Endoscopic retrograde cholangiopancreatography (ERCP) in Norway

Patterns of activity and undesired events

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Scientific environment

Over 15 years ago, when I specialized in gastrointestinal surgery at the Central Hospital of Akershus, a Scandinavian network was established that dealt with different treatment aspects of gallstone disease. The focus was the implementation of new diagnostic and therapeutic techniques, but they also assessed the quality of these treatments. All Norwegian hospitals were involved; in addition, the Norwegian Gastroenterological Association (*Norsk Gastroenterologisk Forening* [NGF]), the Scandinavian Association of Digestive Endoscopy (SADE), and the Norwegian Surgical Association (*Norsk Kirurgisk Forening* [NKF]) were natural partners in this process.

A preliminary, internet-based endoscopic retrograde cholangio-pancreatography (ERCP) registry was established, and data was collected between 2003 and 2006. However, this PhD project, which included data from several hospitals, primarily started with the initiation of a particular ERCP registry within the Gastronet* at the end of 2006. In 2009, working as a surgeon at the Department of Gastroenterological Surgery at Stavanger University Hospital, I have been fortunate to be able to increase my efforts related to this project. As a PhD student, I have also been part of the Surgical Research Group at Stavanger University Hospital, a fruitful, stimulating environment. This research group has a good mix of a few experienced academic surgeons and a number of fellow surgeons that would like to expand their surgical competence to include research and scientific skills.

The ERCP registry is currently improving with regard to its importance and relevance; in October 2012, the registry obtained status from the government as a national registry [$].

NSFs FAGGRUPPE AV SYKEPLEIERE
I GASTROENTEROLOGI

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* Gastronet is the Quality Assurance platform in endoscopy for the Norwegian gastroenterological association

[$] According to letter from The Ministry of Health and Care Services, October 2012, reference 200602512/TOG

"Cure sometimes,

Treat often,

Comfort always"

Hippocrates (460–377 BC)

"There is a way to do better – find it!"

Thomas Alva Edison (1847–1931 AC)

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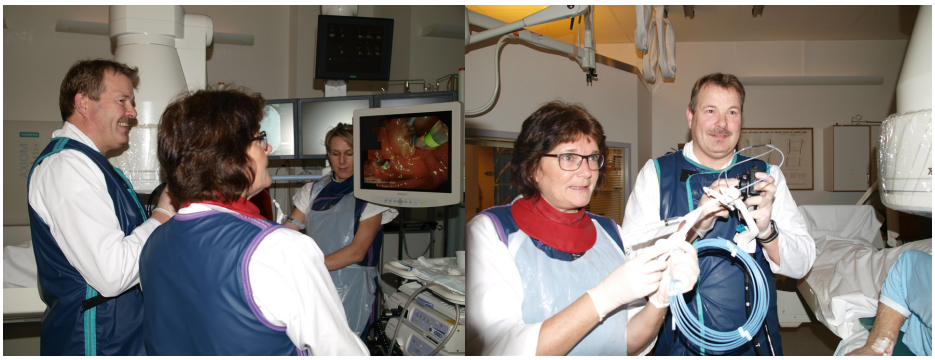

Figure 1. *ERCP at Stavanger University Hospital. Photo. Private*

1. Acknowledgements

After years of particular interest and clinical devotion to the field of gastrointestinal surgery and endoscopy, my supervisor, Professor Jon Arne Søreide MD, PhD, challenged me to embark on this project. Along the road, his support, his continuous inspiration, and his motivation have been of great importance for the completion of this work. He has guided me into an academic world, which has opened my eyes, and he encouraged me to take a step forward, and I think, upwards. During moments of darkness and disappointment, he was always there to bring back the enthusiasm. I am forever grateful for his advice, corrections, and constructive feedback throughout the research process. Without his support and patience, this project would not have been completed.

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This work would not have been possible without the cooperation of colleagues and health professionals at all the Norwegian ERCP units, and at the 14 centers, which reported to the ERCP registry, particularly between 2007 and 2009. I also want to express my sincere gratitude to all co-workers at the Gastroenterological Endoscopy Unit at Stavanger University Hospital for their continuous and important support, and for their fruitful co-operation over many years.

I would like to express my sincere appreciation to the Stavanger University Hospital, The Regional Health Trust of Southeastern Norway, the Regional Health Trust of Western Norway, the Norwegian Gastroenterological association, and the Folke Hermansens Cancer research fund, which made this project financially possible. The present executives at Stavanger University Hospital have also been very supportive in giving me the opportunity to complete this work, particularly the Head of the Department of Gastroenterological surgery, Bjørn Nedrebø, MD, and our Director of the Division of Surgery, Inger Cathrine Bryne.

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It is not possible to thank all the individuals that contributed to this work, which was motivated by a common interest among my Norwegian colleagues to focus on outcome and improve quality. Nevertheless, many thanks to all of you, and hopefully, the work will continue in the capacity of a governmentally approved national registry over the coming years.

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Finally, my sincere thanks and appreciation go to my loved ones, my wife June and our daughter Ida Tomine. Without their great patience and understanding through all the ups and downs, this work would not have been finished.

Stavanger, December 2012

Tom B. Glomsaker

2. List of publications

Paper I

Glomsaker T, Søreide K, Aabakken L, Søreide JA.
A national audit of temporal trends in endoscopic retrograde cholangiopancreatography in Norway.
Scand J Gastroenterol 2011; 46:116-21.

Paper II

Glomsaker T, Søreide K, Hoff G, Aabakken L, Søreide JA.
Contemporary use of endoscopic retrograde cholangiopancreatography (ERCP): A Norwegian prospective, Multicenter study.
Scand J Gastroenterol 2011; 46:1144-51.

Paper III

Glomsaker T, Hoff G, Kvaløy JK, Søreide K, Aabakken L, Søreide JA.

Patterns and predictive factors of complications after endoscopic retrograde cholangiopancreatography (ERCP).

Br J Surg, DOI: 10.1002/bjs.8992, Epub Date, 2012/12/12

Paper IV

Glomsaker T, Hoff G, Kvaløy JK, Søreide K, Aabakken L, Søreide JA

Patient-Reported Outcome Measures After Endoscopic Retrograde Cholangiopancreatography: A Prospective, Multicenter Study.

Submitted, 2012

3. Abstract

Background: Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for the treatment of common bile duct stones (CBDS) and palliative decompression of malignant strictures. However, concerns remain regarding procedure-related complications and patient discomfort and pain. National data on ERCP are lacking, and international data on risk factors for complications and patient experiences are sparse and ambiguous.

Objectives: In this project, we wanted to (1) collect national figures on ERCP activity and local routines in Norway over a period of 11 years, between 1998 and 2008; (2) describe and evaluate routine clinical ERCP practices in Norway over three years (2007 –2009); (3) evaluate the incidence of complications and (30-day) mortality, and identify possible risk factors for undesired outcomes after ERCP; and (4) evaluate patient pain and satisfaction after ERCP, and investigate potential predictors of pain and dissatisfaction.

Methods: Based on surveys conducted in all Norwegian hospitals, data were collected on ERCP activity at four time points. As a part of a voluntary, national, Quality Assurance (QA) program in Gastronet, ERCP procedures were registered prospectively at 14 different hospitals in Norway, and these data were collected for the present study. Based on consecutive, registration and reporting, including a 30-day follow up from 11 hospitals, a descriptive evaluation of the ERCP activity per se, and specifically of complications was performed. Statistical analyses were performed

to identify independent risk factors for complications, procedure-related pain, and patient dissatisfaction.

Results: In the first paper, a total of 42,260 procedures were reported over 11 years (average 3842 procedures per year, range 3492-4632). During that time, the number of hospitals that offered ERCP decreased from 41 to 35, and the annual number of procedures decreased by 13% (from 4632 to 4036). However, the number of ERCP-trained endoscopists in Norway remained stable (≈100). The proportion of surgical procedures decreased from 40% to 32% (p<0.001) during the first 6 years. Regional variations in ERCP volumes decreased during the study period. In paper 2, 3781 procedures performed at 14 hospitals were registered. Reliable data from 3683 procedures (53% females and 47% males) were available for evaluation. In 2488 (67%) of the ERCP procedures, the patients were at least 60 years of age. High comorbidity (ASA score 3-4) was reported in 33% of patients. The main indication for ERCP was a need for evaluation and therapy of common bile duct (CBD)-related symptoms and signs. A pre-cut sphincterotomy (EST) was performed in 5% of procedures, and a guide-wire was employed to facilitate duct access in 61% of procedures. The median total procedure time was 28 min (IQR 19-40). CBD stones (CBDS) or strictures of the CBD were diagnosed in over 75% of procedures. Specific diseases related to the pancreatic ducts were reported in only 6% of procedures. Biliary EST was performed in 46% of procedures. In addition to EST, CBDS treatment and CBD stent insertions or manipulations were the most common procedures.

In papers 3 and 4, 2808 ERCP procedures were reported; of these, 2573 (91.6%) were therapeutic. CBD cannulation was achieved in 2557 (91.1%) procedures. Complications occurred in 327 (11.6%) procedures, including cholangitis (n=100; 3.6%), pancreatitis (n=88; 3.1%), bleeding (n=66; 2.4%), perforation (n=25; 0.9%), and cardiovascular-respiratory events (n=32; 1.1%). Older age, high ASA score, annual ERCP volumes >150 procedures/center, and pre-cut ESTs were independent predictive factors for severe complications. Overall, the 30-day mortality was 2.2% (63 patients), with a possible procedure-related mortality rate of 1.4% (39 patients). The patient questionnaire was returned for 52.6% of procedures. Moderate or severe pain, respectively, was experienced in 15.5% and 14.0% of procedures *during* the ERCP and in 10.8% and 7.7% of procedures *after* the ERCP. In addition, female gender, EST, and longer procedure times were independent predictors of increased pain *during* the ERCP. The performing hospital was an independent predictor ($p<0.001$) of procedural pain experience. In 90.9% of procedures, the patients were satisfied with the information provided; overall, 98.3% of patients were satisfied with the treatment. However, the occurrences of specific complications after ERCP, and pain during or after the procedure were independent predictors for dissatisfaction with the treatment.

Conclusions: Regional variation in the number of ERCPs performed appeared to have diminished. Patient selection, indications, and procedures employed in Norway were consistent with international guidelines and recommendations. Disease patterns partly differed from patterns reported both in middle Europe and in the US. ERCP-

related morbidity and mortality and differences between units in reported outcome remain a concern. A mandatory, electronic, national registry with more resources is needed to continue a QA program for ERCP.

4. Abbreviations

ERCP = Endoscopic Retrograde Cholangiopancreatography

MRCP = Magnetic Resonance Cholangiopancreatography

EUS = Endoscopic Ultrasound

CT= Computed Tomography

SEMS = Self-Expanding Metal Stents

PEP = Post-ERCP Pancreatitis

EST = Endoscopic Sphincterotomy

ESWL = Extra-corporal Shock-Wave Lithotripsy

CBDS = Common Bile Duct Stones

PROMs = Patient-Reported Outcome Measures

QA = Quality Assurance

VRS = Verbal Rating Scale

ASA = American Society of Anesthesiologists

OR = Odds Ratio

CI = Confidence Interval

RCT = Randomized Controlled Trial

MDT = Multi-Disciplinary Team

PTC = Percutaneous Transhepatic Cholangiography

RR = Risk Ratio

BSD = Balloon Sphincter Dilatation

PD = Pancreatic Duct

5. Definitions

5.1 ERCP

An ERCP procedure was defined as an endoscopic procedure *with an intention to* cannulate the bile duct and/or pancreatic duct and visualize the ducts with a contrast medium. Thus, an intended ERCP that failed to cannulate was reported as an ERCP procedure.

5.2 Pre-cut sphincterotomy

Any pre-cannulation diathermy cut to the sphincter to gain ductal access, regardless of the method employed, was considered a pre-cut sphincterotomy (PCS).

5.3 Complications in ERCP

A complication was defined as a condition or an event that was unfavorable to patient health, caused irreversible damage, or required a change in therapeutic policy. Complications occurred in relation to the procedure and during the first 30 days after ERCP[1].

5.4 Elective and emergency procedures

Procedures performed during normal working hours, from Monday through Friday between 08:00 and 16:00 hours, were defined as *elective*, even though a proportion of these procedures were considered clinically urgent. Procedures completed on weekends and during late afternoons and nights, outside normal working hours, were defined as *emergency* procedures.

5.5 Grading the severity of complications

The "Cotton grading scale" for complications of ERCP and EST[2]

	Bleeding	**Perforation**	**Pancreatitis**	**Cholangitis**	**Basket impaction**
1 (mild)	Clinical (i.e., not just endoscopic) evidence of bleeding. Hemoglobin drop <3g, and no need for transfusions	Possible, or only very slight leak of fluid or contrast, treatable by fluids and suction for 3 days or less	Clinical pancreatitis with serum amylase > three times over normal 24 hours after ERCP; required admission or prolongation of planned admission to 2-3 days	>38 °C 24-48 hours	Basket released spontaneously or by repeat endoscopy
2 (moderate)	Transfusion (4 units or less), no angiographic intervention or surgery	Any definite perforation treated medically 4-10 days	Pancreatitis requiring hospitalization of 4-10 days	Febrile or septic illness required more than 3 days of hospital treatment or endoscopic or percutaneous intervention	Percutaneous intervention
3* (severe)	Transfusion (5 units or more), or intervention (angiographic or surgical)	Medical treatment for more than 10 days, or intervention (percutaneous or surgical)	Hospitalization for more than 10 days or hemorrhagic pancreatitis, phlegmon, or pseudocyst, or intervention (percutaneous or surgery)	Septic shock or surgery	Surgery

**Any intensive care unit admission after a procedure grades the complication as severe (grade 3). Other rare complications can be graded by length of needed hospitalization.*

The "Dindo-Clavien grading scale"* for severity of Surgical Complications[3]

Grade I	Any deviation from the normal postoperative course that did not require pharmacological treatment or surgical, endoscopic, or radiological intervention. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU management
Grade V	Death of a patient

** The complete classification comprises more details on subgroups*

5.6 Grading ERCP difficulty and complexity

Procedure complexity Grades 1-5*, according to Schutz and Abott, 2000[4]

Grade 1	Simple diagnostic ERCP - standard diagnostic cholangiogram; standard diagnostic pancreatogram
Grade 2	Simple therapeutic ERCP - standard biliary sphincterotomy; removal of 1-2 small common duct stones (≤1cm); nasobiliary drain placement
Grade 3	Complex diagnostic ERCP - diagnostic cholangiogram; Billroth II anatomy; biliary cytology; diagnostic pancreatogram; minor papilla cannulation; pancreatic cytology.
Grade 4	Complex therapeutic ERCP – multiple (≥3) or large (>1cm) common bile duct stones; cystic duct or gallbladder stone removal; common bile duct stricture dilatation; common duct stenting (plastic or metal)
Grade 5	Very advanced ERCP – precut biliary sphincterotomy; stone removal with lithotripsy (any type); intrahepatic stone removal; intrahepatic stricture dilation; biliary therapy, Billroth II anatomy; cholangioscopy; all pancreatic therapies (pancreatic sphincterotomy stenting, stricture dilation, or stone removal, any minor papilla therapy); any pseudocyst drainage (transpapillary, transgastric, transduodenal); pancreatoscopy

** If an ERCP was previously unsuccessful, it was given a B modifier.*

Procedure complexity Grades 1-3, according to Cotton et al, 2002[5]

	Diagnostic	Therapeutic
Grade 1: standard	Selective deep cannulation, diagnostic sampling	Biliary sphincterotomy, stones <10 mm, stents for leaks, and distal tumors
Grade 2: advanced	Billroth II diagnostics, minor papilla cannulation	Stones >10 mm, stent placement in hilar tumors, benign biliary strictures
Grade 3: tertiary	Manometry, Whipple, Roux-en-Y, Intraductal endoscopy	Billroth II therapeutics, intrahepatic stones, pancreatic therapies

Procedure complexity Grades 1-4, according to the ASGE[§] criteria, 2011[6]

Grade 1	Deep cannulation of duct of interest; main papilla, sampling; biliary stent removal/exchange
Grade 2	Biliary stone extraction <10 mm; treat biliary leaks; treat extrahepatic benign and malignant strictures; place prophylactic pancreatic stents
Grade 3	Biliary stone extraction >10 mm; minor papilla cannulation in pancreas divisum, and therapy; removal of internally migrated stents; intraductal imaging, biopsy, FNA; manage of acute or recurrent pancreatitis; treat pancreatic strictures; removal of pancreatic stones, mobile and <5 mm; treat hilar tumors; treat benign biliary strictures, hilum and above; manage suspected sphincter of Oddi dysfunction (with or without manometry)
Grade 4	Remove internally migrated pancreatic stents; intraductal image-guided therapy (e.g., photodynamic therapy, electrohydraulic lithotripsy); removal of pancreatic stones, impacted and/or >5 mm; intrahepatic stones; pseudocyst drainage, necrosectomy; ampullectomy; ERCP after Whipple or Roux-en-Y bariatric surgery

§ ASGE = American Society of Gastrointestinal Endoscopy

5.7 American Society of Anesthesiologists (ASA) Score

ASA Score to assess patient physical status (PS) before surgery[7]

PS 1	Normal healthy patient for elective operation
PS 2	Patient with mild systemic disease
PS 3	Patient with a severe systemic disease that limited activity but was not incapacitating
PS 4	Patient with an incapacitating systemic disease that was a constant threat to life
PS 5	Moribund patient not expected to survive 24 hours with or without operation

5.8 Hospital culture on safety

Levels of organizational safety observances, according to Parker and Hudson[8]

Level of safety	Safety Viewpoint	Characterization
Level 1	Pathological	Why do we need to waste our time on risk management and safety issues?
Level 2	Reactive	We take risk seriously and do something every time we have an incident
Level 3	Calculative	We have systems in place to manage all possible risks
Level 4	Proactive	We are always on the alert, thinking of risks that might emerge
Level 5	Generative	Risk management is an integral part of everything we do

5.9 Sphincter Oddi dysfunction (SOD) classification

Modified Milwaukee Classification of SOD[9]

Type 1	Pain + abnormal hepatic or pancreatic enzymes on 2 occasions + dilated common bile duct/pancreatic duct
Type 2	Pain + either abnormal enzymes or dilated common bile duct/pancreatic duct
Type 3	Pain alone

6. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) was first introduced by the surgeon, William S. McCune (1909-1998)[10] and co-workers, in the US, as a diagnostic tool for evaluating diseases of the biliary tract and pancreas. Eventually, it became a therapeutic modality for various conditions in the same region, including benign (e.g., common bile duct stones, strictures) and malignant diseases (e.g., tumor obstruction of the bile duct). Despite its relatively short history, ERCP is of great importance in current clinical practice. ERCP was a revolutionary method at its introduction, and it provided new insights into imaging and therapeutic approaches, particularly in the field of hepato-pancreato-biliary (HPB) disorders. Diagnostic approaches have changed over the past 40 years, with the introduction of new imaging modalities[11, 12], modified surgical techniques[13], and improved anesthesia[14]. Furthermore, demands for documentation and quality have changed[15]. These changes have caused a shift in the role of ERCP in the algorithm for evaluating the biliary tract in routine clinical practice[16, 17]. Although the ERCP procedure has evolved technically, it continues to be associated with potentially serious complications[18] and discomfort for patients[19].

ERCP procedures are prevalent at university hospitals but also at general community hospitals. The procedure can be performed by both medical gastroenterologists and gastroenterologic surgeons[20]. However, there is a lack of systematic knowledge about the general use and possible side effects of ERCP, and, in particular, patient-reported experiences[21-23]. The clinical application of ERCP has

developed differently in various countries, and reported outcomes or differences in outcomes between various centers or countries should be interpreted with great caution[24, 25].

The concept of a national registry was first suggested in relation to a Scandinavian joint project (*Scandinavian Gallstone Group*) between 1998 and 1999, which involved a number of Nordic surgeons and physicians that had a special interest in endoscopy and diseases of the biliary tract and pancreas. The main focus was on complications of ERCP, but also, there was great concern over the fact that the new laparoscopic technique was associated with an increased incidence of bile duct injuries[26-28]. National registries and evaluations of cholecystectomy practices were established in Norway[29], Sweden[30], Finland[31], and Denmark[32]. Furthermore, an international debate was initiated on the safety of treatments for common bile duct stones (CBDS). At the same time, laparoscopic cholangiography[33] was established as a surgical method, and laparoscopy was used in treating CBDS with transcystic extraction or choledochotomy [34-37]. A multicenter study by the European Association for Endoscopic Surgery (EAES)[38] concluded that a primary, one-stage, laparoscopic treatment of CBDS was equivalent to a two-stage treatment with ERCP and an eventual laparoscopic cholecystectomy. Also, a later Cochrane report[39] concluded that a surgical one-stage procedure was at least equivalent to a two-stage procedure, and they suggested that primary surgery was perhaps the method of choice. Of note, a laparoscopic approach to CBDS is technically demanding, with challenging logistics for the surgical team. The quest for better solutions was a hot topic of discussion at

international and national meetings. Surgeons and gastroenterologists in Scandinavia convened frequently to discuss solutions; clearly, there was a need for more research and knowledge. As a direct consequence of those observations, a Danish group[40] later proposed a Scandinavian ERCP registry. Although that registry did not come to fruition, registries for cholecystectomy and ERCP were established in Sweden[41], and an ERCP registry was established in Norway[42].

Over the last decade, technical improvements have occurred in endoscopy and laparoscopy fields, but also more attention on palliative care[43] and safety aspects have been considered more frequently in medical care[44]. This dimension and change in focus was displayed in the statement issued by the WHO, which recognized surgical complications as a worldwide health problem and introduced the surgical checklist[44]. Nevertheless, the questions raised in the early '90s currently persist on the treatment of gallstones, and concerns over ERCP complications remain unresolved.

This project investigated Norwegian ERCP data to determine the volumes and distributions of ERCP among different regions and hospitals in our country. Within the ERCP population, we evaluated demographic patterns, the distributions of various ERCP procedures, and the frequency of undesired outcomes. We also summarized patient-reported experiences with ERCP.

6.1. Historical perspectives

6.1.1 Endoscopy – steps in gaining new insights

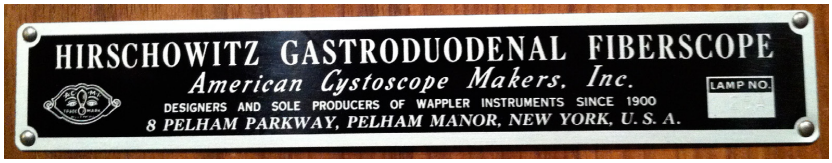
The evaluation of internal organs through human natural orifices has been a great interest for physicians, since very early in medical history. Hippocrates (460–377 BC) used a rectal specula to treat fistulae; this approach was also mentioned by Galen in "Levicom"[45].

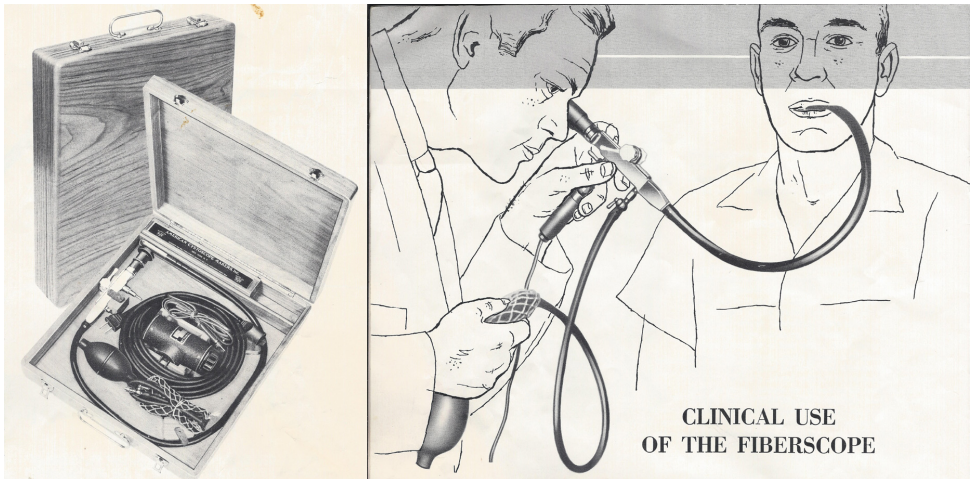
Upper gastrointestinal endoscopy into the esophagus was first described by John Aylwin Bevan in 1868, who used reflected candlelight[46] to visualize and remove foreign bodies from the esophagus. In 1868, Adolf Kussmaul[47] reported that he used reflected sunlight and a stiff "gastroscope" to look into the stomach ("Magenspiegelung"). Two years later, L. Waldenburg improved the esophagoscope with a telescope[45]. In 1887, Karl Stoerk introduced a right-angled esophagoscope[45].

Max Nitze was one of the pioneers in developing modern instruments. He focused mainly on the urinary bladder and developed the first cystoscope (1877)[45]. His inventions, combined with improved optical systems with light sources in the tips of telescopes, made it possible for Johann von Mickulics (1881) to construct the first rigid gastroscope with air insufflation[45]. Further improvements were achieved by his pupil, Georg Kelling (1898), who introduced a "flexible" esophagoscope and a gastroscope with a flexible tip and a miniature electric globe[45]. In 1936, Rudolf

Schindler introduced a semi-flexible gastroscope [45]. However, visualization of the whole stomach remained incomplete.

The modern flexible fiber gastroscope was developed by Basil Isaac Hirschowitz in 1958[48]. Importantly, this invention was preceded by the work of Harold H. Hopkins (1954) and Karl Storz[45] in designing endoscopes with improved optical parameters, miniaturized parts, light transmission through glas-fiber, and wide viewing angles.





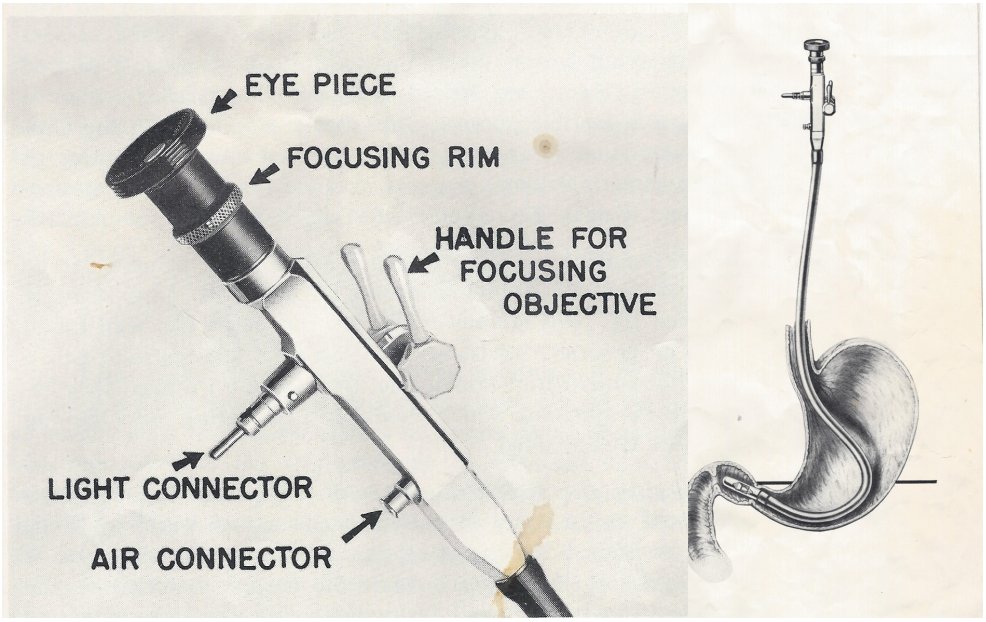


Figure 2. *From the original user manual of the Hirschowitz Fiberscope*

After black and white television was developed, the first bronchoscopy published on TV was reported in France in 1956[45]. The first miniature endoscopic television camera was developed in Australia in 1962 by George Berci[45]. Two developmental breakthroughs came with the introduction of the CCD (charged–coupled device) in 1983 and the first report of a choledochoscopy in 1985[45]. Later, improvements in miniature chip technology and imaging quality made it possible to install a camera on the tip of a rigid or flexible instrument, engineer space for larger working channels, and improve illumination and flexibility. The television technique was a revolutionary in laparoscopy and changed the surgical field at beginning of the '90s, but implicated also great improvements in the flexible endoscopy. The imaging quality reached a higher level in 1992, when high-fidelity display (HDTV) was introduced into an endoscopic system[45].

Figure 3. A modern duodenoscope used for ERCP
Courtesy of Olympus Norge AS

6.1.2 Flexible gastrointestinal endoscopy – introduction in Norway

In Norway, the first flexible endoscopy was performed in 1960 by Asbjørn Nilsen Sr, MD at the Akershus Central Hospital[49]. He used a Hirschowitz gastroscope from the US. In 1964, a dedicated Gastroenterological unit was established by Johannes Myren, MD at Ullevål University Hospital, Oslo[50]. This important unit soon became incorporated into the specialist education curriculum for gastroenterologists and gastroenterological surgeons. During the '60s, flexible endoscopy was introduced, but it was more generally implemented clinically in the early '70s. In 1975, at least 20 Norwegian hospitals had organized endoscopic units[50].

6.1.3 ERCP – the evolution of a new tool

In the '60s, there were no adequate imaging techniques for the pancreas; thus, patients with clinical signs of biliary obstruction and pancreatic malignancies were commonly treated with surgical interventions[51]. Moreover, endoscopes were not

designed for inserting into the duodenum or for guiding therapy. The Hirschowitz gastroscope[48] was limited in its flexibility, navigation, working channels, and length.

In 1968, the first pancreatogram, produced with endoscopic cannulation of the papilla of Vater, was reported by surgeons, William S. McCune and Paul E. Shorb, and gastroenterologist and engineer, Herbert Moscovitz, at the George Washington University in Washington DC. Their combined knowledge from radiology and endoscopy was applied to develop a new procedure[10]. At the same time, Japanese groups were developing improved duodenoscopes and instruments for cannulating the pancreatic and bile ducts[52, 53]. Soon afterwards, the new method was introduced in Europe[51]. Initially, ERCP was called endoscopic cholangiopancreatography (ECPG) in Japan[51]. This was the beginning of the ERCP era, and activity was boosted after a workshop organized by Olympus Optical at the *2nd European Congress of Digestive Endoscopy*, in Paris 1972[51]. Olympus had improved the duodenoscope by elongating their gastroscope from 92 cm to 105 cm, implementing an "elevator" for steering the instrument/catheter, enlarging the working channel, and rebuilding the optical lenses to create a single, side-viewing lens.

Figure 4. *The modern tip of an ERCP-scope illustrating the miniaturization and the use of the elevator and rotating catheters*

Courtesy of Olympus Norge AS

The breakthrough in developing therapeutic ERCP came with the introduction of endoscopic sphincterotomy (EST) by German[54] and Japanese[55] groups 1973. Interestingly, in 1974, Drs. Meinhard Classen (1936-present) and Ludwig Demling (1921-1995) had been aware of potential side effects, particularly pancreatitis, following open surgery[54]. Kawai and co-workers performed their first sphincterotomies with great enthusiasm and they reported no complications. In particular, they successfully treated impacted CBDS in the papilla or the lower part of the CBD, and they claimed: *"This is a completely safe and easy manipulation, and the patient's discomfort is minimal compared to the surgical procedure. However, the indication for this technique must be strictly selected"*[55]. Thus, EST and stone extraction were limited to patients at high surgical risk or those that had previously undergone cholecystectomies. This opinion persisted until the beginning of the '90s, when a paradigm shift was introduced (reported at the *9th World Congress of Gastroenterology*, 1990, Sydney). The new paradigm made ERCP with EST the gold

standard for CBDS treatment, applicable to all patients[49], including those with "gallbladder in situ"[56]. Nevertheless, some controversy existed regarding the indication for EST in young patients. This therapeutic shift was clearly more driven by eminence than by evidence, but consequently, many patients with CBDS were moved from the operating theater into the endoscopic unit.

Two important reasons for the paradigm shift were the historical prevalence of mortality and morbidity after open surgery[57, 58] and the lack of long-term follow-up in studies that compared ERCP and surgery. Historically, this is of interest, because at the end of the 18th century, patients with gallstones were placed in the domain of internal medicine. With the introduction of cholecystectomy, passionate discussions took place between surgeons and internists regarding the treatment of gallstones[59]. Later, with the paradigm shift, patients with gallstones were returned to the domain of gastroenterologists.

Over time, ERCP was developed technically, and endoscopists became more skilled. A new important crossroad was the introduction of the endoscopic drainage procedure, as reported by Nib Sohendra and Frederix Reijnders[60] concurrent with Laurence and Cotton, in 1980[61]. This new procedure was a revolutionary lifesaving procedure in the management of patients with obstructive cholangitis. It was also used pre-operatively for treating and relieving obstructive jaundice, and it was considered a definitive palliative treatment for patients with incurable malignancies or at high surgical risk. The introduction of self-expandable metal stents (SEMS) has improved palliative applications by increasing the diameter to improve patency.

Currently, highly specialized centers have improved instruments that allow direct cholangioscopy (including the Spyglass), the potential for biopsies, and direct treatment of stones and tumors in the bile duct[62, 63]. Access to the papilla of Vater has remained a challenge in patients with previous diverting operations in the stomach or duodenum. During the ‘70s and ‘80s, patients with a previous Billroth II resection were commonly observed in ERCP practice[64]. This patient group has diminished, but other diverting operations, like the gastric bypass, have become more common and have presented new challenges[65]. The introduction of single and double balloon scopes has made it possible to perform ERCP, even in groups with Roux-Y reconstructions[66].

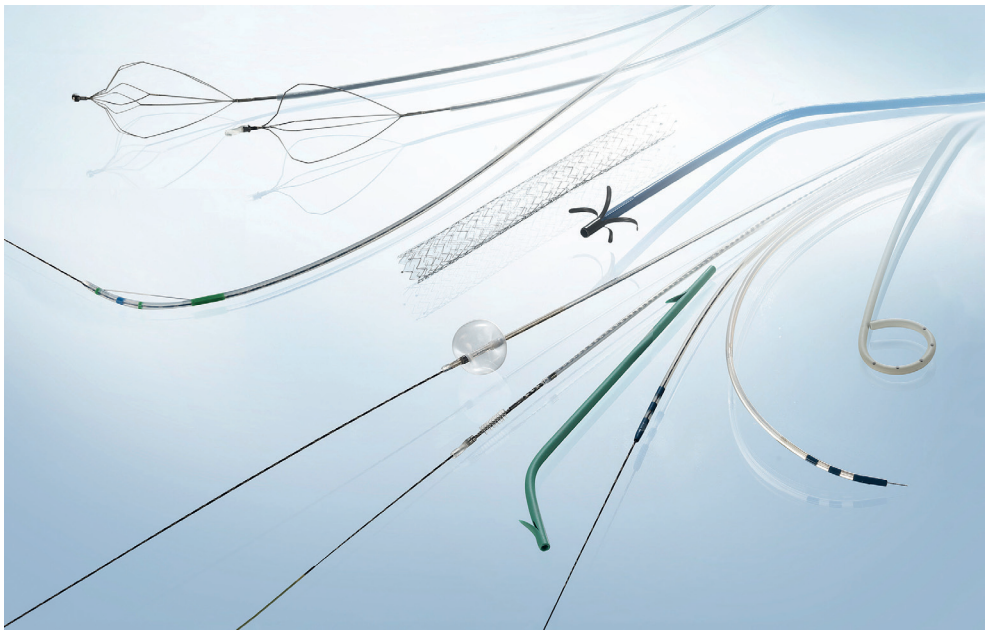


Figure 5. *Instruments and stents available for different therapy in ERCP*

Courtesy of Olympus Norge AS

As a part of a minimally invasive strategy, ERCP has continued to develop and it has found new applications with the team approach. The combination of PTC and ERCP is used in difficult cases, for peroperative ERCP and stone extraction in an one stage procedure together with laparoscopic cholecystectomy[67], and for introducing new intraductal therapy modalities in tumor treatments[68]. Studies that evaluated alternative treatments remain sparse or lacking.

6.1.4 ERCP – introduction in Norway

In 1972, a radiologist from Malmö, Sweden, Lennart Wehlin, (1922-1983), introduced the ERCP in Scandinavia[49, 67], after a visit to Japan, where he obtained a JF-B Olympus duodenoscope. Until 1973, he was the only endoscopist in Scandinavia that performed the ERCP (personal communication, Arne R. Rosseland). In March 1974, after visiting Aksel Kruse, MD (radiologist) in Aarhus, Denmark, the Norwegian surgeon, Arne R. Rosseland, MD, introduced this technique at the Telemark Central Hospital in Skien[69]. Shortly thereafter, a gastroenterologist, Magne Osnes, MD, implemented ERCP procedures at the Ullevål University Hospital in Oslo[70, 71]. Aksel Kruse performed the first EST in Scandinavia in 1975, closely followed by Magne Osnes in Norway[49]. Drs. Osnes and Rosseland contributed substantially to the general implementation of ERCP in Norway and Scandinavia[72]. The Norwegian pioneers provided results of international importance and relevance on the use of ERCP in treating gallstone pancreatitis, in examining the implications of juxtapapillary duodenal diverticula, in facilitating brush cytology for diagnosis of malignancies, in draining the bile duct, and in treating CBDS in patients with

previous Billroth II gastric resections[64, 73-81]. Drs. Osnes and Rosseland initiated several Scandinavian collaborations, and they were among the "founding fathers" of the Scandinavian Association of Digestive Endoscopy (SADE), established in 1976[49]. This organization has remained important in the further development of endoscopy and in the education of clinicians in Scandinavian countries.

Figure 6. *Arne R. Rosseland and Magne Osnes. Photo. Aksel Kruse*

Exact statistics are incomplete on the total ERCP activity during the first 30 years after its introduction in Norway, but surveys were performed by Johannes Myren et al[50]. They reported that 2078 ERCPs (51/100,000 inhabitants) were performed in 1978, and this increased to 4116 ERCPs (143/100,000) in 1985. Before 1975, four hospitals had started using the procedure. In 1980 and 1985, 16 hospitals

and 30 hospitals, respectively, could offer ERCP[72]. In 1985, therapeutic ERCPs were performed at five university hospitals, at four central hospitals, and at three general district hospitals.

6.1.5 A new era in imaging and treatment in HPB diseases

ERCP virtually revolutionized imaging and expanded the diagnostic tools in the field of HPB diseases; in addition, it was early recognized that ERCP could be very useful in treating CBDS with cholangitis and in patients that had received previous cholecystectomies. The very promising results and enthusiasm were followed by early, rapid implementation of the ERCP procedure at many hospitals. However, the efficacy of ERCP lacked evidential support from controlled studies. In parallel to the rapid developments in endoscopic diagnostic and therapeutic methods, there were improvements in anesthesia that focused on fast track surgery, safety, mini-invasive surgery, and data and video recording technology; there were also radical improvements in imaging, in general. The "laparoscopic revolution" in the last decade of the 20th century dramatically changed the everyday practice of surgeons[82].

6.1.6 ERCP – a diagnostic and therapeutic tool

The indications for ERCP have developed and changed. Over the last decade, ERCP has been regarded a therapeutic modality, and rarely as a diagnostic tool[83, 84]. This shift was supported by recognition of the complications associated with the procedure and by the introduction of new imaging methods (i.e., MRI/MRCP, endoscopic ultrasound, improved CT, and external ultrasound). Nevertheless, as shown by Baron

et al[15] in 2006, there are many indications for ERCP (**Textbox 1**). However, with new developments, the indications have changed[85].

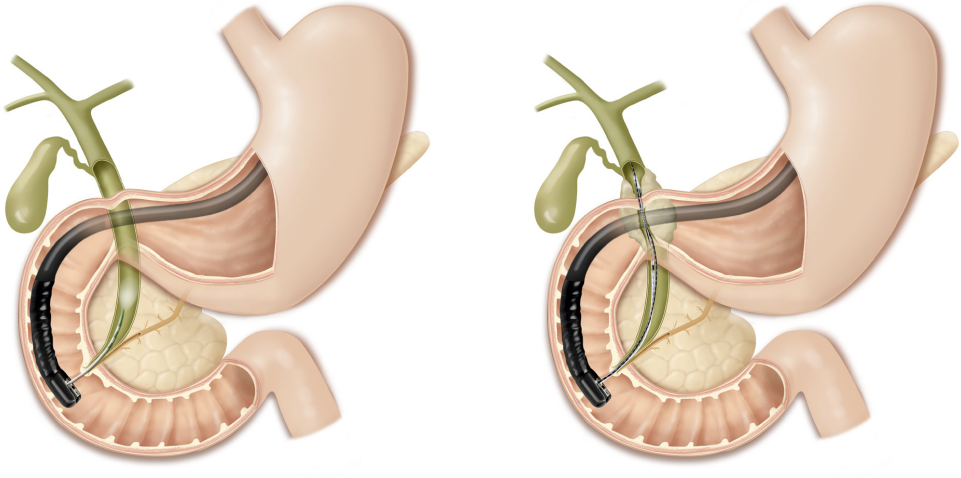


Figure 7. *ERCP as a diagnostic tool*. *Courtesy of Olympus Norge AS*

ERCP remains an important method for mapping and drainage in biliary injuries and sclerosing cholangitis. ERCP is also used in treating specific pancreatic disorders, including stones in the pancreatic duct, and drainage procedures that involve an EST on the minor papilla in patients with symptomatic pancreas divisum. The general role of ERCP is controversial in the treatment of chronic pancreatitis, where pain is a dominant symptom. ERCP can be used to perform transpapillary drainage of pseudocysts, when there is communication with the pancreatic duct; in addition, ERCP can be used to acquire samples from the duct, when a mass is suspected to be precancerous or malignant. Reports from North America frequently include patients with sphincter of Oddi dysfunction (SOD)[25, 86]; this condition is

typically encountered in young females. The definition and identification of SOD remains controversial, and thus, there is no consensus on the appropriate indications or the best treatment[87, 88].

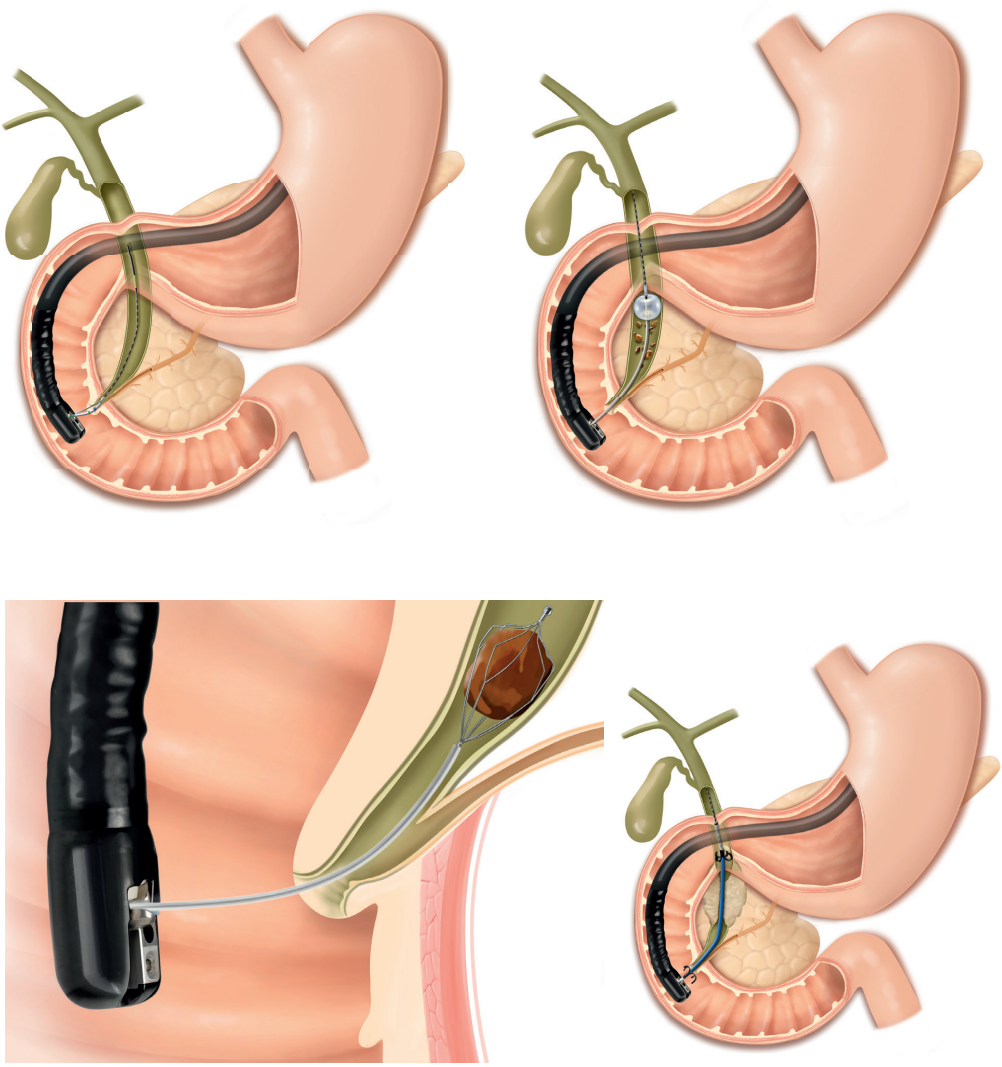


Figure 8. *ERCP as a therapeutic tool*. *Courtesy of Olympus Norge AS*

Textbox 1*:* Indications for ERCP, according to Baron et al[15] 2006

A. Jaundice thought to result from biliary obstruction
B. Clinical and biochemical or imaging data suggestive of pancreatic or biliary tract disease
C. Signs or symptoms suggesting pancreatic malignancy when direct imaging results are equivocal or normal
D. Pancreatitis of unknown etiology
E. Preoperative evaluation of chronic pancreatitis or pancreatic pseudocysts
F. Sphincter of Oddi manometry
G. Endoscopic sphincterotomy for:

1. *Choledocholithiasis*
2. *Papillary stenosis or sphincter of Oddi dysfunction, which causes disability*
3. *Facilitation of biliary stent placement or balloon dilatation*
4. *Sump syndrome*
5. *Choledochocele*
6. *Ampullary carcinoma in poor surgical candidates*
7. *Access to pancreatic duct*

H. Stent placement across benign or malignant strictures, fistulae, postoperative bile leak, or large common bile duct stones
I. Balloon dilatation of ductal strictures
J. Nasobiliary drain placement
K. Pseudocyst drainage in appropriate cases
L. Tissue sampling from pancreatic or bile ducts
M. Pancreatic therapeutics

6.1.7 Prevalence of gallbladder stones, CBDS, and cholecystectomy

The prevalence of gallstones is higher in Western countries (10-15%) than in Africa and Asia (3-5%)[89]. Gallstones are also more common in women than in men, and the prevalence increases with age. According to studies from Sweden[90-92], the frequencies of gallstones in women and men at age 40 is 11% and 4%, respectively, and at age 60, it increases to 25% and 15%, respectively. More than 50% of women aged 80 have gallstones or a previous cholecystectomy. It is estimated that 60-80% of patients with gallstones have no symptoms and require no treatment[93]. When an asymptomatic

gallstone is diagnosed, the estimated risk of developing symptoms is about 10% within 5 years[94, 95]; however, lower risk has also been reported[96]. In Scandinavia, the median rate of annual cholecystectomies per 100,000 inhabitants varied in 1989-95 among different countries (Norway 62.3, Denmark 68.2, Sweden 121.7, Finland 142.0)[97]. This rate tended to increase after the introduction of laparoscopic surgery.

6.1.8 ERCP and gallstone disease

Currently, most clinicians agree that ERCP should not be used as a diagnostic tool for CBDS[84]. However, other controversies persist over how to manage CBDS and complications from gallstones[98]. Cholecystectomy was introduced in 1882 by the German surgeon, Carl Johann August Langenbuch (1846-1901), in Berlin. In 1889, Knowsley Thornton in London, and in 1890, Ludvig Courvoiser in Basel entertained the notion of exploring the CBD and removing CBDS[99]. In the early era, surgery was associated with high complication rates, including significant mortality; thus, surgery was controversial[57, 100]. However, before the ERCP era, surgery was the only option for a cure. With the introduction of antibiotics and better anesthesia methods, the complication rates decreased and the results improved[58, 101].

With the introduction of laparoscopic cholecystectomy by Erich Mühe in Böblingen, Germany in 1985[102] and by Philippe Mouret in France in 1987[103], a new era began in the treatment of gallstones. In 1989, Dr. Bjørn Nilsen at Gjøvik hospital performed the first laparoscopic cholecystectomy in Norway[104], and this method was implemented rapidly during the early '90s[26].

Until the beginning of the '90s, the "gold standard" treatment for extraction of CBDS was open cholecystectomy and choledochotomy[49]. The laparoscopic bile duct stone extraction method was established early. Although this option was feasible[34, 36, 37], it was introduced slowly internationally, due to difficult logistics, a challenging technical procedure, prolonged operating times, and high cost. Later, reports indicated that the laparoscopic approach to CBDS was the method of choice, and the outcome was at least equivalent to a two-stage procedure with ERCP and subsequent cholecystectomy[38, 39].

The risk of CBDS increases with age, and the estimated prevalence is 5-15% in patients that are candidates for cholecystectomy[105, 106 107, 108]. In the beginning of the '90s, diagnostic tools, including MRCP, were not generally available for diagnosing CBDS[20], and routine laparoscopic cholangiography was not generally accepted. When in doubt, a pre-operative ERCP was recommended. Accordingly, a large number of "unnecessary" negative ERCPs were performed, and these included complications. The pioneering work of Hauer-Jensen et al [109-111] and the observations of Trondsen and co-workers [112] made it possible to predict CBDS more systematically. This, combined with the general focus on avoiding unnecessary complications and ERCPs, led to a shift to using ERCP more restrictively. Of note, ERCP use decreased in the late '90s, before MRCP became generally available[20].

In many countries, endoscopy is not included in the field of surgery; instead, it has been delegated to gastroenterologists. In Scandinavian countries, surgeons have

been deeply involved in the development of endoscopy; this has facilitated the discussion of the entire treatment sequence for gallstone disease.

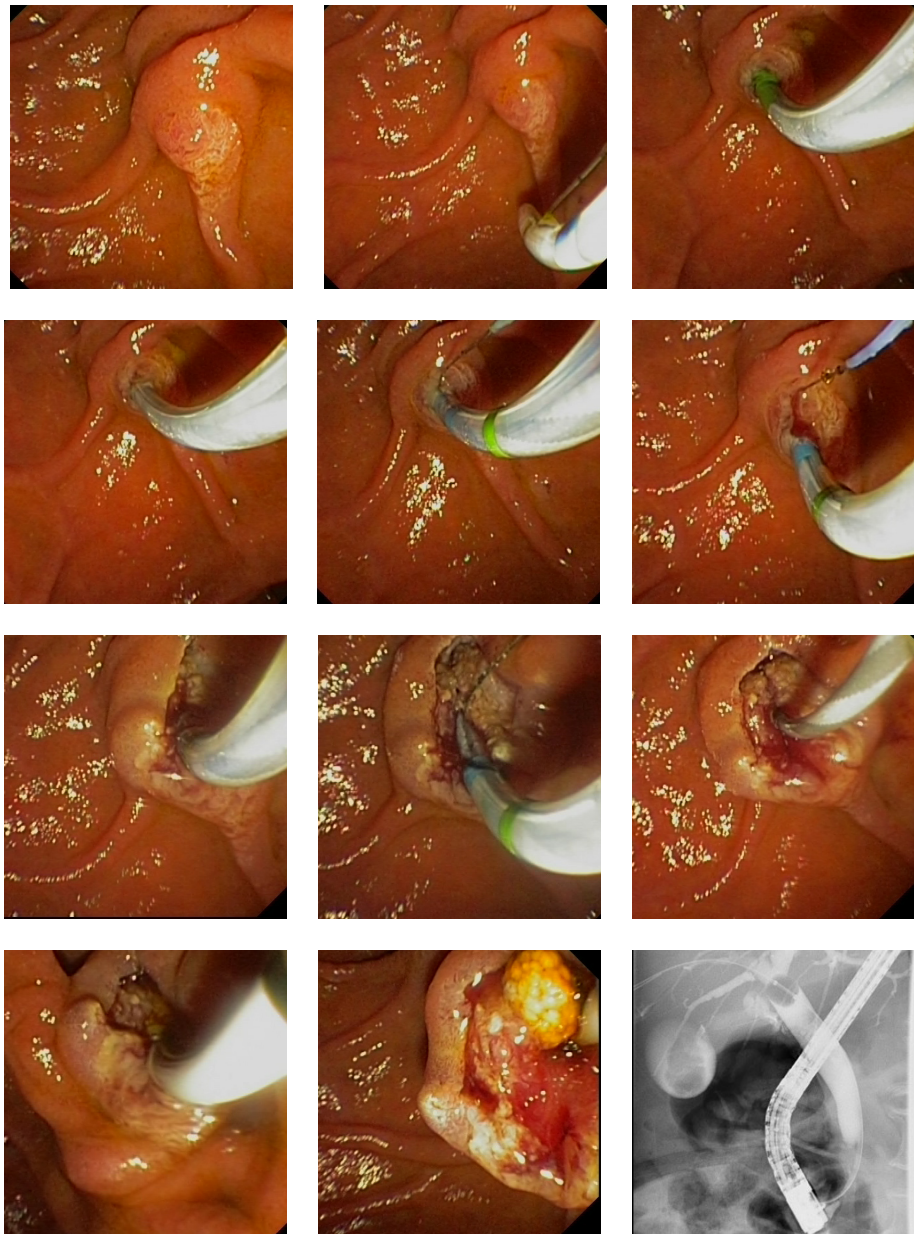


Figure 9. *ERCP and EST with balloon-extraction of CBDS. Photos. Private*

Controversy has continued over whether the gallbladder should be left in situ after EST[113]. For example, the following questions remain unresolved:

i. When is a cholecystectomy not indicated; does age or grade of comorbidity matter? [114]
ii. Is ERCP pre-, peri- or post-operatively necessary or justified in case of a complicated CBDS disease, or is a straight-forward open or laparoscopic one-stage procedure indicated?[39] [13]
iii. How many attempts should be allowed before surgery is indicated?
iv. Are other options, including ESWL, laser lithotripsy, or oral cholangioscopy warranted before surgical treatment is indicated?

Major concern remains over reports of increased mortality associated with endoscopically treated CBDS and prolonged, repeated hospital stays[39]. It is agreed that fulminant cholangitis should be treated with urgent, endoscopic, emergency drainage[115]. It is also the general opinion that a predicted, severe pancreatitis with CBDS should be treated with an emergency ERCP and EST[116].

6.1.9 Malignancies in the HPB region

Malignancies in the HPB region are often non-resectable, and are associated with a dismal prognosis [117], although some long-term survivors have been encountered[118]. In older patients, although the tumor may be resectable, comorbidity and age may pose important contraindications to a Whipple procedure. Another scenario is a patient with symptomatic, occlusive icterus and cholangitis that may need a bridge to surgery[119, 120]. This indication is more controversial[121], particularly when no cholangitis is present.

The second most important indication for ERCP is palliative drainage of strictures in the CBD[122, 123]. Obstruction may be caused by cholangio-carcinoma, pancreatic cancer, duodenal cancer, tumor in the papilla of Vater, or secondary tumors in the region. Few studies have evaluated ERCP in terms of improvements in quality of life and patient symptoms[124]. Most studies have focused on feasibility, effects on blood tests (jaundice relief), and technical aspects[123]. However, it is generally thought that jaundice relief is an improvement in the patient's condition, particularly when itching is a major symptom. There is no consensus for when the ERCP should be performed in patients with a poor prognosis, particularly during the present era when, in many other aspects, a multi-disciplinary team (MDT) approach is commonly used to achieve a tailored treatment. Reports have indicated that patients are likely to attain a better outcome when a MDT is involved before an ERCP[125].

An important part of ERCP is the inclusion of a multidisciplinary discussion about treating patients with malignancies[126, 127]. In many cases, a patient with jaundice is hospitalized without a clear diagnosis. An important step for these patients is to formulate a plan that facilitates making the right decisions. For example, in principle, ERCP is not indicated before performing non-invasive imaging (ultrasound, EUS, CT scan, MRI)[11], except in patients with severe cholangitis. Not uncommonly, a diagnosis is not possible from imaging results, and it becomes necessary to perform an ERCP to acquire biopsies or tissue for cytology. In cases with obstruction, a drain must be placed to avoid cholangitis. At the moment an ERCP is performed, the endoscopist should be aware of the certainty of the diagnosis, whether surgery is an

option, or whether it is clear that surgery cannot offer a cure. The strategy for applying drainage depends on the subsequent treatment[120, 123]. Also, it is important to consider the patient's life expectancy. This topic remains an ongoing issue of debate, and it has paralleled the development of new, improved, self-expanding stents. In some cases, when it is not possible to achieve drainage with ERCP alone, other options include intervention radiology[128] with percutaneous transhepatic cholangiography (PTC), interventional endoscopic ultrasound (EUS), and combined ERCP/PTC as "rendezvous" procedures or surgery.

7. Complications of ERCP

7.1 Definitions of complications

What is a complication[1, 129]? The answer may not be straight-forward, particularly when a registry or database is planned. These issues have been addressed by Sokol et al[130] and in editorials[129]. Moreover, surgeons and gastroenterologists may deal with complications differently. For surgeons, events during the first 30 days after surgery are likely to be related to the intervention[1]. In the ERCP literature, this has not been made clear[21, 25]. The evolution and growing understanding of ERCP, however, has forced a renewed focus on ways to prevent complications[131].

7.2 Severity and grading

Once an undesired event is defined as a complication, the challenge is to grade the severity. The majority of post ERCP events have minor or no clinical consequences for the patients. Traditionally, many ERCP reports have used the severity classification of Cotton et al[2] . This classification takes into consideration various parameters that describe severity, depending on the type of complication. The most important parameter is the length of hospitalization. Currently, particularly in the Scandinavian health care system, this is an imprecise description of treatment consequences, because most patients that receive ERCP are hospitalized due to comorbidity. An alternate classification is the Dindo-Clavien classification[3], which is

not dependent on length of hospitalization, but rather, the required treatment for the complication. None of the classifications are optimal, and a new classification system adapted to the ERCP procedure should be considered. Of particular concern are the failed (unsuccessful) procedures or partly successful procedures; these make repeat-procedures necessary, including the risk of associated complications related to comorbidity, other invasive treatment and sedation (particularly cardiovascular and pulmonary events).

Generally, and to some extent surprisingly, deaths that occur during the first 30 days are frequently reported as unrelated to the procedure or not reported in ERCP literature. However, in Sweden[41] and Denmark[40], the 30-day mortality was more than 5%. These numbers bring into question whether fatal complications are underreported (**Table 1**). It is difficult to be certain of the true number of deaths that were caused directly or indirectly by ERCP.

Freeman[132] described an awareness of the entire spectrum of outcomes, beyond immediate complications. He included technical failures, ineffectiveness of the procedure in resolving the actual problem, the long-term sequelae, costs, extended hospitalization, and patient satisfaction. The terminology seems to have changed from complications to adverse events, and then, to "unplanned events". Freeman[132] pointed out that adverse events must be considered in the context of an entire clinical outcome. For example, one alternative to a minor complication could be a failed procedure with no complication; however, eventually, that patient would require a repeated procedure, surgery, or radiological intervention[132].

7.3 Heterogeneous reporting

As shown in **Table 1**, there is a wide range of reported ERCP complications. Freeman[132] lists four important reasons for this:

i. *Definitions used*
ii. *Thoroughness of detection*
iii. *Patient-related factors*
iv. *Procedural variables, including pancreatic stents and extent of procedure*

All these factors make it necessary to use caution when interpreting the outcome. For example, it is important to be aware that, when few complications are reported, it may not necessarily indicate better quality of care. In addition to these four important factors, the population studied is of great importance for the outcome. For example, even in a highly specialized center with selected patients (e.g., referred for uncommon pancreatic disorders, benign strictures, or SOD), a study population is likely to include individuals that differ significantly in age, gender, and comorbidity. Moreover, when the study population is confined to a randomized controlled trial, the exclusion criteria may make the results inappropriate for generalization to a general population.

7.4 Risk factors for complications

In **Table 1**, we have collected prospective series of ERCPs and focused on prospective studies that registered patient complications, but we also included a few

reviews. There are few large multicenter cohort studies[23, 24, 41, 133-141], particularly studies with a 30-day follow-up.

Table 1. Complications in ERCP

	Type of study	Number of ERCPs	Pancreatitis (%)	Bleeding (%)	Infection (%)	Perforation (%)	CR (%)	Total (%)	Death (%)	mort30d (%)
Leese et al 1985[142]	Prospective single center	394	2.0	4.8	1.8	0.8	-	10.4	0.8	3.3
Sherman et al 1991[143]	Prospective single center	423	4.0	1.4	0.9	0.5	-	-	-	1.7
Cotton et al 1991[2]	review	7729	1.9	3.0	1.7	1.0		8.2	1.3	-
Boender et al 1994[144]	Prospective single center	242	1.7	6.2	5.4	1.7	-	14.0	-	-
Freeman et al 1996[24]	**Prospective multicenter**	**2347**	**5.4**	**2.0**	**1.5**	**0.3**	**0.3**	**9.8**	**0.4**	**2.6**
Tanner et al 1996[141]	**Prospective multicenter**	**255**	**2.8**	**2.0**				**6.0**	**0.0**	-
Deans et al 1997[140]	**Prospective multicenter**	**1000**	**1.0**	**0.4**	**0.7**	**0.3**	-	**2.4**	**0.2**	-
Dickinson et al 1998[145]	Prospective single center	430	2.8	0.2	0.0	0.2	-	3.3	0.2	-
Loperfido et al 1998[133]	**Prospective multicenter**	**3356**	**1.3**	**0.76**	**0.87**	**0.58**		**4.0**	**0.39**	**1.4**
Choudari et al 2000[146]	Prospective single center	562	8.7	0.4	0.7	0.7	-	10.1	0.2	-
Tzovaras et al 2000[147]	Prospective single center	372	1.3	0.26	1.9	0.26	0.26	5.6		1.3
Rabenstein et al 2000[148]	Prospective single center	438	4.3	2.3	0.9	0.0	-	7.5	0.5	6.4
Masci et al 2001[134]	**Prospective multicenter**	**2444**	**1.8**	**1.13**	**0.57**	**0.65**	**0.2**	**4.95**	**0.12**	-
Vandervoort et al 2002[149]	Prospective single center	1223	7.2	0.8	0.7	0.08	0.8	11.2	016	-
Barthet et al 2002[150]	Prospective single center	1159	2.5	0.7	1.7	2.2		6.3	0.5	0.9
Lal et al 2003[151]	Prospective single center	210	4.76	2.38	-	-		9.5	0	0.0
Christensen et al 2004[40]	Prospective single center	1177	3.8	0.9	5.0	1.1	2.3	15.9	1.0	5.8
Ong et al 2005[152]	Prospective single center	336	5.4	0.8	2.4	-		9.8	0.3	1.8
Suissa et al 2005[153]	Prospective single center	701	4.3	1.4	3.7	1.3		10.8	0,6	0.8
Köklü et al 2005[154]	Prospective single center	299	2.0	4.0	1.3	1.3	-	9.0	-	4.0
Andriulli et al 2007[18]	Systematic review	16855	3.47	1.34	1.44	0.6	1.33	6.85	0.33	-
Williams et al 2007[23]	**Prospective multicenter**	**5264**	**1.5**	**0,9**	**1.1**	**0.4**		**5.1**	**0.4**	**2.7**
Vitte et al 2007[135]	**Prospective multicenter**	**2708**	**3**	**1.5**	**1.9**	**0.9**		**9.1**	**0.8**	**4**
Kapral et al 2008[136]	**Prospective multicenter**	**3132**	**5.1**	**3.7**	**1,9**	**0,5**	**0.9**	**12.6**	**0.1**	-
Wang et al 2009[138]	**Prospective multicenter**	**3178**	**4.3**	**1.7**	**0.3**	**0.3**	**0.1**	**7.9**	**0.3**	-
Cotton et al 2009[25]	Prospective single center	11497	2.6	0,3	-	-	-	4,2	0.06	-
Enochsson et al 2010[41]	**Prospective multicenter**	**11074**	**2.7**	**1.5**	-	**0.9**	-	**12.3**	-	**5.9**
Liao et al[125] 2011	Prospective single center	1909	6.0	1.8	1.5	0.2	-	9.6	0.1	-
Glomsaker et al [139]	**Prospective, multicenter**	**2808**	**3.1**	**2.4**	**3.6**	**0.9**	**1.1**	**11.6**	**1.4**	**2.2**
Kapral et al 2012[137]	**Prospective, multicenter**	**13513**	**4.2**	**3.6**	**1.4**	**0.6**	**1.2**	**10.1**	**0.1**	-

7.4.1 Risk factors for overall complications

Relatively few multicenter studies[24, 133-136, 138, 139, 155] have focused on risk factors for complications, and several have reported conflicting results. However, the identified independent risk factors include female gender, juxtapapillary diverticulum, over 10 min for cannulation, suspected SOD, cirrhosis, difficult cannulation, pre-cut EST, percutaneous biliary access, and low ERCP case volumes (**Table 2**). The majority of undesired events and complications after ERCP were not classified as severe and the long-term events are described differently.

Table 2. Significant risk factors that predicted overall complications in ERCP, based on multivariate regression analysis results from multicenter studies

Study and publication year	Country	Risk factor 1	Risk factor 2	Risk factor 3	Risk factor 4	Risk factor 5
Freeman et al 1996[24]	USA/Canada 1992-94	**Difficulty of cannulation**, OR 3.05	**Pre-cut EST**, OR 3.61	**Combined PTC/ERCP**, OR 3.40	**Suspected SOD**, OR 2.90	**Cirrhosis**, OR 2.63
Loperfido et al 1998[133]	Italy 1992-94	**Less than 200 ERCPs per year in center**, RR# 2.90	**Pre-cut ES**, RR 1.867			
Masci et al 2001[134]	Italy 1997-98	**Age ≤60 years**, OR 1.53	**Failed removal of CBDS,** OR 2.52			
Vitte et al 2007[135]	France 1999-2000	**Use of guidewire**, OR 1.54	**Difficult cannulation** (Easy cannulation, OR 0.5)	**Center with <200 ERCPs** (Center >200 ERCP, OR 0.36)		
Williams et al 2007[155]	England 2004	**Pre-cut ES** OR 1.55				
Kapral et al 2008[136]	Austria 2006	**Endoscopist <50 ERCPs per year**				
Wang et al 2009[138]	China 2006-7	**Female** OR 1.52	**Periampullary diverticulum** OR 2.02	**Cannulation time > 10min** OR 1.51	**≥1 Pancreatic deep wire pass** OR 1.80	**Pre-cut ES with needleknife** OR 2.70
Glomsaker et al 2012[139]	Norway 2007-9	**Pre-cut ES** OR 3.01	**Older age**	**Increasing comorbidity**	**>150 ERCP per year in center** OR 1.74	**No treatment for CBDS** (Treatment for CBDS, OR 0.46)

RR= Risk Ratio

7.4.2 Risk factors for Post-ERCP Pancreatitis (PEP)

PEP is the best known complication associated with ERCP. In 1975[156], a retrospective study reported a 7.4% frequency of acute pancreatitis following ERCP, and a systematic review[18] in 2007 indicated that PEP was the most common complication reported, with a frequency of 3.47%. Risk factors were studied in some multicenter studies (**Table 3**). The identified independent risk factors included suspected SOD, biliary/pancreatic pain, young age, pre-cut sphincterotomy, normal bilirubin, history of PEP, difficult or failed cannulation, pancreatic duct injection, pancreatic sphincterotomy (particularly of the minor papilla), balloon dilatation of an intact sphincter, absence of chronic pancreatitis, more than 10 cannulation attempts, failed removal of CBDS, trainee involvement, and cannulation of the main pancreatic duct[24, 86, 133, 134, 138, 139, 155, 157-159]. Moreover, the presence of more than one risk factor can increase the risk dramatically[86].

Table 3. Significant risk factors that predicted pancreatitis after ERCP, based on multivariate regression analysis results from prospective, multicenter studies

Study	Country	Risk factor 1	Risk factor 2	Risk factor 3	Risk factor 4	Risk factor 5	Risk factor 6	Risk factor 7
Freeman et al 1996[24]	USA/ Canada 1992-94	**Suspected SOD**, OR 5.01	**Pre-cut EST**, OR 4.34	**Difficult cannulation** OR 2.40	**Young age** OR 2.14	**No. Of pancreatic contrast-injections**, OR 1.35		
Loperfido et al 1998[133]	Italy 1992-94	**Small bile duct** RR # 3.79	**Age < 70 years**, RR 2.87	**Pancreatic opacification** RR 2.90				
Freeman et al 2001[86]	USA 1995-98	**History of PEP** OR 5.35	**Biliary BSD*** OR 4.51	**Moderate to difficult cannulation** OR 3.41	**Pancreatic EST** OR 3.07	**≥1 pancreatic contrast injections** OR 2.72	**Female gender** OR 2.51	**Abscence of chronic pancreatitis** OR 1.87
Masci et al 2001[134]	Italy 1997-98	**Failed removal of CBDS** OR 3.35	**Pre-cut ES**, OR 2.80	**Age ≤60 years** OR 2.11				
Williams et al 2007[155]	England 2004	**Cannulation attempts >1 vs. <1** OR 3.14	**Female gender** OR 2.22	**Hospital type DGH§ vs. University** OR 2.41	**Age (per 5 year decrease)** OR 1.02			
Cheng et al 2006[157]	US 2004	**Minor papilla ES** OR 3.8	**Suspected SOD** OR 2.6	**History of PEP** OR 2.0	**Age<60 years** OR 1.6	**≥2 pancreatic duct injection** OR 1.5	**Trainee involve-ment** OR 1.5	
Wang et al 2009[138]	China 2006-7	**Pre-cut ES with needle knife** OR 4.34	**≥1 Pancreatic deep wire pass** OR 2.77	**Female** OR 1.84	**Cannulation-time > 10 min** OR 1.59			
Testoni et al 2010[159]	Italy 2007	**>10 attempts cannulating Vaters papilla** OR 14.9	**Previous PEP** OR 8.7	**Pre-cut ES** OR 3.1	**Main PD$ cannulation** OR 2.1	**Biliary/ pancreatic pain** OR 1.9		
Glomsaker et al 2012[139]	Norway 2007-9	**Pre-cut ES** OR 2.82	**Stent place-ment in PD** OR 1.88	**>150 ERCP per year in center** OR 1.70	**Lower Comorbidity rate**			

* BSD=Ballon Sphincter Dilatation, # RR= Risk Ratio, § DGH=District General Hospital, $ PD= Pancreatic Duct

7.4.3 Can PEP be prevented?

The first, most important goal is to apply ERCP in patients with an appropriate indication[160] and to use non-invasive techniques as diagnostic tools whenever possible. Second, it is important to estimate risk prior to the ERCP to avoid procedures that might increase risk (**Table 3**). When it is necessary to perform an ERCP in a high-risk patient, several lines of evidence have suggested that a pancreatic stent can decrease the risk of complications[161-163], particularly the development of severe pancreatitis. In patients with gallbladder stones, where a laparoscopic cholecystectomy is indicated, a combined one-stage laparoscopic-endoscopic "Rendez-vous" procedure is a good alternative[164]. Fredrik Swahn and co-workers[67] have shown that this method reduced the incidence of PEP.

7.4.4 Technical and pharmacological factors

The use of diathermia during an EST induces thermal injury to the papilla. In the early ERCP era, there was evidence that PEP was associated less with the use of pure cutting current than with the use of blended current[165]. Modern automatic current delivery systems have eliminated this problem in many ways, but the operator should be careful not to use excessive heat in the papilla.

The pre-cut EST procedure remains controversial, particularly in inexperienced hands. An early pre-cut can reduce the incidence of PEP[166, 167], but not the incidence of overall complications[167]. Furthermore, a meta-analysis showed that the overall cannulation success rate did not improve with the pre-cut EST[166].

A guide-wire is widely used in performing a cannulation. In a meta-analysis study, Cheung et al[168] reported that lower PEP rates were associated with a guide-wire, compared to conventional contrast agents, for guiding cannulation. In addition, they reported higher cannulation success rates and less PEP after pancreatic duct entry with the guide-wire approach.

Several pharmacological agents have been tested for preventing PEP[158, 169-172], but no regimes have been generally accepted and implemented. However, the ESGE[173] have recommended in their guidelines that, to prevent PEP in high-risk patients, clinicians should administer non-steroidal inflammatory drugs (NSAIDs), use specific cannulation techniques, and place temporary pancreatic stents.

7.4.5 Risk factors for cholangitis

Cholangitis as a complication of ERCP that can be challenging to diagnose; thus, reports of this complication differ. Cholangitis can be both an indication and a complication. PEP occurs directly, within the first hours after ERCP, but cholangitis can occur as a fulminant, uncontrolled sepsis within the first hours of an ERCP, or alternatively, it can occur days or even weeks later. It can be difficult to recognize mild cholangitis in a patient with multi-morbidity.

The main risk factors for cholangitis are failure to drain or incomplete drainage[24, 157]. With plastic stents in particular, stent failure and occlusion are often associated with secondary cholangitis[174], but these complications are often not reported. Freeman et al[24] reported risk factors for cholangitis, including jaundice, a

procedure with combined PTC and ERCP, and lack of endoscopist experience. It may be logical to introduce antibiotics as a prophylactic for preventing post-ERCP cholangitis. However, the use of antibiotics does not appear to be systematic[175]. A meta-analysis performed in 1999[176] concluded that antibiotics could reduce the incidence of bacteremia, but not sepsis/cholangitis. A more recent meta-analysis[177] concluded that prophylactic antibiotics can reduce bacteremia and may prevent cholangitis and septicemia after ERCP, but the effects are difficult to discern in patients with uncomplicated ERCP. They recommended that future research should determine whether antibiotics would be effective during or after an ERCP that failed to relieve biliary obstruction.

7.4.6 Risk factors for bleeding

Most bleeding entails oozing from the EST site, with no or minor clinical consequences. When bleeding requires an intervention (injection of epinephrine and/or a clip), the complication should be recorded and reported; but this definition is unclear, or at least difficult to implement in a registry. Arterial bleeding, which stops spontaneously, can be challenging to identify, because it resembles a temporary pause due to a vessel spasm. Known risk factors for bleeding include general coagulopathy, anticoagulation <3 days after ES, presence of cholangitis prior to ERCP, bleeding during EST, and a low ERCP case volume[132]. An important way to prevent bleeding is to avoid a fast “zipper cut”[51] and perform a controlled, slow EST.

7.4.7 Risk factors for perforation

Clinically relevant perforations are dangerous; the main risk factor is a difficult cannulation. A likely risk factor for bowel perforation is a previous gastric Billroth II resection[132]. According to Enns et al[178], risk factors for perforations include a suspected SOD, older age, a dilated bile duct, EST, and long procedure duration. Surgery is typically required for esophageal, gastric, and duodenal perforations, but rarely for EST and guidewire perforations[178].

7.4.8 Risk factors for cardiac-, vascular- and pulmonary complications

According to Freeman et al[132], death from ERCP is rare, but it is most often related to cardiopulmonary complications. In a large series of reported (**Table 1**) complications, cardiovascular and pulmonary events were never or rarely reported. Christensen et al[40] specifically focused on these events, and they reported a frequency of 2.3%. Interestingly, a Danish group[40] and Swedish group[41] reported a 30-day mortality rate of 5.8% and 5.9%, respectively. The causes of death were not stated, but there is reason to believe that the frequency might be explained by death from causes other than the primary disease. Interestingly, it is challenging to determine when a death is related to the procedure. In a study by Colton et al[21], a patient underwent a repeat procedure with EST and a balloon sweep to clear a metallic stent. The patient had a myocardial infarction 3 days later and died. A peer review committee concluded that

the death was not attributable to the ERCP. This illustrates a need for more consistent definitions for procedure-related death.

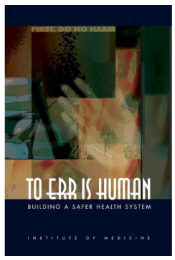
7.5 Strategies for reducing complications

Freeman[132] stated that complications can be reduced by taking the following actions:

i. *Improve training*
ii. *Encourage endoscopists and endoscopists in training to pay more attention to potential risk factors*
iii. *Carefully consider indications for the ERCP*
iv. *Refer complex or high risk cases to centers of excellence with appropriate competence and skills*
v. *Reduce the number of endoscopists that perform ERCPs to increase the individual case volume*

Although all these actions are feasible, their implementation may vary considerably in different countries. Variability may be due to many factors, including the type of health care system, national traditions, geography, travelling distance, personal opinions, and local circumstances, to mention a few.

7.5.1 Safety and safety culture



The book "*To err is human*", by the Committee on the Quality of Health Care in America[179], has been regarded as an important wake-up call. It

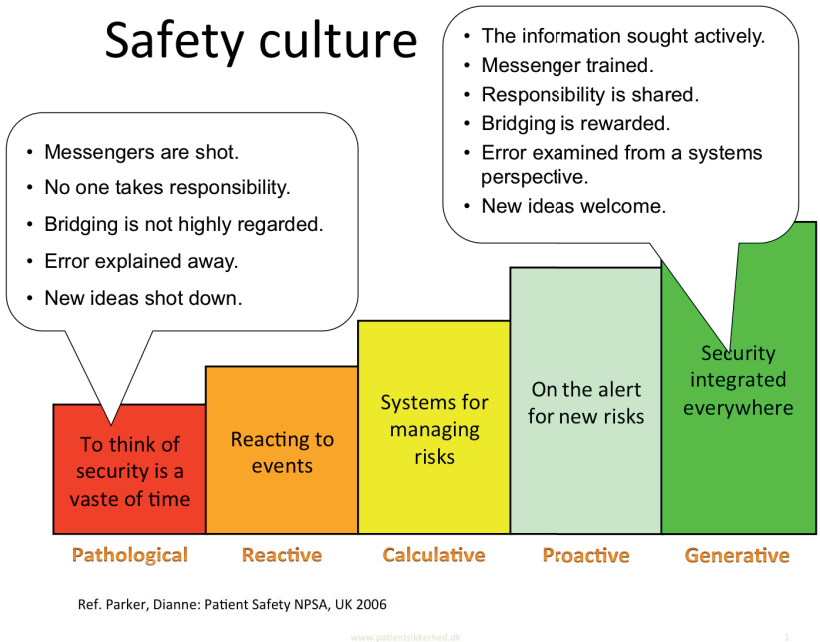
has started a new era with regard to patient safety. Great concern has arisen over the morbidity and mortality reports from hospitals. It has been challenging to find a successful way to improve these rates.

The WHO has addressed this problem with the surgical checklist[44], which showed that a simple change in practice can greatly reduce undesired events. The rectal cancer registry in Norway[180] has proven that a focus on standardization and registration of surgical techniques can improve surgical outcome. It is difficult to calculate how much the registration alone (a Hawthorne effect, if it exists[181]) has influenced the results; however, the centralization of data has initiated a manner of self-justification, by promoting an open dialogue for discussing outcomes.

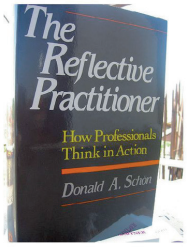
In all Norwegian hospitals, there is a system for reporting undesired events. One concern is that there are differences between departments and hospitals in the numbers and types of reported events. Peter Hjort[182] showed that a significant number of undesired events occur in Norwegian hospitals.

An interesting field of research is the investigation of the role of the "hospital culture" (see 1.5.8) in reporting and dealing with safety. Kirk et al[8] have shown that it is important to improve this culture. When one does not recognize a problem, it is difficult to resolve. Conversely, when one actively looks for challenges in daily activities, and one identifies undesired events with the goal of improving quality, then not unsurprisingly, more events will be reported. The **Figure 1**, adapted from Dianne Parker, UK, illustrate some of the challenges.

Figure 10. Safety culture in organizations



To improve patient safety, the whole team must be involved and know what to look for in preventing undesired events. In healthcare, as in other practical fields, the individual professionals involved are mainly responsible for quality.



In his book, Donald Schön[183] described the quality generated at the moment healthcare is given, and how "*reflection in action*" is important in every situation. It is important to have a good health organization and an excellent team, but we often underestimate the skills and performance of the individuals directly responsible.

Anesthesiologists stress the focus on safety, particularly the pre-procedure evaluation in children and older patients with comorbidity[14].

7.6 Sedation for ERCP

Most patients need some sedation to tolerate an ERCP procedure. There are different approaches to sedation; for the majority of cases in Norway, the policy is to use a benzodiazepine, often in combination with an opiate. In other countries, sedation with Propofol is used more frequently [41]. It has been difficult to show clinical differences in the safety of these drugs, but there are differences[184, 185] in administration routines, in recovery times, and in pain experience[19]. The main challenges are the pre-procedural evaluation and the peri-/post-procedural observations in patients with increased risk of developing complications and/or pain. It is also a question about costs and organization.

7.7 Guidelines in ERCP

In Norway, we have no national, updated guidelines for ERCP practices or education. The book published by the Scandinavian Association of Digestive Endoscopy (SADE) gives advice for some issues, but it is not systematically updated. In most cases, international guidelines are used when they exist; in practice, the guidelines most commonly used are those developed by the European Society of Gastrointestinal Endoscopy (ESGE)[173, 186-188] and the American Society of

Gastrointestinal Endoscopy (ASGE)[85, 189-191], and national societies adapt[192] to these. This practice may be complicated, because those guidelines were based on evidence from other populations and different health care systems. The reference program[115] from Denmark gives some advice on the treatment of gallstone disease, with evidence-based recommendations. Interestingly, some surgical societies, like The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), have also published important guidelines on both ERCP and surgery[193].

7.8 Proposed quality Indicators for ERCP

To develop a national registry in a QA program, it is essential to identify core indicators that can be registered and evaluated. Baron et al[15] introduced a set of quality indicators, based on existing evidence. These will change over time, and they will be based on evidence from well-conducted scientific studies. As shown by Petersen[194], quality indicators are necessary and important in setting up QA programs.

Textbox 2

Quality Indicator	*Grade of recommendation**
1. *Appropriate indication*	*3*
2. *Informed consent*	*3*
3. *Assessment of procedural difficulty*	*3*
4. *Prophylactic antibiotics*	*2B*
5. *Cannulation rates*	
-Desired duct	*1C*
-Use of precut	*2C*
6. *Extraction of common bile duct stones*	*1C*
7. *Biliary stent placement*	*1C*
8. *Complete documentation*	*3*
9. *Complication rates: Pancreatitis, bleeding, perforation, and cholangitis*	*1C*

**Adapted from Guyatt G, Sinclair J, Cook D, Jaeschke R, Schunemann H, Pauker S. Moving from evidence to action: grading recommendations—a qualitative approach. In: Guyatt G, Rennie D, eds. Users' guides to the medical literature. Chicago: AMA Press; 2002. pp. 599-608.*

8. Data collection and validation

8.1 Gastronet

Gastronet (http://www.kreftregisteret.no/en/research/projects/Gastronet/) is the QA platform in endoscopy for the Norwegian gastroenterological association. Gastronet is an important network between Norwegian hospitals. From October 2012, Gastronet has gained status as a National registry in endoscopy (colonoscopy and ERCP). The main focus is on quality improvement of gastrointestinal endoscopy services. The Gastronet secretariat receives paper-based reports on gastrointestinal endoscopic examinations from approximately 30 hospitals in Norway. Matching reports from each examination are received from the patients. These reports include scores on service, discomfort, and pain. This concept was developed from the quality assurance programme in the Norwegian Colorectal Cancer Prevention (NORCCAP) study. The endoscopy data and patient reports are scanned, and data are stored in the Gastronet database. The Gastronet concept (particularly the patient reports) has been used in several research projects.

8.2. Methodological considerations

Voluntary registration

Gastronet is a voluntary network of professionals with enthusiastic interest in endoscopy. All reporting is based on voluntary participation. The Gastronet network owns all data generated.

Gastronet has no authority to use sanctions or force centers to participate or improve the registration rate. Through meetings, results are reviewed, and center-specific challenges are discussed. This has been well received, and it has motivated the continued involvement of participants. It is a challenge to volunteer to participate in a registry, when all procedures must be included. Everyone involved must do the job necessary to ensure a quality registry. Unfortunately, it has proven to be a major challenge, particularly in the largest hospitals, to motivate all endoscopists to volunteer. Consequently, when we examined risk factors, it was necessary to exclude data from three centers due to insufficient consecutive registration. If we had a government mandate for registration and reporting, like e.g., The Cancer Registry of Norway, we would have potential sanctions to impose on non-participating centers and centers that showed insufficient quality in daily registration.

Paper or electronic registration form

In the last 10 years, we have performed surveys on Norwegian ERCP units to obtain input on how to organize a registry. In 2003, a majority believed that it was time for

an internet-based registry. This was initiated, but there were a number of challenges related to implementation. First, in 2003, Norwegian hospitals did not have the technology to use the internet for completing the registration procedure. Second, it was difficult to get a reliable server. Third, it was not possible to reconstruct incorrect registrations. There was also some concern about data security. That initial experience with electronic registration convinced us to use a paper form; thus, from 2007, the Gastronet registry was based on paper forms, until improved data solutions were available. Paper registration allows the endoscopist to complete the registration, independent of computer systems at the time of the procedure. The form can easily be taken up after 30 days for completion, and errors can be corrected. It also facilitates explaining in writing how complications were handled.

However, the paper form also has drawbacks. For example, they lack the ability to access a "popup" menu, which makes it easier to follow the uniform definitions. Also, it is complicated to automate the handling of records with periodic reports and statistics. Scanning and manual handling are time-consuming and expensive. In an electronic form, variables can be set to “compulsory” to ensure these are completed before the user can proceed; this feature can be used to avoid missing data. In a paper form, variables can be “skipped over”, and it is difficult to reconstruct them when entering the data into the database.

An important reason for using paper forms was the ability to match the endoscopist’s report with the patient’s report. This matching would have been

complicated with an electronic reporting system, due to mechanisms for maintaining data security and patient anonymity.

Registration variables and logistics

What variables should be registered? Principally, the general opinion was that only important, core variables should be registered, and registration must be feasible, as described by Naylor et al[195]. Feedback from network members has strongly indicated that it would be difficult to expect endoscopists to complete a form that exceeds one A4 page. This was the starting point when the registration form was drafted in 2006. A strict prioritization of included variables was undertaken. Over the nearly six years of registry existence, only minor revisions have been made, based on continuing discussions. We have not conducted a basic revision in the interest of maintaining a time period with constant variables. With our current experience, it is clear that more parameters should have been included from the start, like difficulty, repeat-procedures, a more exact diagnosis code/procedure code, and use of antibiotics. We should also have had more accurate registration of clinical successes and consequences. Moreover, we have identified some parameters as not useful.

Limitations of the registry

An important limitation of our registry is the fact that we do not have the option of identifying a patient after they have been registered into the database. Thus, is not possible to follow a patient from a given procedure to subsequent events, like surgery, death, other complications, or readmissions after 30 days. It is also

impossible to go back to the original file for quality control and validation purposes. Many patients are aged and seriously ill, either due to comorbidity or to the diagnosed disease. This has been an argument for not including patient consent as a requirement for registration in this database. Discussions of this question have been conducted on a national level, and this process is ongoing. Based on data from Denmark[40] and Sweden[41], the 30-day mortality after ERCPs is above 5%; it is of great interest to follow this group of patients and assess the outcome in our country. A registry that permitted following the whole course of patient treatment would provide more information about safety and risks related to the ERCP procedure. The optimum logistics would be to construct direct, automatic communication with the Death registry, The Norwegian patient registry, and the National cancer registry. In Sweden[41], they have permission to link to the Death registry. Our data have indicated that, despite an accurate follow up, the 30-day mortality was underreported.

9. Statistical analysis

PASW Statistics 18.0 for Mac (SPSS Inc., Chicago, IL) was used for all statistical analyses. Descriptive statistics are presented as numbers and percentages. Also, as appropriate, median or mean values are given, with the range or inter quartile range (IQR). Chi-square or Fisher's exact tests were applied, when appropriate, to compare categorical variables; the Mann-Whitney U test was used for comparing continuous variables. Risk factors were analyzed with univariate logistic regression analyses. Variables with a $p<0.25$ in univariate analyses were included in multivariate logistic regression modeling. Both stepwise forward and backward selection procedures were performed to identify variables that should be included in the final model. A case-wise process was used to delete cases with missing values. Goodness-of-fit was verified by the Hosmer-Lemeshow test. Risk is presented in terms of the odds ratio (OR) and 95% confidence interval (CI). All test results were two-tailed, and statistical significance was defined as $p<0.05$.

10. Aims of the studies

I. Describe national ERCP figures in Norway over the period of 1998-2008

II. Describe and evaluate the routine clinical ERCP practice in Norway over a 3-year period from 2007 to 2009

III. Evaluate the incidence of complications and (30-day) mortality, and identify possible risk factors for these undesired outcomes after ERCP.

IV. Evaluate patient-reported outcome measures (PROMs) with a focus on experienced pain and patient satisfaction after ERCP, and identify predictors of pain and dissatisfaction.

11. Results

11.1 Results of Study I

Glomsaker T, Søreide K, Aabakken L, Søreide JA.
A national audit of temporal trends in endoscopic retrograde cholangiopancreatography in Norway.
Scand J Gastroenterol 2011; 46:116-21.

Four national surveys were conducted during the 11-year study period, and all Norwegian hospitals participated. A total of 42,260 procedures were reported (average 3842 procedures per year, range 3492-4632). The number of hospitals that offered ERCP decreased from 41 to 35, and the annual number of procedures decreased by 13% (from 4632 to 4036), but the number of ERCP-endoscopists remained constant at ~100. The proportion of procedures performed by surgeons decreased from 40% to 32% ($p<0.001$) during the first half of the study period; the number of GI surgeons that performed ERCP remained constant in the latter half of the study (46% and 48% for 2004 and 2008, respectively). In 2004, 15 endoscopists enrolled in a formal ERCP training program, including 8 (53%) surgeons. This number increased to 21, including 10 surgeons (48%) in 2008. Regional variations in ERCP volumes leveled off over the study period. Despite the decrease in ERCP procedures and hospitals that offered ERCP over time, the proportion of low- and high-volume centers remained constant.

11.2 Results of Study II

Glomsaker T, Søreide K, Hoff G, Aabakken L, Søreide JA.
Contemporary use of endoscopic retrograde cholangiopancreatography (ERCP): A Norwegian prospective, multicenter study.
Scand J Gastroenterol 2011;46:1144-51.

A total of 3781 procedures, performed at 14 hospitals, were registered during the 3-year study period. Reliable data from 3683 procedures were available for evaluation, including 53% females and 47% males. In 2488 (67%) ERCP procedures, patients were at least 60 years old. High comorbidity (ASA score 3-4) was observed in 33% of patients. The main indication for ERCP was the need to evaluate and treat bile duct-related symptoms and signs. Successful bile duct cannulation was achieved in 89% of patients. A pre-cut was used in 5% of the procedures, and a guidewire was employed to facilitate duct access in 61%. The median total procedure time was 28 min (IQR 19-40). Urgent ERCP procedures were performed outside normal working hours in 2% of cases. CBDS or anatomical strictures of the bile ducts were diagnosed in over 75% of the procedures. Specific diseases related to the pancreatic ducts were reported in only 6% of cases. EPT of the bile duct was performed in 46% of procedures. In addition to EPT, CBDS treatment and insertions or alterations of bile duct stents were the most common procedures.

The study population included a large proportion of patients that were older and had significant comorbidity. Patient selection, indications, and procedures used in

Norway were consistent with international guidelines and recommendations. Disease patterns partly differed from those reported in middle Europe and the US.

11.3 Results of Study III

Glomsaker T., Hoff G., Kvaløy JK., Søreide K., Aabakken L., Søreide JA. Patterns and predictive factors of complications after endoscopic retrograde cholangiopancreatography (ERCP).
Br J Surg, *DOI: 10.1002/bjs.8992, Epub Date, 2012/12/12*

This prospective, multicenter, cohort study was conducted in 11 Norwegian hospitals, located in universities and general districts. The prevalence and risk of complications and (30-day) mortality from ERCP were assessed with uni- and multivariate regressions.

Out of 2808 ERCP procedures, 2573 (91.6%) were therapeutic. Over half the patients were 70 years or older. CBD cannulation was achieved in 2557 (91.1%) procedures. Complications occurred in 327 (11.6%) procedures, including cholangitis (n=100; 3.6%), pancreatitis (n=88; 3.1%), bleeding (n=66; 2.4%), perforation (n=25; 0.9%), and cardiovascular-respiratory events (n=32; 1.1%). The multivariate regression analysis showed that severe complications could be predicted by older age, high ASA score, center volumes greater than 150 ERCP procedures annually, and pre-cut sphincterotomy. Overall, the 30-day mortality was 2.2% (63 patients), with a possible procedure-related mortality rate of 1.4% (39 patients). Malignancy was diagnosed in 46 (73.0%) patients that died.

ERCP carries a considerable risk of complications. Morbidity and mortality are related to patient age and comorbidity, hospital volume of ERCP procedures, and the type of intervention.

11.4 Results of Study IV

Glomsaker T., Hoff G., Kvaløy JK., Søreide K., Aabakken L., Søreide JA. Patient-reported outcome measures (PROMs) after Endoscopic Retrograde Cholangiopancreatography (ERCP): a prospective, multicenter study. ***Submitted, 2012***

Between 2007 and 2009, prospective data were recorded from consecutive ERCP procedures at 11 hospitals. We analyzed data on patient demographics, clinical characteristics, complications, and information on undesirable events reported during a 30-day follow-up period. Patients completed a short questionnaire the day after the ERCP to report sources of pain, discomfort, and general satisfaction related to the ERCP. Data from 2808 ERCP procedures were included. The patient questionnaire was returned for 52.6% of the procedures; responders and non-responders had similar demographics. Moderate or severe pain was experienced *during* 15.5% and 14.0% of the ERCP procedures, respectively, and *after* 10.8% and 7.7% of the ERCP procedures, respectively. In addition, we identified independent predictors of increased pain *during* the ERCP and predictors of procedure-related pains. These were female gender, endoscopic sphincterotomy (EST), and longer procedure times. The performing hospital was an independent predictor ($p<0.001$) of procedural pain experience. Overall, 98.3% of patients were satisfied with the treatment, and 90.9%

were satisfied with the information provided. However, specific complications after ERCP and pain during or after ERCP were independent predictors for dissatisfaction with the treatment.

12. Discussion

In all fields, technological progress has dramatically changed everyday practice over the last three decades, particularly in healthcare. New developments have appeared so rapidly, that it is highly challenging to generate strong evidence for clinical decisions. In the field of HPB diseases, new approaches in imaging, mini-invasive access, endoscopy, and laparoscopy have changed the field considerably. However, although most developments have improved outcome, improvements in care remain to be realized. Knowledge of basic outcomes and the quality of general clinical practice is important, when evaluating potential changes in disease management.

The main goal of this study has been to provide some basic knowledge and to evaluate ERCP activity prospectively as part of a quality improvement program in the Gastronet network. This study has focused on some of the key research questions for quality assessments cited by Baron[15] . As Naylor et al[195] stated, it is a challenge in busy, everyday, clinical practice to set up a quality assurance program.

Characteristics of ERCP activity

During the study period of eleven years, the number of hospitals that offered ERCP decreased, and the majority of centers had low annual procedure volumes. Regional differences in ERCP activity also decreased during that period. This could be partly be explained by the observation that an increasing number ERCPs were referred to the tertiary center at the Oslo University Hospital ("Rikshospitalet"). This indicated that complex or failed procedures became more commonly referred to a higher

competence level. Another explanation is more agreement of indications and contraindications. There could still be some differences in local ERCP availability.

The patients that received ERCP were older, many had comorbidities, and most were treated in the hospital and not as outpatients. Bile duct-related disorders were the most common indications for ERCP, and CBDS and malignant strictures were the most common diseases treated. The most common procedures were biliary EST and placement of biliary stents. Pancreatic therapy, particularly for SOD therapy, is a rare therapy options in community practices; most cases are performed in tertiary centers. No centers in Norway perform biliary manometry. The success rate of cannulating the desired duct was in line with recommendations[196], but concern remains over low success rates in difficult cannulations, when pre-cut ESTs are used.

National ERCP practice and international standards

The clinical use of ERCP in Norway corresponds well with international reports, particularly those from Europe[23, 40, 41]. A clear difference was in the higher proportion of SOD diagnoses[86] [25] reported in North America. The relatively low overall use of ERCP in Norway[20] may indicate the strict application of indications or limited access to the procedure in some parts of the country.

Current international guidelines emphasize that weekly and annual procedure volumes are important for adequate education and competence[196, 197]. The relationship between procedure volumes and outcomes remains controversial[15, 198], but a relationship is recognized between cannulation success rates and procedure volumes.

In a community setting, it can be difficult to assess how the individual endoscopist's skills might impact outcome, and perhaps this factor is underestimated. It is important to have excellent technical skills, but it is also important to achieve high quality performance, to assess risk adequately in decision-making, and to focus on selecting the right procedure, on the right patient, at the right time. All this comes with experience and competence. In Norway, both gastroenterologists and surgeons perform ERCPs, but gastroenterologists increasingly appear to be more involved than surgeons. Although both surgeons and gastroenterologists are trained, there is no formalized educational program and no accrediting guidelines.

In this multicenter study, we were forced to de-identify patients after registration, due to a mandate from The Norwegian Data Protection Authority. Thus, we did not follow patients longer than 30 days or follow up on complications. We did determine that the centers differed significantly in performance and outcome. Tanner et al[141] described similar differences in a survey in England; this supported the notion that a QA program is needed for all hospitals involved in ERCP. ERCP remains the most dangerous of all endoscopic procedures, and evidence has shown that the risk of ERCP has not decreased over time[18], despite many improvements.

In a voluntary, multicenter registry, registration of daily activity must include all local endoscopists involved in ERCP. Differences in registration between centers can affect assessments of outcome, but there is also a risk that differences may be due to differences in hospital culture regarding safety (chapter 1.5.9). Poor attitudes toward safety can lead to some centers underreporting adverse events. Karina Aase et

al[199] described the culture in Norwegian hospitals regarding safety. They found that Norwegians tolerated a lower level of safety than hospitals in the US and in the petroleum industry.

Complication patterns

ERCP was rapidly accepted in the community, and it is currently used widely. The procedure is less than 50 years old, but from an academic viewpoint, many questions remain related to whether the evidence really supports the wide acceptance of ERCP. **Table 1** shows the reports on complications. Only a few large, multi-center studies were published, and most exhibited several factors that might bias the results. First, the study populations were different, due to the selection process and demographics. Some studies only included patients that required EST, others included more than 30% of patients with SOD. Several had different definitions for complications, and follow up times were different. Thus, it is not clear whether the rates of undesired effects after ERCP are correct. In addition, there was a tendency to claim that the outcome was unrelated to ERCP, and that it was due to other procedures, comorbidity, or the diagnosed disease.

Our results showed that ERCP was associated with undesired events, severe complications, and death. Our numbers were considered low estimations, because some centers may have underreported the adverse events. In general, our results were consistent with other reports, but we observed higher mortality rates than studies from the US. Enochsson et al[41] and Christenen et al[40] showed that the actual 30-day mortality for ERCP was over 5%. The definition of procedure-related death is

unresolved. We found that a majority of deaths during the first 30 days was related to malignancy, and about 50% of deaths occurred during the first 10 days after the procedure.

Risk factors for complications

We identified independent risk factors for severe complications and for pancreatitis. We also investigated risk factors for the most common complications[139]. Our results differed, in some respects, from earlier studies. Morbidity and mortality were related to patient age and comorbidity, the hospital ERCP procedure volume, and the type of intervention. We also showed that the classic categorization of complications and severity described by Cotton 1991[2] could be replaced with a newer classification of surgical complications described by Dindo-Clavien[3]. The latter classification had the advantage that hospitalization time did not influence the grading of severity. Earlier reports on complications and risk factors are based on studies with patient populations that did not represent populations served in Scandinavian practice. This make our results important to set up a QA program for Norway.

A risk analysis with a multivariate regression model presents many challenges. First, the number of events must represent the appropriate statistical power. Second, the variables may not be independent; for example hospital type, annual volume, a specific center, sedation used, were not independent variables. In the statistical evaluation, we tested different variables in the model and used different cut off values to identify the best model. In general, the final results of a risk factor analysis may be influenced by the variables included and the definitions and cut off values for these

variables. The heterogeneity of reports in methods and inclusion of variables, make it difficult to compare and to conclude.

Post ERCP cholangitis, pancreatitis, and pre-cut EST

This study included a large number of patients with post-ERCP cholangitis. However, these data should be interpreted with caution, because there may be differences in the way this specific complication was reported. Cholangitis can be an indication for ERCP, it can be exacerbated by ERCP, and it can develop days to weeks after the procedure. To distinguish between these possibilities, it would be necessary to look closely at the use of antibiotics and definitions. In the future, an improved common understanding of how to report on this condition is warranted.

Pancreatitis is the best known, and most feared complication of ERCP. Improvements in quality will naturally attempt to avoid ERCP in patients at risk, when possible[160]. Our data did not include any death during 30-days for this group, but the group included severe cases consistent with the literature. Younger patients with CBDS that are candidates for cholecystectomy should be considered for a one-stage procedure consistent with surgical guidelines[193]. This approach will present challenges to clinician competence, operating and endoscopy logistics, and technical facilities.

We found that pre-cut EST was a risk factor for severe complications, consistent with many reports. We also found a low cannulation success rate with pre-cut ESTs. It is important to have good working conditions in a complicated

cannulation. It requires an adequately sedated patient. The individual endoscopist must judge when to perform a pre-cut EST, but it is important to be aware of the risk for the patient. This is related to what can be expected and achieved. A low threshold should be used for referring complicated ERCPs or calling a colleague.

Self-reported patient experiences

Nearly one third of the patients in our study (Paper IV) reported moderate to severe pain during the procedure, consistent with other reports[19]. We identified several risk factors for pain related to ERCP, including patient characteristics, procedural difficulties, and organizational factors. It is difficult to estimate how much pain and discomfort is acceptable. We have identified significant differences in pain levels between centers, and also among different sedation regimes. The literature is sparse on patient-reported outcomes related to ERCP[19, 21-23]. However, in an era when patients expect to take part in decisions regarding treatment, it is crucial to have accurate information on sedation and treatment alternatives. In developing new methods for measuring overall patient satisfaction, the evaluation of pain is a prominent, important factor.

Conclusions

This study has provided important new knowledge about ERCP activity in Norwegian hospitals. We estimated the prevalence of ERCP activity, described the demographics, and provided a pattern of indications and procedures. Moreover, we have described morbidity and mortality related to the procedure, although those

figures may be regarded as minimum estimations. Based on the collected data, we identified potential risk factors for complications and pain. In an international context, these national data add to the understanding of ERCP as an invasive tool.

This study revealed that differences exist in the use of various procedures, and also in reported outcomes. The latter may be true differences, but may also reflect different institutional viewpoints on safety, different understandings or definitions of indications, or different follow-up procedures applied at different hospitals.

The results clearly showed that ERCP remains a dangerous endoscopic procedure, and further research and QA programs are required. The Gastronet and a national ERCP registry may play an important role in the future. Through mutual effort and contributions from all involved, improving quality in all aspects is likely to translate into improved safety and better outcomes for patients referred for ERCP.

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14. Appendix

Registration form *(in Norwegian)*

Legeskjema, Gastronet, ERCP ***Mottatt samtykke*** ☐

Skjemaet fylles ut av lege/sykepleier og sendes
Elin Hørtha STHF *etter 1 mnd komplikasjonsregistrering*
(Versjon 290110)

10

Navnelapp

Skjemanr ☐ Senternr ☐ +

Us.dato: ☐☐☐☐☐☐ Ø.hjelp utenom kjernearbeidstid ☐ CO2 til insufflering ☐ Luft insufflering ☐

Pasient skjema delt ut; Ja ☐ Nei ☐ Dersom "Nei", årsak; ☐

ASA-score

1 (frisk) ☐ 2 (mild syst sykd) ☐ 3 (alvorlig syst sykd) ☐ 4 (svær syst sykd) ☐ 5 (moribund) ☐ +

Indikasjon

Terapi av galleveier ☐ Terapi i pancreas ☐ Terapi i papille ☐ Prøvetaking ☐ Komplik.etter kirurgi ☐

Sedasjon

Midazolam ☐,☐ mg Diazepam ☐,☐ mg Pethidin ☐☐ mg Propofol ☐☐ mg

Rapifen ☐,☐ mg Fentanyl ☐☐☐ mikrog Oxynorm ☐,☐ mg Annet: ☐

Gjennomføring

Kanylering	*galle*	*pancreas*	***Prosedyre***	*Galle*	*Pancreas*	
Ønskelig	☐	☐	Sfinkterotomi	☐	☐	
Gjennomført	☐	☐	Dilatasjon	☐	☐	
Precut for tilgang	☐		Steinbehandling	☐	☐	
Guidewire for tilgang	☐		Stentplassering	☐	☐	Metall ☐
VED EPT; Skjæring	☐		Stentskifting	☐	☐	
Blandet strøm	☐		Stentfjerning	☐	☐	
Koagulasjon	☐		Prøvetaking	☐	☐	

Total prosedyretid min ☐☐ Annet: ☐

Er målsettingen med u.s. oppnådd: Ja ☐ Nei ☐ komm.: ☐

Funn	*galle*	*pancreas*
Normale funn	☐	☐
Stein	☐	☐
Striktur	☐	☐
Lekkasje	☐	☐

Annet: ☐

Komplikasjoner (kryss av **"Ingen"** eller fyll ut med grad)

Perop: Blødning ☐ Perforasjon ☐ Fastkiling ☐
Kardiovask ☐ Respiratorisk ☐ **Ingen** ☐

Postop: Dato (oppstått/oppdaget) ☐☐☐☐☐☐ +
Pankreatitt ☐ Kolangitt ☐ Blødning ☐
Kardiovask ☐ Respiratorisk ☐ **Ingen** ☐

Stentokklusjon: ☐ Stentperforasjon: ☐
Annet (Sett kryss, evt skriv bak på arket): ☐

Alvorlighetsgr: 1) ingen konsekvens ☐ 2) Direkte (perop) endoskopisk interv ☐ 3) (Forlenget) innlegg ☐
4) Kirurgisk behandling ☐ 5) ERCP-rel.mors ☐ 6) død 30 dgr post-ERCP ☐

Grad av konsekvens for pas:

1)Ingen mén ☐ 2)Varig mén ☐ 3)Mors ☐

Kommentarer (sett kryss og evt skriv bak på arket): ☐ +

+

Lege 1: ☐☐☐☐☐☐ Lege 2: ☐☐☐☐☐☐ Spl 1 ☐☐☐☐☐☐ Spl 2 ☐☐☐☐☐☐

+ +

Pasientskjema, Gastronet, ERCP
Dette skjemaet ber vi deg fylle ut og returnere
i vedlagte svarkonvolutt **dagen etter undersøkelsen**
(Versjon 290110)

10

Navnelapp

Skjemanr Senternr Us dato

Lege 1 Lege 2 Spl 1 Spl 2

1 ***Er du fornøyd med behandlingen du fikk?*** Ja Nei +

2 ***Var undersøkelsen ubehagelig?***

Nei

Ja litt Middels Svært ubehagelig

3 ***Har du hatt magesmerter eller annet ubehag etter undersøkelsen?***

Nei

Ja litt Middels Svært mye

Hvis ja, beskriv plagene nøyere!

Hvis ja, hvor lenge varte plagene?

Under 1 time 1-3 timer 3-6 timer Mer enn 6 timer

4 ***Er du fornøyd med informasjonen du fikk om undersøkelsen?*** +

Ja Ikke helt Nei

Kommentarer og forslag til forbedringer