde geweest na Ranking het Dak, ik mis onze avonturen en de NVGE catwalk! Purse first! Lieve *Fanny*, jouw discipline is ongekend en jaloersmakend, wat mis ik jouw lach en de koffiemomentjes op het dak. Lieve *Stella*, jouw vrolijkheid is aanstekelijk en wat heb ik genoten van onze trip naar Marokko. Lieve *Carlijn*, onze eerste stappen samen in het Amphia en wat leuk was het dat je daarna ook naar het Erasmus kwam. Bijzonder dat we inmiddels van woonplaats hebben geruild, ik stel voor dat we elkaar de nieuwe plaatselijke highlights snel showen! Lieve *Loes*, jaloers op jouw werkethos, maar ook enorm genoten van jouw Adriaan imitatie! Lieve *Jorn*, *Eveline* en *Renske*, de laatste roddels onder het genot van een cappuccino, even doorspreken hoe de zaken ervoor staan op Tempa, ik mis het! Lieve *Steffi*, wat fijn dat jij bij ons kwam promoveren, ik baal enorm dat we maar kort hebben samen kunnen werken. Lieve *Rozanne*, wat een geluk dat Maren jou als opvolger koos en ik er nu een maatje bij heb, ik kan niet wachten op nog meer avonturen. Lieve *Anne*, het partyteam is pas compleet met zijn vieren, wat een feest dat jij ook op het Dak kwam, het is weer tijd voor zeiltochten en feestjes.

Team achterhoede, liefste *Maren*, *Joany* en *Louisa* start spreading the news, de tickets kunnen worden geboekt, New York, New York!! Mijn promotie had er nooit gekomen zonder jullie, was nooit zo leuk geweest zonder jullie en zou ik zelfs overdoen zolang het maar met jullie is! Lieve *Louisa,* wat ben ik jaloers op jouw organisatietalent en planning en wat een feest dat we ook samen enorm buiten de lijntjes kunnen kleuren! Lieve *Joany*, ik moet al lachen voordat ik iets op papier heb. Wat hebben wij mooie tijden meegemaakt en wat hoop ik dat we het onszelf gunnen die tijden dubbel en dwars over te doen!

Mijn paranimfen. Lieve *Maren*, zoals jij al eerder zei, vanaf het moment dat wij elkaar zagen wisten we dat het goed zat. Iedereen dacht als die twee op een kamer gaan zitten komt het nooit goed met die promotie, maar juist die stap was er één in de goede richting, want wij zorgen dat elke poster strak staat, elke presentatie vlekkeloos verloopt en over alles goed wordt nagedacht onder het genot van de laatste roddels en een bak koffie. Maar het meest belangrijk is dat collega's ook echte maatjes kunnen worden en daar ben ik enorm dankbaar voor! Lieve *Julia*, soms weet je gewoon dat het goed is, toen ik jou ontmoette was het meteen goed. Samen dansen, koken en vooral chillen, wat hebben we veel mooie dingen meegemaakt in de afgelopen jaren en wat was ons paleis echt een thuis. Dank dat jullie vandaag, maar eigenlijk altijd, naast me willen staan!

Werk neemt een bijzondere plek in in mijn leven, maar het stelt allemaal niet zo veel voor zonder fijne vrienden en familie. Zonder iemand tekort te willen doen, wil ik een aantal mensen in het bijzonder noemen. Lieve *Claire*, *Laura* en *Franca*, jullie kennen me

als geen ander en weten vaak precies wat ik nodig heb. Ik kan met jullie lachen en ook huilen. Onze vriendschap is me enorm dierbaar en ik kan niet wachten op de avonturen die nog mogen komen! Lieve *Robin*, vaak wil ik schreeuwen geloof in jezelf, ik ben trots, maar bovenal geniet ik van je lach en gezelligheid! Lieve *Yteke* met niemand anders kan ik beter op boevenpad gaan dan met jou, maar ook mijn hart luchten, het is tijd voor nieuwe avonturen! Lieve *Esther* en *Eva*, samen onze eerste stappen in de wereld van de geneeskunde, ik vind het bijzonder dat jullie er vandaag ook bij zijn en ben enorm dankbaar voor onze vriendschap. Lieve *Fleur*, wij zijn het voorbeeld dat kwaliteit boven kwantiteit gaat, wij hoeven elkaar niet wekelijks te zien of te spreken om te weten dat de vriendschap goed is, maar ik stel voor dat we het borrelen en de tripjes weer beter op gaan pakken! Lieve *Dames van MINX,* wat mis ik de onbezorgde studententijd soms, wat hoop ik jullie weer wat vaker te kunnen zien! Lieve *Zomibo*, dank voor al die geweldige momenten van ontspanning!

Lieve *familie*, dank voor jullie onuitputtelijke interesse in mijn onderzoek en vooral jullie steun de afgelopen jaren. Lieve *oma*, wat bijzonder dat jij er vandaag bij kan zijn. De telefoontjes in Corona tijd waren een goede ontspanning voor mij, bijzonder hoe je altijd precies weet wat we allemaal nog doen en dat je altijd aan ons denkt. Lieve tante *Marion*, jij bent er letterlijk vanaf mijn eerste stapjes bij en hebt me geholpen verschillende (carrière) stappen te maken. Dankjewel voor alle zorg als ik weer even moest luchten, de reisjes, casino bezoeken en borrels! Lieve *schoonfamilie*, dank voor het warme welkom in de familie en jullie interesse en betrokkenheid bij mijn promotie.

Lieve *Max*, *Julia* en *Emily,* wat ben ik gelukkig met jullie als broer en zussen, dank dat jullie er altijd voor mij zijn. Niet alleen in de interesse die jullie tonen, maar bovenal voor de gezelligheid en ontspanning. Ik hoop met heel mijn hart dat ik dat ook voor jullie mag zijn. Ik ben ongelooflijk trots! Lieve *Beryl, Beer en Tim,* dank voor jullie liefde en thuis voor mijn broertje en zusjes.

Lieve *pap en mam*, die paar woorden op de laatste pagina's van mijn proefschrift kunnen met geen mogelijkheid beschrijven hoe ongelooflijk dankbaar ik jullie ben. De onvoorwaardelijke liefde, het grensoverschrijdende geloof in mijn kunnen en de ruimte die jullie ons allen geven om de doelen na te streven die we voor ogen hebben. *Mam*, jouw vermogen om alle ballen in de lucht te houden is bewonderenswaardig en de rust die je daarmee uitstraalt jaloersmakend, maar jouw zorgzaamheid is het mooist. Bij jullie ben ik altijd echt thuis. *Pap*, de gelijkenis die ik zie tussen jou en mij is soms angstaanjagend, maar een beter voorbeeld kan ik me niet wensen. Jouw kennis is onuitputtelijk en jouw interesses stimulerend. Ik hou enorm van jullie!

Lieve *Björn*, de laatste woorden zijn voor jou. Wie had ooit kunnen bedenken dat mijn eerste carnaval als inwoner van Den Bosch me zoveel moois kon brengen. Jouw no-nonsense en rust zijn van enorme meerwaarde geweest in het laatste jaar van mijn promotie en daarbij is het heel bijzonder om onze passie voor de geneeskunde te kunnen delen. Dankjewel dat jij mij elke dag het vertrouwen geeft dat ik het kan. Ik kan niet wachten op alles wat we samen nog gaan beleven!

ABOUT THE AUTHOR

Sophia Elisabeth van der Wiel was born on May 9th, 1988 in Amsterdam, The Netherlands. She grew up in Amsterdam and Rotterdam as the oldest of four children. After graduating secondary school in 2007, Sophia started her medical education at Maastricht University in Maastricht, the Netherlands. After obtaining her bachelor's degree in 2010, Sophia performed clinical rotations in several hospitals in the Netherlands and abroad in Pretoria, South Africa. In 2013 she obtained her Medical degree. After graduation she started working as a resident not in training at the department of Internal Medicine at Amphia Hospital in Breda, during this residency she developed a specific interest in Gastroenterology and Hepatology. As of August 2015 she started her PhD program at the department of Gastroenterology and Hepatology as described in this dissertation under supervision of Prof.dr. M.J. Bruno and dr. A.D. Koch. In 2019, she started as a resident not in training at the department of Gastroenterology and Hepatology at Jeroen Bosch Hospital in 's-Hertogenbosch. From Januay 2020 onwards she started with her training in Gastroenterology and Hepatology at Jeroen Bosch Hospital in 's-Hertogenbosch (program director R.C.H. Scheffer). She will continu her residency at Radboud University Medical Center in Nijmegen (program director Dr. M.C.A. van Kouwen). Together with Björn, Sophia lives in 's-Hertogenbosch.