Universidade do Minho
Escola de Ciências da Saúde

Luís Miguel da Silva Araújo Lopes

NEEDLE-KNIFE FISTULOTOMY IN DEEP BILIARY CANNULATION

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Tese de Doutoramento em Medicina

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"If you are not willing to learn, no one can help you. If you are determined to learn, no one can stop you."

Zig Ziglar

À Manuela, como sempre

Aos meus filhos, Pedro e Carolina

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Resumo

A colangiopancreatografia retrógrada endoscópica (CPRE) é uma técnica de endoscopia de intervenção frequentemente usada no tratamento de patologia biliar e pancreática. A canulação selectiva da via biliar é um passo determinante numa CPRE. No entanto, mesmo entre endoscopistas experientes, a canulação biliar pode não ser conseguida entre 15% a 35% dos doentes. Nesta situação, se a decisão é de prosseguir com o procedimento, a técnica de acesso de recurso mais utilizada é o pre-corte com faca papilótomo. Esta técnica tem diversas variantes, sendo as mais comuns o pre-corte clássico e a fistulotomia. O pre-corte é um dos assuntos mais controversos em endoscopia digestiva, em termos de segurança, sucesso e *timing* na canulação. Além disso, não existem recomendações sobre qual o treino adequado para a sua aprendizagem, bem como, o número de procedimentos a efectuar para alcançar competência. Os objectivos principais desta tese foram delineados para responder a estes problemas. Deste modo, três trabalhos de investigação foram realizados.

No estudo 1 avaliamos a eficácia e a segurança da fistulotomia, através da análise de uma base de dados de CPREs, num hospital geral com grande volume de CPREs. O estudo envolveu 204 doentes consecutivos submetidos a fistulotomia, entre Novembro de 2006 e Dezembro de 2010.

O estudo 2 testou uma estratégia de fistulotomia precoce *versus* a estratégia mais comum de pre-corte tardio após múltiplas tentativas de canulação. Para tal foi realizado um estudo de *cohort* prospectivo, entre Janeiro de 2011 e Fevereiro de 2012, envolvendo 350 doentes com papilas naive, sendo estes alocados de forma equitativa a uma das estratégias, por uma pessoa independente, não envolvida no estudo. Os principais *outcomes* medidos foram: taxa de canulação biliar, sucesso da fistulotomia, complicações pós-CPRE e a duração da CPRE.

No último estudo, a curva de aprendizagem da fistulotomia de três endoscopistas foi analisada de forma a obter padrões que poderiam auxiliar na formulação de recomendações para a aprendizagem. Entre Novembro de 1997 e Março de 2011, as primeiras 120 fistulotomias realizadas por cada um dos endoscopistas, em vários hospitais, foram selecionadas (360 doentes). Cada grupo de 120 doentes foi ordenado de forma cronológica para reconhecimento de tendências.

A fistulotomia é uma técnica eficaz e segura para facilitar o acesso à via biliar no contexto de uma canulação biliar difícil; nos doentes com vias biliares finas (≤ 4 mm), deverão ser tomadas medidas adicionais de prevenção de pancreatite pós-CPRE. Uma estratégia de fistulotomia precoce diminui de forma significativa a duração da CPRE, sendo comparável em termos de eficácia e segurança em relação a uma estratégia clássica de uma fistulotomia tardia. Caso uma canulação biliar não seja conseguida nos primeiros 5 minutos, a primeira opção poderá ser passar de imediato para uma fistulotomia. Um endoscopista com experiência em CPRE pode aprender a fistulotomia sem dificuldades e com poucas complicações; no entanto, recomendamos um treino estruturado a todos os futuros endoscopistas de intervenção, em centros com grande volume de CPREs. Propomos a realização de 20 fistulotomias supervisionadas antes da avaliação da competência; esta implicaria um sucesso primário na fistulotomia acima dos 70%.

Estas recomendações apenas se aplicam a centros com grande volume de CPREs e com experiência em fistulotomias. Como tal, advertimos sobre os riscos da aplicação destas recomendações por endoscopistas pouco experientes ou em centros de baixo volume.

Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic interventional procedure commonly used in the management of biliary and pancreatic disorders. Selective cannulation of the common bile duct (CBD) is the hallmark for a successful biliary ERCP. However, even in experienced hands, biliary cannulation may fail in up to 15%-35%. If the decision is to continue with the procedure, needle-knife precut has become the method of choice in achieving a CBD cannulation. The two most common variations are the classic precut and the needle-knife fistulotomy (NKF). This rescue method is however one of the most debatable issues in endoscopy in terms of safety, success and optimal timing in the cannulation. Moreover, there is no consensus on what constitutes adequate training for precut, as well as the number of procedures required to achieve technical competency. The main objectives of this thesis were delineated to help clarify these problems. Consequently, three studies were carried out.

In the first study, the success and safety of NKF was assessed from the analysis of an ERCP database, in a high-volume general hospital. The study involved 204 consecutive patients, submitted to NKF between November 2006 and December 2010.

The second study assessed an early fistulotomy strategy against the current practice of a late precut after multiple biliary attempts. This prospective cohort study, between January 2011 and February 2012, involved 350 patients with naive papilla, equally assigned to one of the two strategies by an independent person not involved in the study. Biliary cannulation rate, NKF success, post-ERCP complications and ERCP duration were the main outcomes.

Lastly, the third study analyzed the learning curve of three endoscopists performing NKF, seeking to obtain patterns to formulate training

recommendations. Between November 1997 and March 2011, the first 120 consecutive NKFs performed by three endoscopists in different centers were selected (360 patients). Each group of 120 patients was chronologically ordered for trends depiction.

NKF is a safe and highly effective method of accessing the bile duct in the setting of a difficult biliary cannulation, however extra caution is required in patients with thin bile ducts. An early precut strategy dramatically decreases the duration of an ERCP, while being at least as safe and effective as a late fistulotomy approach. If a successful biliary cannulation is not achieved within the first 5 minutes, the endoscopist's first choice could be to proceed directly to a fistulotomy. A skillful endoscopist may expect to master NKF easily and with few complications, however a formal training period is recommended for all future ERCP endoscopists in high-volume centers. A minimum of twenty NKFs is proposed to first attest competency, in which a success rate above 70% must be achieved.

These recommendations are not applicable outside high-volume centers, experienced in NKF. Therefore we advise against unwarranted application of these recommendations by inexperienced endoscopists or low-volume centers.

Abbreviations

CT - Computed tomography

ERCP - Endoscopic retrograde cholangiopancreatography

EUS - Endoscopic ultrasound

NKF - Needle-knife fistulotomy

NKP - Needle-knife precut

NSAIDs - Non-steroidal anti-inflammatory drugs

MRI - Magnetic resonance imaging

PEP - Post-ERCP pancreatitis

SOD - Sphincter of *Oddi* dysfunction

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PART I

Introduction

1 ERCP and biliary cannulation

1.1 Introduction and development

In 1968 William S. McCune *et al.* reported the first X-ray pictures of the biliary and pancreatic ducts obtained after cannulation of the ampulla of Vater, using an Eder semirigid endoscope (McCune *et al.* 1968). This disruptive technique was about to dramatically change the diagnosis and therapy of many biliary and pancreatic disorders.

During the next two years Oi and Tagaki *et al.* reported a significant improvement in the technique using a new side-viewing instrument (Oi 1970; Takagi *et al.* 1970). The procedure then spread quickly to Europe and the United States.

In 1974 Kawai *et al.* reported the first biliary sphincterotomy, immediately followed by Classen *et al.* in Germany, pulling ERCP into the therapeutic arena (Kawai *et al.* 1974; Classen & Demling 1974). The incision of the sphincter of Oddi by means of special accessories allowed the development of multiple interventional procedures, which ultimately supplanted many established surgical procedures. ERCP became an accepted option in the treatment of choledocholithiasis and papillary stenosis during the late 1970s (Siegel 1980; Freeman *et al.* 2001). The introduction of biliary stenting in 1980 further expanded its therapeutic applications into the management of biliary obstruction (Laurence & Cotton 1980; Soehendra & Reynders-Frederix 1980).

Meanwhile, innovations in other fields were unfolding. Beginning in the mid-1980s the world assisted a tremendous development in non-invasive imaging of the pancreas and biliary tree. Ultrasound, CT, MRI and endoscopic ultrasound allowed the non-invasive evaluation of suspected biliary and

pancreatic disorders, with increasing accuracy. As a consequence, the indications of ERCP for purely diagnosis purposes almost vanished. In the twenty-first century, ERCP is almost exclusively a therapeutic procedure that should be offered after proper patient selection, in a multidisciplinary environment weighting other alternatives techniques (Bruins Slot *et al.* 1996; Cohen *et al.* 2002). Focus is now shifting decisively to quality improvement and training issues, in order to assure patients receive the best possible treatment by well-trained and skillful ERCP endoscopists. Several professional entities, such as the American Society of Gastrointestinal Endoscopy (ASGE) reflect these trends by developing and updating several quality indicators for ERCP thus considering quality a strategic priority (Johanson *et al.* 2002).

1.2 Biliary cannulation - standard approach

Selective cannulation of the common bile duct (CBD) is the most important and demanding step in a biliary ERCP. This step along with post-ERCP pancreatitis (PEP), have always been the major problems an ERCP endoscopist has faced (Bourke *et al.* 2009; Fazel *et al.* 2003; Udd *et al.* 2010). In the early years, biliary cannulation was performed by means of repetitive probing with a catheter. Subsequently, a variety of cannulation accessories emerged and the available options expanded for the practitioner (Freeman & Guda 2005; Bailey *et al.* 2010; Testoni *et al.* 2011).

Currently, most endoscopists first attempt a deep biliary cannulation using a papillotome often in conjunction with a guidewire (Vandervoort & Carr-Locke 1996; Freeman & Guda 2005; Misra & Dwivedi 2009; Bourke *et al.* 2009). The preference for papillotomes (over catheters) is founded on the higher success rate of deep biliary cannulation and the fact that most ERCPs are now therapeutic (Cortas *et al.* 1999; Schwacha *et al.* 2000; Laasch *et al.* 2003; Misra 2009; Choudhary *et al.* 2014). When this initial approach fails it is common practice to either use a different device, such as a catheter, or try a different type of papillotome or guidewire. The chosen strategy will largely depend on the personal preference of the endoscopist as well as the anatomy of the patient.

The cannulation technique in a standard approach begins with an evaluation of the possible orientation of the common bile duct by inspecting the papillary mound. The papillotome (or a catheter) is advanced and gently inserted in the top left-hand corner in the 11 o'clock direction. After advancing 1 or 2

mm beyond the edge of the papilla, the papillotome should be bowed, and the duodenoscope ajusted, in order to obtain a correct alignment between the axis of the bile duct and the device. Generally at this moment after applying gentle pressure, or gentle tapping, the papillotome is able to pass through the sphincter and pops into the duct. The wire than can be advanced, the direction usually differentiates the biliary from the pancreatic duct. An alternative approach is to use a wire to cannulate the bile duct, sometimes assisted by small injection of contrast in the ampulla to delineate the distal segments, especially if the papilla is small (Bourke *et al.* 2009; Bailey *et al.* 2010; Testoni *et al.* 2011). However, even in experienced hands, biliary cannulation may fail in up to 15%-35% of cases when using a standard approach alone, in the first ERCP (Freeman & Guda 2005; Testoni *et al.* 2011). In this situation, the endoscopist is facing a difficult biliary cannulation and an intraprocedural decision has to be taken regarding the next most appropriate step (Vandervoort & Carr-Locke 1996; Misra 2009).

1.3 Difficult biliary cannulation

The decision to proceed with the ERCP should take into account several factors, including the seriousness of the indication for ERCP, the clinical condition of the patient, the expertise of the endoscopist and the alternative techniques available (Vandervoort & Tham 2006; Misra & Dwivedi 2009). A difficult biliary cannulation is defined as a situation where the experienced endoscopist, using a standard approach, fails within a certain time or after a certain number of unsuccessful attempts (Vandervoort & Carr-Locke 1996; Misra 2009; Lynch & Evans 2010; Udd *et al.* 2010; Testoni *et al.* 2011; Lee *et al.* 2014). In a recent large survey on cannulation techniques conducted in the Scandinavian countries the three most common criteria for a cannulation to be defined as difficult were: time needed, number of biliary attempts and the need to use NKF (Löhr *et al.* 2012). The definition found in previous studies is diverse, arbitrary and depends largely on the judgment of the endoscopist (Johanson *et al.* 2002; Udd *et al.* 2010). The reported time limit varies between 10 to 30 minutes. The maximum number of insertions of a guidewire or contrast injections into the main pancreatic duct varies between three and five, and the set limit for biliary attempts varies between five and ten (Freeman 1997; Kaffes *et al.* 2005; de Weerth *et al.* 2006; Zhou *et al.* 2006; Udd *et al.* 2010; Lim *et al.* 2012). For comparative purposes, this

arbitrary definition is an obvious limitation and it would be important to define objective criteria on this topic in the near future (Akaraviputh *et al.* 2008).

1.4 Advanced cannulation techniques - the precut

When the intraprocedural decision is to proceed with the ERCP, additional cannulation techniques are needed. Precut papillotomy is the most common choice for achieving biliary access after a failed difficult biliary cannulation (Harewood & Baron 2002; Sriram *et al.* 2003; Laohavichitra *et al.* 2007; Robison *et al.* 2007; Akaraviputh *et al.* 2008; Fukatsu *et al.* 2008; Ang *et al.* 2011). There are however other endoscopic options such as persistence with the standard attempts, the placement of a pancreatic guidewire (or stent) to assist the biliary cannulation, transpancreatic sphincterotomy, ampullectomy for duct access and the EUS-guided cholangiography (Goff 1995; Harewood & Baron 2002; Herreros de Tejada *et al.* 2009; Udd *et al.* 2010; Testoni *et al.* 2011; Dhir *et al.* 2012).

Choosing the most appropriate approach depends on the skills of the endoscopist, resources available and the case mix of the department (Hogan 1988; Jowell *et al.* 1996; Bourke *et al.* 2009). Precut papillotomy with a traction papillotome was first reported by Siegel in 1980 (Siegel 1980). This technique was used in 18 of the first 100 patients in which sphincterotomy was performed in his series. In 1986 Huibregtse *et al.* published the first report of a classic precut performed with a needle knife, in a group of 190 patients over a period of four years and a half. In their series, the immediate success in achieving a deep biliary cannulation was 53% (Huibregtse *et al.* 1986).

The utilization of precut varies between centers, from none to as many as 50% of all cannulation attempts in naive papillas (Tweedle & Martin 1991; Freeman *et al.* 1996; Rollhauser *et al.* 1998; Parlak *et al.* 2007). The term 'precut' refers to the action of performing sphincterotomy before CBD access is achieved (Vandervoort & Tham 2006; Parlak *et al.* 2007; Choudhary *et al.* 2014). This rescue strategy comprises several different techniques characterized by an incision in the roof of the papilla in order to expose the bile duct and the biliary orifice (Freeman *et al.* 1996; Sriram *et al.* 2003). There are basically two devices available to perform the precut, namely the Erlangen-type sphincterotome designed by Nib Sohendra and the needle-knife papillotome (Binmoeller *et al.* 1996; Loperfido *et al.* 1998), although other devices were reported (Seifert *et al.* 1999; Heiss *et al.*

2002; Hashiba *et al.* 2004; Liu *et al.* 2013). The most common of these techniques is the freehand needle-knife precut in which the incision is either initiated in the papillary orifice (classic precut), or a puncture is performed directly in the common bile duct a few millimeters above the orifice (needle-knife fistulotomy - NKF) (Freeman *et al.* 1996; Loperfido *et al.* 1998; Lynch & Evans 2010). Studies which have compared these different techniques are also scarce and hampered by the lack of a standardized nomenclature (Loperfido *et al.* 1998; Abu-Hamda *et al.* 2005; Ang *et al.* 2010). Moreover, there is no definite data demonstrating the superiority of an individual precut technique in terms of safety or success (Harewood & Baron 2002; Abu-Hamda *et al.* 2005; Donnellan *et al.* 2010). Theoretically, NKF may present a lower rate of pancreatitis compared with the classic precut, as the pancreatic orifice is avoided. Nonetheless, further studies are required to clarify this issue (Mavrogiannis *et al.* 1999; Artifon *et al.* 2007; Udd *et al.* 2010; Dumonceau *et al.* 2010; Katsinelos *et al.* 2012). The second major approach involves the use of an Erlangen-type papillotome. This device has a very short-nose, measuring less than 1 mm; the catheter tip is inserted in the papillary orifice, and a cut is performed towards the 11 o'clock direction (Sriram *et al.* 2003; de Weerth *et al.* 2006).

2
Rationale for needle-knife fistulotomy in deep biliary cannulation and subsequent studies

There are few issues in endoscopy as controversial as the use of the precut sphincterotomy to gain bile duct access (Bruins Slot *et al.* 1996; Freeman 1997; O'Connor *et al.* 1997; Lim *et al.* 2012). Considerable controversy continues to exist about 'precut papillotomy' in general and 'needle-knife papillotomy' in particular, with some experts warning against the increased risk of complications, namely, bleeding, pancreatitis and perforation (Shakoor & Geenen 1992; Vandervoort & Carr-Locke 1996; Cotton 2010). Although precut is known to increase the overall biliary cannulation rate, several prospective studies refer to precut as an independent risk factor for post-ERCP complications, varying from 2% to 34% (Kasmin *et al.* 1996; Freeman *et al.* 1996; Donnellan *et al.* 2010). In addition, the success of the precut itself also varies in the literature from 53% to 88%, probably reflecting different cannulation techniques attempted for varying lengths of time, before the endoscopist decides to perform the procedure (Vandervoort & Carr-Locke 1996; Kevans *et al.* 2010; Donnellan *et al.* 2012; Kim *et al.* 2012). Two multicenter prospective studies, one from Italy (Loperfido *et al.* 1998) and the other from the United Sates (Freeman *et al.* 2001), which used multivariate analysis found that precut on its own, significantly increased the risk of complications compared with standard sphincterotomy. A meta-analysis from Masci *et al.* demonstrated that

precut was a highly significant risk for post-ERCP pancreatitis even after adjusting for other variables, with a relative risk of 2.7 (Masci *et al.* 2003). However, several reports and three recent meta-analysis, with studies from high-volume tertiary hospitals, report a low percentage of complications, especially pancreatitis (Foutch 1995; Bruins Slot *et al.* 1996; Kasmin *et al.* 1996; Lynch & Evans 2010; Kahaleh *et al.* 2004; Cennamo *et al.* 2010; Gong *et al.* 2010; Choudhary *et al.* 2014). As the use of precut generally follows a difficult cannulation, it remains a matter of debate whether the increased risk is related to the precut itself or is linked to the manipulation of the papilla that precedes it. A difficult cannulation (which is *per se* a risk factor for post-ERCP complications) is characterized by reiterated biliary attempts and/or manipulation (passage of wires and injection of contrast) of the main pancreatic duct (MPD), which is in itself likely to induce trauma, edema and inflammation to the papillary bed, thus obstructing the MPD drainage (Cortas *et al.* 1999; Schwacha *et al.* 2000; Fazel *et al.* 2003; Udd *et al.* 2010).

There are few prospective evaluations of the safety and efficacy of needle-knife precut, and studies of its early use in difficult cannulation have been inconclusive (Abu-Hamda *et al.* 2005; Bailey *et al.* 2010). Furthermore, there is an urgent need to clarify the optimal timing to perform the precut (Vandervoort & Carr-Locke 1996; Fazel *et al.* 2003; Misra & Dwivedi 2009; Dumonceau *et al.* 2010), as the ideal moment remains unclear (Freeman *et al.* 2001; Misra 2009; Choudhary *et al.* 2014). Should it be performed shortly after an unsuccessful 'easy' cannulation, before the risk of PEP escalates rapidly, as some authors argue (Bruins Slot *et al.* 1996; Kaffes *et al.* 2005; Bailey *et al.* 2010); or should we persist with multiple cannulation attempts for a further defined period of time, resorting to NKF only if, after this defined period of time, deep cannulation of the bile duct is not achieved (Misra 2009; Dumonceau *et al.* 2010)? Furthermore, what are the other dimensions of the potential impact of an early precut in the ERCP? For example in procedure duration (Misra & Dwivedi 2009; Dumonceau *et al.* 2010). This is another important topic, rarely addressed, and if an early precut strategy is proven to be as safe and successful as the classic approach, this could have major impact on future recommendations (Sherman *et al.* 1991; Boender *et al.* 1994; Chen *et al.* 1994; Vandervoort & Carr-Locke 1996; Misra 2009). Therefore, there is an obvious need for well-designed prospective studies comparing an early precut *versus* the current practice of only resorting to precut when multiple attempts of

cannulation have failed (Freeman *et al.* 1996; Cennamo *et al.* 2010; Gong *et al.* 2010; Choudhary *et al.* 2014). In addition, further studies are needed to attest the reproducibility of the results achieved by large tertiary centers in other settings.

Another issue is training, while there are guidelines for appropriate training in ERCP, there are none for NKF (Laasch *et al.* 2003; Chutkan *et al.* 2006; Akaraviputh *et al.* 2008) and in the literature only five reports have evaluated the learning curve for NKF, all of which relating the experience of single endoscopists (Rollhauser *et al.* 1998; Harewood & Baron 2002; Robison *et al.* 2007; Akaraviputh *et al.* 2008; Fukatsu *et al.* 2009). Given the potential usefulness, a question immediately arises: how is competency in this procedure achieved? Although in ERCP it is suggested that a trainee should perform a minimum of 180-200 procedures to achieve competency, the learning curve associated with NKF is uncertain (Hogan 1988; Jowell *et al.* 1996; Chutkan *et al.* 2006).

To address these pending issues, three aims were formulated (Chapter 3).

3 Aims

1 - To assess the efficacy and safety of the needle-knife fistulotomy in the setting of a difficult biliary cannulation, in regular practice.

2 - To determine the efficacy and safety of two alternative strategies in the setting of a difficult biliary cannulation: an early precut fistulotomy *versus* the standard late precut fistulotomy.

3 - To evaluate the learning curve of needle-knife fistulotomy and infer the number of procedures required for technical competency.

PART II

Results

4

Safety and efficacy of needle-knife fistulotomy

Safety and efficacy of precut needle-knife fistulotomy
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ORIGINAL ARTICLE

Safety and efficacy of precut needle-knife fistulotomy

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Abstract

Objective. Although precut is considered an useful alternative when standard methods of biliary access have failed, there is some controversy about it's safety. The study aim was to evaluate the effectiveness of needle-knife fistulotomy (NKF) after a difficult biliary cannulation and whether common bile duct (CBD) diameter influenced complications. ***Material and methods.*** Between November 2006 and December 2010, a total of 1087 consecutive patients with naive papilla were submitted to endoscopic retrograde cholangiopancreatography (ERCP) for biliary access, in an affiliated university hospital. If the biliary cannulation was unsuccessful after 12–15 min, a NKF was performed. The main outcomes were biliary cannulation rate, NKF success and post-ERCP complications. ***Results.*** Biliary cannulation by standard methods was successful in 883 patients (81%). In the remaining 204 patients, NKF was performed and allowed CBD access in 166 (81%), leading to a 96% cannulation rate. A second ERCP was performed in 25 patients, with an NKF success of 90% and an overall biliary cannulation rate of 98%. The post-ERCP complication rate was 7.9% ($n = 16$) with a 6.4% pancreatitis rate and no deaths. The complication for patients with a CBD ≤ to 4 mm was 13.9% compared with 4.5% in the remaining patients (OR = 3.39, $p = 0.024$). ***Conclusions.*** NKF is a safe and highly useful method of accessing the CBD in the setting of a difficult biliary cannulation. Despite its safety profile, extra caution is needed when applying NKF to patients with thin bile ducts.

Key Words: *complications, ERCP, fistulotomy, precut*

Introduction and background

Endoscopic retrograde cholangiopancreatography (ERCP) is an advanced endoscopic procedure commonly used in the diagnosis and treatment of a variety of benign and malignant ampullary, biliary and pancreatic disorders [1]. Selective cannulation of the common bile duct (CBD) is the most important step to obtain a successful biliary ERCP [2]. In the vast majority of patients, deep biliary cannulation is achieved using a catheter or a sphincterotome with or without a guidewire (standard technique) [3].

However, even in experienced hands, biliary cannulation may fail in up to 15–35% of cases when using standard methods alone, in the first ERCP [3,4]. In this subset of patients, additional cannulation techniques are needed to access the bile duct in order to continue with the ERCP [1,5]. Precut is the most common strategy used when conventional methods of cannulation have failed [2,6]. This rescue strategy comprises several different techniques wherein the bile duct and the biliary orifice are exposed after incising the papilla. The most common of these techniques is the freehand needle-knife precut in which the incision is either initiated in the papillary orifice (classic precut) or a few millimeters above (needle knife fistulotomy or fistulotomy, NKF) [2,3,7].

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Although precut is known to increase the primary biliary cannulation rate, the safety rate of this rescue technique is still under debate and it has been shown to be an independent risk factor for post-ERCP pancreatitis [3,4,8,9]. Moreover, certain reports suggest that a nondilated CBD diameter may be a risk factor for complications, especially in the setting of Sphincter of Oddi Dysfunction (SOD) [10–12].

The main aim of the study was to evaluate the safety and efficacy of NKF in patients after a failed difficult biliary cannulation and secondly to determine whether terminal CBD diameter influenced the development of complications.

Methods

Setting and selection of participants

Between November 2006 and December 2010, a total of 1698 ERCPs were performed in our institution. Of these 1698 ERCPs, 1260 were performed on patients with naive papilla for biliary indications in our institution. From this group, 1087 were selected for a retrospective evaluation. Of the patients, 173 were not included as they fell into one of the following exclusion criteria: a) periampullary diverticulum (n = 126), b) Billroth II gastrectomy (n = 22), c) abnormal coagulation studies (n = 14), d) tumors of the papilla (n = 11). These criteria either precluded the use of the precut (c) or included anatomical features, which could negatively influence the technical safety of the procedure (a, b and d) [13].

All patients were prepared and sedated (by an anesthesiologist) as standard medical practice, and all procedures were performed by two experienced endoscopists (with a workload of >200 ERCPs/year and a mean of more than 10% of NKF per year), using a therapeutic videoduodenoscope (TJF 160 VR, Olympus Corporation, Melville, NY). ERCP was performed with the patient lying prone on the X-ray table. Informed consent for the procedure was obtained from all patients. The hospital's Ethics Committee approved this study.

ERCP and NKF procedures

Selective cannulation of the bile duct was initially attempted with a triple lumen sphincterotome (Ultratome XL, Boston Scientific, Natick, MA) preloaded with contrast and a guidewire (Jagwire, Boston Scientific, Natick, MA). If the attempts failed to yield deep biliary cannulation, a different biliary catheter or guidewire could be used at the discretion of the endoscopist. If cannulation was unsuccessful after 12–15 min (ERCP unit policy followed by the two endoscopists), a NKF was performed using a needle-knife (Olympus KD-11Q, Olympus Corporation, Melville, NY) with electrosurgical current in the endocut mode 120W, effect 3 (Olympus-PSD 60, Olympus Corporation, Melville, NY).

The NKF procedure was performed using a freehand technique, making a puncture in the papilla above the orifice, and then cutting on an 11-o'clock axis (regular orientation of the intraduodenal segment of the bile duct) either upward or downwards, depending on where the incision started in the papillary mound, while maintaining at least a 3-mm incision-free distance from the papillary orifice. The direction of the cut varied according to the anatomy of the patient and the discretion of the endoscopist. The cut was slowly extended until the muscle of the intraduodenal portion of the CBD was exposed; then a small cut was performed in the muscle with the needle knife creating a fistula. The cannulation of the bile duct was performed directly with the closed needle knife if it slipped easily up, or in a minority of cases, after gently probing the fistula with a preloaded wire in a papillotome. The selective cannulation was confirmed by the injection of a low-osmolality non-ionic radiological contrast (Ultravist, Iopromide, Bayer Schering Pharma, Berlin, Germany), and the needle knife was exchanged over the wire for a triple lumen sphincterotome. After deep cannulation was achieved, a cholangiogram was taken. If necessary, the sphincterotomy was extended with a standard sphincterotome (usually until the limit of the papillary mound) in the endocut mode and the necessary therapeutic maneuvers were performed. Once the ERCP was completed, all patients were admitted to the inpatient area of the hospital and observed for 24 h, before discharge. When deep cannulation of the bile duct was unsuccessful after NKF, a second ERCP was scheduled 7–14 days later.

Pharmacologic prophylaxis of post-ERCP pancreatitis was not performed during the period of the study, and prophylactic pancreatic stents were not used.

Variables and data collection

Data on each procedure was collected by the endoscopist in a predetermined form following each ERCP and subsequently recorded in the unit's endoscopic electronic database by a research nurse. The endoscopic database included a large number of variables, such as demographic data, ASA status, indications, anatomic abnormalities, success in biliary/pancreatic cannulation, biliary access technique, therapeutical interventions, technical success and intraprocedural complications. Data on post-procedure complications

(30-day follow-up) was collected retrospectively by the research nurse blinded to the intervention, reviewing the electronic clinical records and discharge information and by contacting the referring physician or the patient's primary care provider, if necessary.

Indications to proceed with the ERCP were determined by the endoscopist based on information provided in the request form and the patient's medical records. Only one indication could be chosen. The presumptive diagnosis of SOD was based on clinical, laboratory and radiologic parameters, according to contemporary criteria [14]. ERCP was not performed on suspected SOD type II or III patients in our unit.

The bile duct diameter was measured in the distal bile duct (20 mm above the papilla) and adjusted for magnification to evaluate the potential relation of the intraduodenal bile duct size with the complications risk. If a stricture was present, the CBD was measured distally to the stricture. When a deep biliary cannulation was not possible after two ERCPs, the CBD diameter was collected from the MRI series. Bile duct diameter was further categorized into four groups: ≤4 mm, 5–8 mm, 9–12 mm and >12 mm.

Complications were defined according to guidelines established by a consensus conference on ERCP complications [15].

Statistical analysis

Statistical analysis was performed using the software package IBM SPSS Statistics version 20.0.0.

Variables were summarized using the mean, standard deviation and range (if continuous and normal distribution) and proportions (if categorical). Differences between groups were tested by using chi-square test for categorical, whereas continuous variables were analyzed using a two-sample t test. The estimates of odds ratio associating specific factors and post-ERCP complications were assessed by multiple regression logistic. A p-Value of <0.05 was considered statistically significant.

Results

Indication for NKF and success rate

During this study period, CBD cannulation by standard methods was successful in 883 patients out of a total of 1087 (81%). For the remaining 204 patients, where the biliary cannulation failed, NKF was performed during the same ERCP (19%). NKF was successful in achieving deep biliary cannulation in 166 of the 204 patients (81%) leading to a 96% (1049/1087) cannulation rate after the addition of NKF in the initial ERCP. A second ERCP was performed in 25 of the 38 patients with failed CBD cannulation in the first ERCP. The CBD was cannulated during the second ERCP in 18 patients (72%) leading to an overall NKF success rate of 90% (184/204) and an overall biliary cannulation success of 98% after two ERCPs (1067/1087) (Table I).

Table I. ERCP and NKF success rate.

	ERCP (n = 1087)
Fistulotomy, n (%)	204 (19)
Biliary cannulation before fistulotomy	81% (883/1087)
Fistulotomy success in the first ERCP	81% (166/204)
Biliary cannulation after fistulotomy in the first ERCP	96% (1049/1087)
Overall fistulotomy success	90% (184/204)
Overall biliary cannulation rate	98% (1067/1087)

In the 204 patients with initial cannulation failure, there were 114 women and 90 men, with a mean age of 66.7 years (ranging from 16 to 95) and 27.9% of patients with ASA III or IV. The indications for NKF were jaundice in 73 patients (36%), choledocholithiasis in 39 patients (19%), biliary or pancreatic cancer in 21 patients (10%), CBD dilation in 20 patients (10%), suspected bile duct injury in 11 patients (5%) and other indications in 7 patients (4%) (Table II).

The main diagnostic findings were choledocholithiasis in 61 patients (33%), malignant biliary strictures in 55 patients (30%), normal cholangiogram in 26 patients (14%), papillary stenosis (SOD type 1) in 11 patients (6%), bile duct dilation in 10 patients (6%), bile leaks in 8 patients (4%), benign biliary strictures in 8 patients (4%) and other diagnosis in 5 patients (3%) (Table III). The main pancreatic duct (MPD) was cannulated and contrast was injected in 43 patients (21%). After deep biliary cannulation, a sphincterotomy with a pull sphincterotome was performed in all patients, with the exception of four.

Table II. Patient's characteristics and indications.

	n (%)
Age *(mean, range)*	66,7 (16–95)
Sex *(male/female)*	90/114
ASA grade III–IV	57 (27.9%)
Indications	
Jaundice	73 (36%)
Choledocholithiasis	39 (19%)
History of gallstone pancreatitis	33 (16%)
Biliary or pancreatic cancer	21 (10%)
Dilated common bile duct	20 (10%)
Iatrogenic bile duct injury	11 (5%)
Other reasons	7 (4%)

Table III. ERCP final diagnosis and complications.

Diagnosis	*n* (%)
Choledocholithiasis	61 (33%)
Malignant biliary stricture	55 (30%)
Normal cholangiogram	26 (14%)
Papillary stenosis or probable SOD	11 (6%)
Bile duct dilation	10 (6%)
Bile leaks	8 (4%)
Benign biliary stricture	8 (4%)
Others	5 (3%)
Complications (<30 days)	16 (7.9%)
Pancreatitis	13 (6.4%)
Mild	11
Moderate	1
Severe	1
Bleeding	2 (1%)
Mild	1
Moderate	1
Perforation	1 (0.5%)
Mild	1
Cholangitis	0

Abbreviation: SOD = Sphincter of Oddi dysfunction.

Complications after NKF

The overall complication rate was 7.9% (16 of 204) and the majority of these were considered mild (81%, 13 of 16) and were treated using conservative measures (Table III) Moreover, the 30-day mortality risk associated with NKS was nil. Pancreatitis was the most common complication observed in a total of 13 patients (6.4%). The complication was graded as mild in 11 patients and as moderate in 1. Only one patient developed a severe pancreatitis and was successfully treated with conservative measures during a 25-day hospitalization period. None of the patients with pancreatitis ($n = 13$), with the exception of one, was diagnosed with SOD and the patient only had a mild pancreatitis.

Bleeding occurred in two patients (1%), one mild hemorrhage (3-g hemoglobin drop and no transfusion), whereas the other patient developed melena 2 days following the NKF, requiring a 4 unit red blood cells transfusion and 8 days of hospitalization (moderate bleeding).

Duodenal perforation occurred in a 65-year-old female, recognized during the ERCP, as contrast was seen outside the duodenum during the NKF attempt and confirmed by CT. The patient was treated with conservative measures (nothing by mouth, nasogastric suction, proton pump inhibitors and antibiotics) and resumed a normal diet after 3 days.

No complications were reported for patients who underwent a second ERCP, following a failed biliary cannulation in the first attempt.

Table IV. CBD diameter and complications rate.

	CBD diameter				
	≤4 mm ($n = 72$)	5–8 mm ($n = 59$)	9–12 mm ($n = 41$)	>12 mm ($n = 32$)	*p*
Complications	13.9%	5.1%	4.9%	3.1%	0.020
Pancreatitis	9.7%	5.1%	4.9%	3.1%	-
Bleeding	2.8%	0	0	0	-
Perforation	1.4%	0	0	0	-

Abbreviation: CBD = common bile duct.

Bile duct diameter and post-ERCP complications

A small bile duct diameter (≤4 mm) was significantly associated to post-ERCP complications by multivariate analysis (Table IV). The post-ERCP complication rate for patients with a bile duct diameter inferior to 4 mm was 13.9% (10 of 72), compared with 4.5% (6 of 132) in patients with a CBD larger than 4 mm. The rate of pancreatitis for patients with a duct <4 mm was 9.7% (6 of 72) when compared with 4.5% (6 of 132) for the remaining patients; this was, however, not statistically significant. There were no SOD patients in the group with the thinner bile duct (<=4 mm). The probability of a patient with a thin bile duct developing a complication when they are submitted to an NKF is approximately 3.4 times greater than for those who have larger bile ducts (odds ratio, OR = 3.39; CI 1.12–9.75; $p = 0.024$) (Table V).

Patient age, ASA status, gender, endoscopist, indication, final diagnosis and pancreatic duct cannulation were not associated with post-ERCP complication by multivariate analysis.

Discussion

Precut papillotomy with a traction papillotome was first reported by Siegel et al. in 1980 [16], and in 1986, Huibregtse et al. [17] reported on precut using a needle knife. Precut papillotomy is the most common choice for achieving a biliary access after a failed difficult biliary cannulation. The decision to proceed with the precut approach should take into account several factors, including the seriousness of

Table V. Post-ERCP complications risk and CBD diameter.

	CBD diameter		
	≤4 mm ($n = 72$)	>4 mm ($n = 132$)	OR (95%CI)
Post-ERCP complications	13.9%	4.5%	3.39 (1.12–9.75)

Abbreviations: CBD = common bile duct; OR = odds ratio.

the indication for ERCP, the clinical condition of the patient, the expertise of the endoscopist and what other techniques are available [3].

With 204 patients, this study includes one of the largest series of NKF approach to date for a single center [18,19]. In our series, precut NKF was highly useful in achieving a deep biliary cannulation in the first ERCP (96%). Resorting to the use of NKF during the first ERCP increased the biliary access, for patients where access to the bile duct was not accessible, from 81% to 96%.

A second ERCP was performed on 25 patients, thus increasing the global biliary cannulation rate from 96% to 98% and resulting in an overall NKF success of 90%. In a meta-analysis from Cennano et al. [20], in the five studies in which a needle-knife precut was performed, the primary success of NKF ranged from 75% to 92%, and the overall NKF success (including repeated ERCPs) varied from 79% to 97%. Our overall biliary cannulation rate above the 95% barrier was comparable to other reports from tertiary centers with experience in precut [3,4,21].

The strategy of performing a second ERCP within a short time-frame when an NKF is unsuccessful in the first ERCP was highly effective and safe, as reported by Kim et al. and Donnellan et al. [22,23]. A 72% success rate in accessing the bile duct was achieved in the 25 rescheduled patients, with no complications. This data supports the strategy of referring patients to a second ERCP, instead of immediately contemplating other techniques such as percutaneous biliary access (most common option) combined endoscopic-percutaneous access, EUS-guided biliary access, or even surgery.

The definition of a difficult biliary cannulation found in previous studies is diverse, arbitrary and depends largely on the judgment of the endoscopist [5]. In a recent large survey conducted in the Scandinavian countries about cannulation techniques, the three most common criteria for a cannulation to be defined as difficult were time needed, number of attempts and the need to use NKF [6]. However, objective criteria have yet to be established in terms of duration, number of biliary attempts and number of unwanted pancreatic duct cannulation or injection. For the purpose of this study, a difficult biliary cannulation was defined as a situation where the endoscopist was unable to cannulate the bile duct using standard methods for 12–15 min. The definition of a difficult cannulation as far as time is concerned also varies considerably in most studies from 10 to 30 min [3,13,19,21,24]. For comparative purposes, this arbitrary definition is an obvious limitation and it would be important to define objective criteria on this topic in the future.

In case of initial failure to cannulate, we always switched to a needle-knife precut (in our case NKF), which is the strategy followed by most endoscopists. In a recent European survey, this was the first option followed by 42% and 100% of the endoscopists, depending on if the MPD had been cannulated or not, respectively [25]. The timing of the switching was arbitrarily defined by the endoscopists involved but in a time range comparable to other tertiary centers that used a similar policy [13,19,24]. The use of a precut technique for biliary access varies between centers from nonexistent to as many as 33–50% of the ERCPs [25]. The rate at our center is 18.7%, which is comparable to the tendency reported in several studies from centers without a restrictive policy on precut, including Bruins Slot et al. [3] (17%) and Kasmin et al. (18%) [11].

There are several described precut techniques that mainly use two accessories a needle knife (free-hand technique) and a traction papillotome [2,7], although other devices such as the Iso-Tome or endoscopic scissors were reported [2]. Studies that compare these different techniques are also scarce and hampered by the lack of a standardized nomenclature [26]. Moreover, there is no definite data demonstrating the superiority of an individual precut technique in terms of safety or success [26]. However, theoretically NKF may present a lower rate of pancreatitis compared with the classic precut, as the pancreatic orifice is avoided, nonetheless, further studies are required to clarify this issue. The direction of the incision during NKF, “downhill” versus “uphill”, was determined by the anatomy of the patient and although the upward incision was the most frequent option, we used the downward approach in 31% of the patients. The downward incision is technically more demanding to perform and is used more commonly by experienced endoscopists [6].

Although precut is known to increase the biliary cannulation rate, several prospective studies refer to precut as an independent risk factor for post-ERCP complications. Several reports and some meta-analysis from randomized controlled trials report a low percentage of complications [3,11,27,28], while others studies, including one meta-analysis report a high level of complications, some of which were severe [8,29].

As the use of the precut generally follows a difficult cannulation, it remains unclear whether the increased risk is related to the precut itself or is linked to the manipulation that precedes it. The prolonged unsuccessful cannulation could induce a poor MPD drainage as a result of trauma or contrast injection into the MPD [8].

Complications occurred in 16 patients (7.9%), which is comparable to other studies performed at high-volume centers with experience in performing precut. The pancreatitis rate was 6.4% ($n = 13$), which is equivalent to commonly quoted rates. Merely one patient had a severe complication (pancreatitis) and there were no fatalities, which emphasize the safety of the procedure, although we must interpret this zero death rate with caution, taking into account the small number of patients enrolled. An interesting finding was the low incidence of bleeding (1%) when compared to 5.5% reported by Bruins Slot et al. or 8.6% reported by Kaffes et al. A possible explanation may result from the settings used in the endocut current, with a relative high coagulation effect. One of the limitations of this study is that the collection of complications following the first 24 h and thereafter was retrospective. This could underestimate the hemorrhage rate, as the possibility of late bleeding does exist.

In our analysis, we confirmed a trend to a higher risk of complications in patients with a thin CBD submitted to NKF. The initial studies that report a small CBD as a risk factor for post-ERCP pancreatitis came from centers with a high percentage of SOD patients, many of whom also had small bile ducts [9]. What is interesting in our findings is that an association between CBD diameter and post-ERCP complications was verified in patients who did not have SOD. In fact, all suspected SOD patients had large bile ducts and only one developed pancreatitis. Our study specifically measured the last 20 mm of the CBD, and not the maximum diameter of the CBD such is reported by Kasmin et al. [11], and by most of the studies published addressing CBD diameter and post-ERCP complications. It was clear that the overall risk of complications was higher in the smaller than 4 mm group (13.9%), versus the remaining patients (4.5%). The risk of pancreatitis in the less-than-4-mm group was also higher (9.7%) than for the remaining patients (4.5%), although not statistically significant. This is a curious observation, especially as there were no SOD patients in this subgroup with narrow bile ducts (which, in any case, would be very improbable as ERCP was not performed in suspected SOD patients type II or III). The probability of developing a complication after NKF was 3.4 times higher in patients with a thin CBD. It is postulated that this risk is related to the technical difficulty in performing the fistulotomy, as the recognition of the duct is more difficult, the precision of the cut is reduced and consequently the probability of injuring the papillary base and the pancreatic duct is higher.

Following 2010, post-ERCP pancreatitis guidelines were published recommending periprocedural rectal administration of NSAIDs in all ERCPs and/or pancreatic stents in high-risk patients [30] These recommendations were not a common practice in our unit before 2010, as the historical overall complications rate, including pancreatitis, was low. It is curious to note that upon the analysis of surveys on the use of prophylatic pancreatic stents among experienced endoscopists, it is in fact a common practice in Canada and the US, while the same is not true for European endoscopists, for various reasons [31]

As no additional measures were employed to minimize the risk of pancreatitis, the results reflect an accurate measure of the safety profile of NKF after a difficult biliary cannulation. The relative high rate of pancreatitis in patients with thin bile ducts, although not severe, suggest the need to implement pancreatic stents in this particular group or alternatively use NKF early on, during the cannulation strategy, as some authors recently proposed [21,27].

In summary, precut NKF is a safe and highly useful method of gaining biliary access in the setting of a difficult biliary cannulation. Despite the safety profile, extra caution is required when applying NKF to patients with thin bile ducts, including patients with no SOD. Although precut is traditionally viewed as a risk factor for pancreatitis, it is possible that in the future this concept is reviewed as recent data suggest that an early precut is as safe as a standard cannulation among experienced endoscopists. Nonetheless, further studies are required to address this timing issue, which could change the recommendation for pancreatic stents in the setting of an early precut.

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Early NKF strategy *versus* standard late precut strategy

Early precut fistulotomy for biliary access: time to change the paradigm of the "the later, the better?"
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ORIGINAL ARTICLE

Early precut fistulotomy for biliary access: time to change the paradigm of "the later, the better?"

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Background: The precut timing during the biliary cannulation algorithm is a subject of controversy. Some studies suggest that early institution of precut is a safe and effective strategy even though the extent to which this approach may affect the duration of the ERCP is seldom addressed.

Objective: To assess the success, safety, and procedure duration of an early precut fistulotomy (group A) versus a classic precut strategy after a difficult biliary cannulation (group B).

Design: Single-center, prospective cohort study.

Setting: University-affiliated hospital.

Patients: A total of 350 patients with a naïve papilla.

Interventions: Standard biliary cannulation followed by needle-knife fistulotomy (NKF).

Main Outcome Measurements: Biliary cannulation rate, NKF success, adverse events, and ERCP duration.

Results: The overall cannulation rate was similar, at 96% and 94% for groups A and B, respectively. The adverse event rate was 6.2% and 6.4%, respectively, with pancreatitis as the most frequent adverse event (group A, 3.9%; group B, 5.2%). The mean ERCP duration was, however, significantly shorter in group A, both when biliary cannulation was achieved without precutting (14 minutes vs 25 minutes, $P < .001$) as well as when biliary cannulation was attempted after NKF (18 minutes vs 31 minutes, $P < .0001$).

Limitations: Single-center study design, referral center.

Conclusions: If the endoscopist is experienced in ERCP and precut techniques, an early precut strategy should be the preferred cannulation strategy because this approach is as safe and effective as the late fistulotomy approach and substantially reduces ERCP duration. (Gastrointest Endosc 2014;■:1-8.)

ERCP is an endoscopic interventional procedure commonly used in the management of biliary and pancreatic disorders.[1] Deep cannulation of the common bile duct (CBD) is one of the most demanding maneuvers performed during ERCP and is a prerequisite for a successful endoscopic biliary intervention. However, even among experienced endoscopists, biliary cannulation may fail in as many as 15% to 35% of the attempts when relying on standard methods alone.[2,3] If the decision is to continue with the ERCP in these patients, then other cannulation techniques are required to gain access to the bile duct.[4,5] Precut, a papilla incisional technique, is one of the available

Abbreviations: ASA, American Society of Anesthesiologists; CBD, common bile duct; NKF, needle-knife fistulotomy.

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options after a difficult biliary cannulation. The 2 most common precut techniques include the classic needle-knife and the needle-knife fistulotomy (NKF).

Although precut is known to increase the biliary cannulation rate, several prospective studies classify precut as an independent risk factor for post-ERCP adverse events.[4,6] Nonetheless, many endoscopists who favor precut argue that the reported high adverse events rates result from the conventional approach of merely resorting to precut after prolonged efforts at biliary cannulation (which is, per se, a risk factor for post-ERCP adverse events) and thus propose its early institution in the cannulation approach.[5,7]

There are studies suggesting that early institution of the precut is a safe and effective strategy even though conflicting results concerning post-ERCP adverse events have been reported when compared with conventional techniques.[8] However, these studies have seldomly addressed the impact of the precut timing in the global ERCP duration.

The aim of this study was to compare 2 alternative biliary cannulation strategies: early precut fistulotomy and late precut fistulotomy.

Take-home Message

- An early precut cannulation strategy is at least as successful and safe as the classic cannulation strategy of using precut only after a difficult cannulation and presents 1 main advantage: there is a substantial reduction in the duration of the ERCP. If the endoscopist is experienced with these techniques, why not consider an early precut strategy the preferred approach?

METHODS

Type of study, setting, and selection of participants

This was a prospective cohort, single-center study that was conducted at a university-affiliated hospital. Between January 2011 and February 2012, all consecutive patients with naïve papillae referred for biliary ERCP, with the ability to give informed consent, were eligible for recruitment. Exclusion criteria were (1) a periampullary diverticulum (defined as a papilla on the edge of or within the diverticulum), (2) Billroth II gastrectomy, (3) abnormal coagulation test results (international normalized ratio >1.5, prothrombin time >3 seconds of the upper limit of normal), and (4) tumors of the papilla (diagnosed during ERCP). These criteria either precluded the use of the precut technique (criterion 3) or potentially decreased its technical safety because of anatomic features (criteria 1, 2, and 4).[9]

The hospital's ethics committee approved this study, and informed consent was obtained from all patients for the procedure.

Study design and definitions

The 2 endoscopists in this study had similar experience in ERCP, performing more than 200 ERCPs per year with a mean of more than 10% of NKFs per year. Before December 2010, the 2 endoscopists regularly used precut fistulotomy as a rescue technique after a difficult biliary cannulation according to the policy of the unit and had comparable results in terms of success, adverse events, and duration of the ERCP. Endoscopist A started using an early precut NKF approximately 2 months before the beginning of the study and completed 20 procedures. After January 2011, endoscopist A started using fistulotomy at an earlier phase, whereas the other endoscopist (endoscopist B) continued with the standard unit cannulation policy. Patients were assigned to each endoscopist according to their available schedules (each endoscopist performed ERCP on a different day of the week) by an administrative assistant blinded to the study, per the standard protocol of the unit. On average, each endoscopist usually was assigned the same number of patients per week.

Group A (early precut fistulotomy strategy). CBD cannulation of patients assigned to endoscopist A was initially attempted by using a standard biliary approach. If biliary access was unsuccessful after 5 minutes or after as many as 5 biliary attempts (by using wire-guided direction as a roadmap for CBD identification before injection) or if there was any pancreatic duct cannulation, an NKF was performed. The NKF time limit was 15 minutes, after which ERCP was discontinued. For the purpose of analysis, this group was subdivided into 2 subgroups: A1 (successful expeditious standard cannulation subgroup) and A2 (early NKF subgroup).

Group B (late precut fistulotomy strategy). CBD cannulation of patients assigned to endoscopist B was initially attempted by using standard biliary cannulation. If the biliary access was unsuccessful after 15 minutes or after as many as 10 biliary attempts (by using wire-guided direction as a roadmap for CBD identification before injection), an NKF was subsequently attempted. The NKF time limit was 15 minutes, after which ERCP was discontinued. For the purpose of analysis, these patients were also divided into 2 subgroups: B1 (successful classic standard cannulation subgroup) and B2 (late NKF subgroup).

Biliary cannulation was confirmed after obtaining a cholangiogram with the catheter inserted selectively in the CBD. After ERCP, all patients were hospitalized for at least 24 hours before discharge. Serum amylase or lipase levels were only obtained if adverse events were suspected. The durations of both ERCP and CBD cannulation were measured from the moment the papillotome was advanced out of the tip of the endoscope in front of the papilla. Data on the procedure (eg, duration, number of biliary attempts, pancreatic duct cannulation) and adverse events were collected by a research nurse present in the ERCP

suite, but not directly involved in the ERCP. Postprocedure adverse events were collected by the research nurse by using the electronic clinical records and, if necessary, contacting the patient or the patient's primary care provider, as necessary. Follow-up data (from 30 days after ERCP) were obtained from all patients.

Adverse events were defined according to guidelines established by a consensus conference on ERCP (Table 1).[10]

ERCP and cannulation techniques

All patients were prepared and sedated by an anesthesiologist as standard medical practice. A therapeutic videoduodenoscope (TJF 160 VR; Olympus Corporation, Melville, NY) was used in all procedures, and diathermy was applied by using electrosurgical current in the 120-W endocut mode, effect 3 (Olympus-PSD 60; Olympus Corporation).

Pharmacological prophylaxis of post-ERCP pancreatitis was not performed during the period of the study, and prophylactic pancreatic stents were not used.

Standard biliary cannulation. Standard cannulation of the bile duct was regularly attempted with a triple-lumen sphincterotome (Ultratome XL; Boston Scientific, Natick, Mass) preloaded with contrast and a guidewire (Jagwire; Boston Scientific). We attempted to cannulate with the tip of the sphincterotome, and, once inside the duct, a wire was advanced. If this was unsuccessful, the endoscopist could opt for another biliary catheter (tapered tip or ball tip) or use different guidewires.

Needle-knife fistulotomy. NKF was performed by using a needle-knife (Olympus KD-11Q; Olympus Corporation). After making a puncture in the papilla above the orifice, the incision was made upward or downward (depending on the position of the initial puncture), along the axis of the bile duct, while maintaining at least a 3-mm distance from the papillary orifice. The cut was slowly extended until the CBD was exposed, followed by a small incision in the muscle. The CBD was then cannulated directly with the closed needle-knife or with a papillotome (wire guided) if the needle-knife did not slide.

Once deep cannulation was achieved, a cholangiogram was obtained by using low-osmolality, nonionic contrast (Ultravist [iopromide]; Bayer Schering Pharma, Berlin, Germany), and the necessary therapeutic maneuvers were performed.

A second ERCP was proposed 7 to 14 days later in case of a failed first ERCP approach; the procedure was performed by the same endoscopist.

Outcome measures

The main outcome measures were successful biliary cannulation, post-ERCP adverse events, and total duration of the ERCP.

Statistical analysis

Statistical analysis was performed by using the SPSS software, version 20.0.0 (IBM, Armonk, NY).

TABLE 1. Consensus definition of ERCP adverse events

Adverse event	Severity	Grading criteria
Pancreatitis	Mild	Clinical pancreatitis, amylase >3 times normal at least 24 h after ERCP, requiring admission (or prolongation of) up to 3 days
	Moderate	Hospitalization of 4-10 days
	Severe	Hospitalization for >10 days or hemorrhagic pancreatitis, pancreatic necrosis, pseudocyst, or percutaneous or surgical intervention
Bleeding	Mild	Clinical evidence of bleeding, decrease in hemoglobin to <3 g/L and no need for transfusion
	Moderate	Transfusion (≤4 units); no angiographic intervention or surgery
	Severe	Transfusion (≥5 units) or intervention (angiographic or surgical)
Perforation	Mild	Possible or only very slight leak of fluid or contrast, treatable by fluids and suction for ≤3 days
	Moderate	Any definite perforation treated for 4-10 days
	Severe	Medical treatment for >10 days or intervention (percutaneous or surgical)

Variables were summarized by using the mean, standard deviation, range (if continuous and normal distribution), and proportions (if categorical). Differences between groups were measured using a χ^2 test for categorical variables, whereas continuous variables were analyzed by using a 2-sample t test. $P < .05$ was considered statistically significant.

RESULTS

A total of 390 patients with naive papilla underwent ERCP from January 2011 to February 2012. After applying the exclusion criteria, 350 patients were included in this study (Fig. 1). The mean age for the entire group was 68.2 years (range 18-102 years), 28% of whom were American Society of Anesthesiologists (ASA) grade III or IV, and 55% of the population were female (n = 193).

Patients were assigned to an early precut fistulotomy strategy (expeditious standard cannulation followed by an early precut fistulotomy in case of failure) (group A,

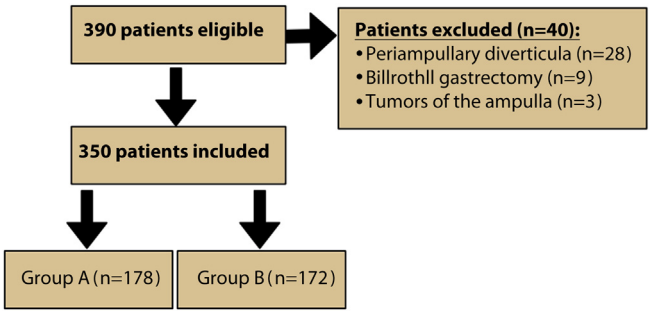

Figure 1. Flowchart of the study design.

n = 178) or a late precut fistulotomy strategy (classic standard biliary cannulation followed by a late fistulotomy in case of failure) (group B, n = 172). Analysis of both groups demonstrated that patients were matched for age, sex, ASA grade, distal CBD diameter, indications, interventions, main pancreatic duct cannulation, and final diagnosis (Table 2). The 2 groups were also comparable according to the grade of ERCP difficulty: grade 1 (group A, 78% vs group B, 80%; $P = .658$), grade 2 (group A, 22% vs group B, 20%; $P = .534$).[11]

Biliary cannulation rate

The biliary cannulation rates are summarized in Table 3. In the early precut fistulotomy strategy, CBD cannulation was successful by using the standard cannulation technique in 130 patients of a total of 178 (73%). An early NKF was performed on the remaining patients, and deep biliary cannulation was achieved in 41 of the 48 patients (85.4%), resulting in a 96% success rate for the first ERCP. In group B, CBD cannulation by the standard technique was successful in 137 patients of a total of 172 patients (79.7%). A late NKF was performed on the remaining patients, and deep biliary cannulation was achieved in 24 of the 35 patients (68.6%), resulting in a 93.6% cannulation rate for the first ERCP in this group.

In group A, a second ERCP was scheduled for 4 of the 7 failures (the other 3 patients were not referred for a second ERCP). The CBD was cannulated during the second ERCP in 4 patients, increasing the NKF success rate to 93.8% (45/48) and overall biliary cannulation success rate to 98.3% after 2 ERCPs (175/178).

In group B, a second ERCP was scheduled for 7 of the 11 patients (the remaining 4 patients were not referred for a second ERCP). The CBD was cannulated during the second ERCP in 5 patients, increasing the NKF success rate to 82.9% (29/35) and overall biliary cannulation success rate to 95.9% after both ERCPs (165/172).

Post-ERCP adverse events

The overall adverse event rate was 6.2% in group A and 6.4% in group B. Pancreatitis was the most common adverse event, with a 3.9% rate in group A and 5.2% rate in group B. Only 1 severe adverse event was reported and managed successfully with conservative measures in the successful expeditious standard cannulation subgroup (Table 4).

Successful standard cannulation subgroups (subgroups A1 and B1). The post-ERCP adverse events rate for patients in whom the biliary duct was successfully accessed by standard techniques was 5.3% in group A1 and 5.8% in group B1. There were 6 patients with pancreatitis in the classic standard cannulation subgroup (4.4%) and 5 patients (3.8%) in the successful expeditious standard cannulation subgroup. The only case of severe pancreatitis occurred in 1 patient in the early precut fistulotomy strategy.

NKF after unsuccessful standard cannulation subgroups (subgroups A2 and B2). The adverse event rate for patients undergoing NKF was 8.3% in subgroup A2 and 8.6% in subgroup B2. The post-ERCP pancreatitis rate was higher in the late precut fistulotomy strategy (subgroup B2) compared with the early precut fistulotomy strategy (subgroup A2) (8.6% vs 4.2%). There were 2 patients (4.2%) with mild bleeding in group A and no bleeding in group B.

Duration of the ERCP procedure

The mean duration of the complete ERCP procedure with the early precut fistulotomy strategy was significantly shorter than with the late precut fistulotomy strategy, both when biliary cannulation was achieved without the precut (14 minutes vs 25 minutes, $P < .001$) as well as when biliary cannulation was attempted with an NKF (18 minutes vs 31 minutes, $P < .001$) (Table 5).

DISCUSSION

The precut timing in the biliary cannulation algorithm is a subject of controversy, even in centers with precut expertise.[7,12,13] This study compared the standard cannulation policy of our unit (late precut fistulotomy) with an alternative cannulation protocol (early precut fistulotomy) adopted by one of the endoscopists. The criteria for switching from a standard cannulation to precut during an ERCP were arbitrarily defined by the judgment of the endoscopists involved, based on their experience as reported in previous studies.[4-6] For comparative purposes, these arbitrary definitions are an obvious limitation, and it would be important to define objective criteria on this topic in the future.

There are several described precut techniques that mainly use 2 accessories: a needle-knife (free-hand technique) and a traction papillotome, although other devices such as the Iso-Tome (MTW Endoskopie, Wesel, Germany) or endoscopic scissors were reported.[14,15] Moreover, there are no definite data demonstrating the superiority of an

TABLE 2. Patient's characteristics, indications, and diagnosis

	Group A (n = 178), no. (%)	Group B (n = 172), no. (%)	*P* value
Age (mean, SD)	69 (15.9)	66.9 (18.8)	.249
Male sex	79 (44)	78 (45)	.470
ASA grade III-IV	44 (25)	47 (27)	.467
History of pancreatitis, no. (%)	14 (8)	11 (6)	.356
Previous failed ERCP, no. (%)	9 (5)	11 (6)	.451
Indications, no. (%)			
Choledocholithiasis	103 (58)	102 (59)	.782
Malignant jaundice	27 (15)	24 (14)	.473
Dilated CBD	18 (10)	18 (10)	.564
Bile leaks	8 (4)	7 (4)	.462
Acute gallstone pancreatitis	8 (4)	9 (5)	.403
Other	14 (8)	12 (7)	.516
Final diagnosis			
Choledocholithiasis	81 (46)	79 (46)	.563
Normal cholangiogram findings	42 (24)	38 (22)	.491
Malignant biliary stricture	33 (18)	31 (18)	.533
Bile leaks	5 (3)	5 (3)	.651
Benign biliary stricture	5 (3)	5 (3)	.597
Other	12 (7)	14 (8)	.552
Pancreatogram	16 (9)	22 (13)	.148
Sphincterotomy	173 (97)	171 (99)	.123

SD, Standard deviation; *ASA*, American Society of Anesthesiologists; *CBD*, common bile duct.

individual precut technique in terms of safety or success.[16] However, theoretically, NKF may have a lower rate of pancreatitis compared with the classic precut technique because the pancreatic orifice is avoided; nonetheless, further studies are required to clarify this issue.[16]

As expected, the biliary cannulation success rate after standard cannulation attempts was higher with the late precut (80%) than the early precut (73%) strategy, although not achieving statistical significance ($P = .092$). The registered CBD cannulation rates following a standard approach are comparable to those of existing studies, such as the 67% cannulation rate reported by Lim et al[17] in less than 5 minutes and the 83% reported by Bruins Slot et al[2] within a time limit of 30 minutes. The overall biliary cannulation rate higher than 90% obtained in this study was also comparable to other reports from tertiary centers.[3,6,9] When a second ERCP was performed in the primary failures, the overall CBD cannulation improved to more than 96% in both groups. The strategy of performing a second ERCP when an NKF is unsuccessful in the first ERCP was highly effective and safe, as previously reported.[17,18] The results suggest that the success rates for these 2 cannulation strategies are similar.

Despite the higher success rate of the standard cannulation in the late precut strategy, the reported 7% difference entailed spending an extra time (11 minutes) on the complete procedure (14 minutes vs 25 minutes). The difference in the ERCP duration when NKF was performed (18.5 minutes vs 31.3 minutes) was based on the initial duration of the standard attempts and not the NKF itself because the average difference in duration of the NKF (albeit statistically significant) between the 2 strategies (5.3 minutes vs 6.5 minutes) was only 1.2 minutes. The shorter duration of the ERCP may be clinically beneficial if one considers the relatively high percentage of elderly and advanced grade ASA patients (>25% grades III/IV). It is important to emphasize that the complexity of the ERCP procedures was comparable, and both endoscopists had previous similar indicators. The impact of lowering the threshold of the precut timing in the total duration of the

TABLE 3. ERCP and NKF success rate

	Group A (n = 178), no. (%)	Group B (n = 172), no. (%)	*P* value
Successful standard cannulation	130 (73)	137 (80)	.092
Fistulotomy attempt	48 (27)	35 (20)	.092
Cannulation success after NKF (first ERCP)	41 (85)	24 (69)	.059
Cannulation success in the first ERCP	171 (96)	161 (94)	.221
Overall fistulotomy success	45 (94)	29 (83)	.509
Overall biliary cannulation rate	175 (98)	165 (96)	.532

NKF, Needle-knife fistulotomy.

TABLE 4. ERCP adverse events

	Group A (n = 178), no. (%)	Group B (n = 172), no. (%)	*P* value
Adverse events (<30 days)	11 (6)	11 (6)	.478
Pancreatitis	7 (4)	9 (5)	–
Bleeding	4 (2)	2 (1)	–
Successful standard cannulation	7 (5)	8 (6)	.921
Pancreatitis	5 (4)	6 (4)	–
Mild	3 (2)	4 (3)	–
Moderate	1 (1)	2 (2)	–
Severe	1 (1)	0 (0)	–
Bleeding (mild)	2 (2)	2 (2)	–
NKF after unsuccessful standard cannulation	4 (8)	3 (9)	.644
Pancreatitis (mild)	2 (4)	3 (9)	–
Bleeding (mild)	2 (4)	0 (0)	–

NKF, Needle-knife fistulotomy.

ERCP has seldomly been addressed in previous studies, and as far as it is known, this is the first study to report this variable in detail when comparing 2 cannulation strategies with different precut timings.

Although precut strategy may increase the rate of a successful cannulation to more than 95%,[2,6,17] several prospective studies have indicated the precut strategy to be an independent risk factor for post-ERCP adverse events, particularly pancreatitis.[4,6,19] The adverse event rate for the precut strategy reported in the medical literature varies from 2% to 30%, depending on several factors, including the expertise of the center, the selection of patients, and the design of the study.[4,20,21] As the use of the precut strategy generally follows a difficult cannulation, it remains a matter of debate whether the increased risk is related to the precut itself or is linked to the manipulation of the papilla that precedes it. A difficult cannulation is characterized by repeated biliary attempts and/or manipulation (wires and injection of contrast) of the main pancreatic duct, which is in likely to induce trauma, edema, and inflammation to the papillary bed, thus obstructing main pancreatic duct drainage.[22] Furthermore, the NKF is technically challenging because of the need to master the control of the needle-knife (especially the depth) as well as the need to be proficient in recognizing the CBD.[23]

Although the overall post-ERCP adverse events were similar with both cannulation strategies (6.2% vs 6.4%), when the NKF subgroups were analyzed, a tendency for a higher pancreatitis risk became apparent, albeit not statistically significant, in the late NKF (8.6% vs 4.2%). The pancreatitis rate for the early precut strategy is comparable between the 2 subgroups (A1, 3.8% and A2, 4.2%),

TABLE 5. ERCP procedure and CBD cannulation duration

	Group A (min)	Group B (min)	*P* value
Duration of CBD cannulation attempts			
Successful standard cannulation, mean (SD)	4.4 (0,5)	12.3 (2,4)	<.001
Successful NKF cannulation, mean (SD)	5.3 (3.9)	6.5 (3.3)	<.001
Failed NKF cannulation, mean (range)	12.2 (2.1-14.1)	11.8 (3.1-13.8)	.187
Total duration of ERCP procedure			
Successful standard cannulation, mean (SD)	14 (10,9)	25 (15,4)	<.001
NKF after unsuccessful standard cannulation, mean (SD)	18,5 (12,8)	31,3 (15,3)	<.001

CBD, Common bile duct; *SD*, standard deviation; *NKF*, needle-knife fistulotomy.

suggesting that the actual procedure of NKF is not the risk factor for pancreatitis. Lim et al[17] also reported a comparable post-ERCP pancreatitis rate between the early NKF patients and the standard cannulation group (4.2% vs 3.4%). The probable culprit is the longer duration of standard attempts, as suggested by the late precut strategy. Another interesting point is the fact that the only severe adverse event occurred in the least probable group: successful expeditious standard cannulation subgroup. An easy biliary cannulation does not preclude a pancreatitis. This supports the notion that the mechanism of post-ERCP pancreatitis is complex and further studies are required to unveil it. We should emphasize that in our unit, we do not perform sphincter of Oddi manometry, nor do we offer or perform ERCP for suspected sphincter of Oddi dysfunction type III patients. All cases of bleeding were mild, with no need for transfusions.

As the historical overall adverse event rate was low, including pancreatitis, prophylactic pancreatic stenting is seldomly performed at our center. In this cohort of patients, no pancreatic stents were used, although currently there is strong evidence recommending periprocedural rectal administration of nonsteroidal anti-inflammatory drugs in all ERCPs and/or pancreatic stents in high-risk patients.[24]

These results suggest that an early precut strategy is at least as successful and safe as the classic cannulation strategy, but with 1 main advantage: there is a substantial reduction in the duration of the ERCP. Additionally, if the endoscopist is experienced in these techniques, why is an early precut strategy not the preferred approach? Because the results were obtained in a unit with expertise in ERCP and NKF, this suggestion cannot be applicable to the average endoscopist, as recommended by other authors.[16]

The main drawback of this study could be considered our study design. The rationale behind this study was that a simple strategy (early NKF strategy) would result in an equal or higher success rate of cannulation, with a similar or lower proportion of adverse events and possibly saving time. Because previous studies reported a diversity of outcomes estimates, the number of patients needed to perform a randomized, controlled trial would be difficult to calculate, and a very large number of patients would be needed if we anticipate differences of 5% in terms of adverse event rates and/or cannulation rates and/or time spent on the fistulotomy that was seldom described before.[9] Thus, we decided to simply describe our experience using (as much as possible) standardized procedures prospectively and for the first time address all 3 outcomes combined. Our data could now give more support for a multicenter trial design to increase the evidence of our recommendations, even though it would be an extremely difficult project to implement.

In conclusion, the early use of a precut fistulotomy is as safe and effective as the classic approach of performing the precut only after a difficult biliary cannulation. Moreover, the results suggest that the risk of post-ERCP pancreatitis may originate from the difficult biliary cannulation and not the fistulotomy itself. In addition, this strategy substantially decreases the time to perform the ERCP, an issue that should be addressed in future studies, taking into consideration other factors such as costs, scheduling, and anesthesia.

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6
Learning curve in NKF

Gaining competence in needle-knife fistulotomy - can I begin on my own?
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(submitted)

Title:

Gaining competence in needle knife fistulotomy - can I begin on my own?

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Abstract

Background and study aims:

While there are guidelines for appropriate training in ERCP, these are non-existent for needle knife precut. The aim of this study was: (1) evaluate the experience curve of three endoscopists in needle knife fistulotomy (NKF); (2) propose a minimum number of NKF procedures to attest proficiency.

Patients and Methods:

Between November 1997 and March 2011, the first 120 consecutive NKF performed by three endoscopists (A, B and C) were selected (360 patients) from three centers. Each group of 120 patients was chronologically ordered into three subgroups of 40. The main outcomes were: NKF use, NKF success and post-ERCP complications.

Results:

The need for NKF did not decrease over time. The NKF success rate in the first attempt for endoscopist A and C in each of the 3 subgroups was 85%/85%, 87,5%/87,5% and 87,5%/90% respectively. Furthermore, both demonstrated a high NKF success in their initial 20 NKFs (85% and 80%, respectively). Endoscopist B however presented a different pattern as the success rate initiated at 60%, then rose to 82,5% and 85% for the last group (p=0,03). Complications were mild (16 of the 19 occurrences) with no clear reduction with increased experience.

Conclusions:

A skillful endoscopist may expect to master NKF easily with few complications. While some endoscopists could begin on their own because of their innate skills, the vast majority should have a formal training period to speed up their learning curve. We propose a minimum of twenty NKF precuts to attest a trainee's competence in this procedure.

KEYWORDS:

ERCP, precut, fistulotomy, learning curve, training

Gaining competence in needle knife fistulotomy - can I begin on my own?

Introduction

The need to decrease costs in all healthcare systems has brought quality measurement to the forefront of modern medicine, endoscopy included[1,2]. High value endoscopy is positively correlated with an adequate training program[3,4]. Concerning endoscopic retrograde cholangiopancreatography (ERCP) the selective cannulation of the common bile duct (CBD) is one of the most demanding maneuvers that an interventional endoscopist is required to master[1]. Even among experienced endoscopists, biliary cannulation is unsuccessful in between 15-30% of cases, when only conventional methods are employed[5,6]. A sustainable cannulation rate above 90% implies the performance of alternative techniques of access, such as the precut. This rescue strategy consists in the incision of the papilla to facilitate the access to the CBD[1,7]. Precut, properly needle knife fistulotomy (NKF), increases the yield of cannulation and appears to be safe, when performed by experienced endoscopists[8,9]. Recent studies support a trend to its early implementation in the cannulation algorithm, as a process to optimize its safety profile and decrease the overall duration of the ERCP[10]. Given the potential usefulness a question immediately arises, how to achieve competency in this procedure? Until now, no national or international recommendations have been issued regarding how much training is necessary for an endoscopist to achieve technical proficiency in performing precut techniques[11]. Although in ERCP it is suggested that a trainee should perform a minimum of 200 procedures to achieve competency, the learning curve associated with NKF is uncertain[12,13]. Given the huge difficulties in performing a large prospective study, due to time constrains (several years of follow-up required) and a limited number of endoscopists performing the technique on a regular basis in order to achieve an adequate sample size, insights from the reported

experience of skilled endoscopists are valuable to support expert based considerations/recommendations. Unfortunately, only a few articles have been published, all of which single endoscopist reports, with some divergent conclusions [11,14-17]. Two of these articles point to the need for further studies with multiple operators. The aim of this study was to evaluate the use, success and complications of needle knife fistulotomy (NKF) over time and to establish a minimum number of NKF procedures to acquire competence. It is the largest cohort reported to date and the first to include three operators.

Patients/Material and Methods

Study design, selection of participants and operators

This cohort retrospective study was carried out with the workload of three experienced endoscopists (>200 ERCPs/ year) in three referral centers for ERCP in Portugal. All patients with naive papilla undergoing an NKF during an ERCP for a biliary indication were eligible for this study. Exclusion criteria were surgically altered gastro-duodenal anatomy, abnormal coagulation tests and tumors of the papilla. For the study purpose, the first 120 consecutive patients submitted to NKF by each endoscopist were selected. The 120 patients were chronologically divided into three groups of 40: group 1 (1st to 40th), group 2 (41th to 80th) and group 3 (80th to 120th). The enrollment period occurred between: November 2006 to December 2010 for Endoscopist A (EA), November 2006 to March 2011 for Endoscopist B (EB) and November 1997 to December 2001 for Endoscopist C (EC). All three endoscopists had previous training in ERCP, but only EA had exposure to NKF during his training program, which did not include hands-on. EA performed part of his program under the supervision of EC. All three began performing the procedure (NKF) in their hospitals without any specific supervision; EA and EC in the first year after training,

while EB only performed his first NKF 10 years after.

All patients gave written consent for the procedure and the Ethic committee of the institutions approved the study.

ERCP and biliary cannulation algorithm

All patients were prepared and sedated (by an anesthesiologist) as standard medical practice. The three endoscopists used a therapeutic videoduodenoscope in all of the ERCPs performed (EA and EB: TJF 160 VR, Olympus Corporation, Melville, NY; EC: Pentax 3440T, Pentax Corporation, Hamburg). If deep biliary cannulation was not successful using a standard technique within a time frame of 12 to 15 minutes, a NFK was performed using a needle-knife (presented as first attempt). After the ERCP was completed, all patients were admitted for observation, for at least 24h before discharge. Whenever the endoscopists failed a deep cannulation of the biliary duct, a second ERCP was scheduled 7-14 days later and performed when possible (presented as global attempt). Prophylaxis of post-ERCP pancreatitis (either with the use of a pancreatic stent or with medication) was not used in any of the studied patients. ERCP was not performed on suspected sphincter of Oddi dysfunction (SOD) type II or III patients.

Standard biliary cannulation

Selective cannulation of the bile duct was initially attempted by EA and EB with a triple lumen sphincterotome (Ultratome XL, Boston Scientific, Natick, MA), preloaded with contrast and a guidewire (Jagwire, Boston Scientific, Natick, MA), and by EC with a double lumen sphincterotome (Ultratome, Boston Scientific, Natick, MA), preloaded with contrast. If biliary cannulation was not achieved using this equipment, a different biliary catheter or guidewire could be used at the discretion of the endoscopist.

Needle-knife fistulotomy

NFK was performed using a needle-knife (EA and EB: Olympus KD -11Q, Olympus Corporation, Melville, NY; EC: Microknife, Boston Scientific, Natick, MA) with electrosurgical current in the endocut mode (EA and EB: Olympus-PSD 60, Olympus Corporation, Melville, NY; EC: ICC200, ERBE, Electromedizin GmbH, Tubingen, Germany).

The NKF procedure was performed by making a puncture in the papilla above the orifice, and then cutting along an 11 o'clock axis either upward or downwards, depending on where the incision started in the papillary mound, while maintaining at least a 3mm free distance from the papillary orifice. The cut was slowly extended until the muscle of the intraduodenal portion of the common bile duct was exposed; then a small cut was performed in the muscle with the needle knife, creating a fistula. The cannulation of the bile duct was performed directly with the closed needle knife, if it slipped easily up, or, in a minority of cases, after gently probing the fistula with a preloaded wire in a papillotome.

The selective cannulation was confirmed by the injection of a low-osmolality non-ionic radiological contrast (Ultravist, Iopromide, Bayer Schering Pharma, Berlin, Germany) and the needle knife was exchanged over the wire for the sphincterotome. After deep cannulation was achieved, a cholangiogram was taken. If necessary, the sphincterotomy was extended with a standard sphincterotome (usually until the limit of the papillary mound) in the endocut mode and the necessary maneuvers were performed.

Variables and Data Collection

Data were prospectively collected by the endoscopists in a detailed form following each ERCP and subsequently registered in the unit's endoscopic database. The database included: demographic data, indications, anatomic abnormalities, biliary/pancreatic cannulation, biliary access technique, diagnosis, therapeutic procedures, intra-procedural and post-ERCP complications. Post-procedural complications (30 day follow-up) were retrospectively collected (research nurse). Intra-procedural and post-procedural complications were defined and graded according to guidelines established by Cotton *et al.*[18,19].

Statistical Analysis

Statistical analysis was performed using the software package IBM SPSS Statistics version 20.0.0. Interval variables were summarized using the mean and standard deviation and nominal/ ordinal variables using proportions. Age, sex, indication, rate of NKF utilization, success in cannulation (first attempt and global) and occurrence of complications were compared between the different groups for each endoscopist. Differences between groups were tested by using Pearson's chi-square test or Fisher's exact test for categorical, whereas continuous variables were analyzed using non-parametric tests (Kruskall Wallis and Mann-Whitney U test). A p value of less than 0.05 was considered statistically significant.

Results

Procedures

The number of ERCPs performed by the three endoscopists during the enrollment period totaled EA=853 (50 months), EB=920 (53 months) and EC=1038 (50 months). From these groups, the number of patients with naive papilla were: EA= 633, EB= 683 and EC= 770.

Demographics and indications

All groups presented a higher percentage of females. The mean age varied from a minimum of 64.4 years (EC/Group2) to a maximum of 69.9 years (EC/Group3). Jaundice and choledocholithiasis were the most common indications for ERCP. No significant differences were observed with regards to age, sex or indications between groups (table 1).

NKF use

The relative frequency of NKF use over the study period for each endoscopist did not exhibit a trend. EA performed NKF as a rescue technique in 18.2%, 19.9% and 18.9% of the ERCPs. For EB, NKF rate in the first group was 15.1%, 20.2% in the second and 16.7% in the last group. EC performed NKF in 13.4%, 17.2% and 16.7% respectively.

Cannulation success

EA's NKF success rate in the first attempt was 85%, 87,5% and 87,5% for the three groups. EC's rate for the first attempt was similar with 85%, 87,5% and 90%. EB however, presented a different pattern as the success rate initiated at 60%, for the first group and then rose during the duration of the study to 82,5% and 85% for the subsequent groups (p=0,03). The overall cannulation rate for all endoscopists in the last group (Group C) was above 90%. With the exception of the temporal positive trend for NKF success for EB, all other differences between groups did not achieve statistical significance (table 2).

The first group of 40 patients for each endoscopist was further subdivided into two groups of 20 in order to evaluate the cannulation success in the early phase of the learning curve (figure 1). The success rate in the initial ERCP for EA and EC was 85% and 80% respectively, while for EB it was 55%.

Adverse events

AEs related to the procedure were mild (16 out of the 19 occurrences) with no decrease registered over the study period (table 3). Pancreatitis was the most common complication; nonetheless, no common apparent trend was registered during the duration of the study. Only one severe case was recorded which was resolved with appropriate treatment. EA exhibited a decrease in the post-ERCP pancreatitis rate from 10% in the first group to 5% in the second. The rate of pancreatitis for EB increased from the first group to the second, but then decreased in the third: 5%, 7.5% and 5%. EC presented a different pattern starting off with 7.5%, and then increasing to 10% in the later groups.

Discussion

In recent years performance measurement in healthcare has become an established practice[2,20]. Growing health care expenditures and increasing awareness of the various stakeholders have transformed quality into one of the most important dimensions in modern medicine. ERCP is a complex endoscopic procedure established in the management of biliary and pancreatic disorders [16,18,19]. In order to assure high-quality endoscopy the ASGE developed several quality indicators for ERCP[12,21].Quality in ERCP lies in adequate training in order to learn the necessary technical and cognitive skills. While there are guidelines for appropriate training in ERCP, there are none for NKF [11,22]. Although much has been published regarding the efficacy and safety of this technique, only five reports have evaluated the learning curve for NKF, all of which relate the experience of single endoscopists[11,14-17]. This study is unique in that it assesses the learning curve of NKF from three endoscopists, in the largest aggregated cohort of patients published to date.

Siegel *et al.*. reported the first precut papillotomy with a traction papillotome in 1980[23]. Subsequently, in 1986, Huibregtse *et al.*. reported a new precut technique, in which the incision of the papillary roof was performed by means of needle knife[24]. Needle knife precut papillotomy (either the classic approach or NKF) is the most common option for achieving CBD cannulation during ERCP when endoscopists face difficult biliary cannulation [25,26]. Given its usefulness in the cannulation algorithm, evidence-based data is needed to support recommendations for adequate training.

The data from this study suggests that the effect of the number of procedures in the NKF success rate is distinct between endoscopists. EA and EC began with a success rate of over 80%, and the improvement afterwards was minimal. Akaraviputh *et al.*. reported a similar pattern when evaluating the success rate of NKF over 5 groups of 50 patients; the rates in the first and in the last group were identical with a value of 88% [16]. The NKF volume, on the other hand,

had a strong positive effect in the yield of cannulation for EB. There was a significant increase in the cannulation rate from an initial 60%, in the first 40 patients, to 85% in the last group. Robinson *et al.*. reported a similar pattern with an increase from 68% to 76 % when comparing the first 50 patients with the subsequent group of 25 [17]. Therefore, our results demonstrate that some degree of improvement exists in the cannulation success rate with NKF as procedural experience increases, although this effect might be greater for some operators and smaller or minimal for others. By combining our results with the results from other studies, we suggest that technical experience is an important determinant of procedural success, for endoscopists with average skill in ERCP who present sub-optimal precut cannulation rates (below 70%) soon after beginning to perform NKF. On the other hand, for those who start with cannulation success rates of 80% or higher, cumulative volume seems to be a less significant influencing factor and innate technical skills and/or younger age at starting may play an important role in certain cases.

Harewood *et al.* reported a decrease for the need of precut over time, suggesting that the procedure appears to decrease with ERCP experience[11]. In his report the rate of NKF decreased from 13% in the first 385 patients to 9% in the last 583 patients. Other authors reported distinct conclusions, such as Rollhauser *et al.* and Fukatsu *et al.* who reported an increase of precut with ERCP experience[14,15]. Our results did not demonstrate a decrease in the use of NKF over time and suggested that each endoscopist tends to maintain a stable baseline level of precut utilization over time. These distinct trends between studies could be explained by personal preferences in the cannulation algorithm, and most importantly by the timing of the precut that each endoscopist considered. Therefore, the proportion of NKF in the total number of biliary attempts should not be interpreted as a surrogate indicator of the cannulation skill of an endoscopist[27].

The overall post-ERCP complications did not demonstrate a decreasing tendency over time. When we look to post-ERCP pancreatitis in particular, the trend is distinct between endoscopists, and once again there is no stable

pattern for a lower rate of pancreatitis as experience is accumulated. EA and EB had a decrease in the rate of pancreatitis from 10% to 5% (between G1 and G2), and from 7,5% to 5% (between G2 and G3), respectively. Nonetheless EC demonstrated an increase from 7,5% to 10% in the last group. EA and EB had the lowest rate of pancreatitis (5%) in the last 40 patients submitted to NKF, while EC had the highest with 10%. Although the number of patients is reduced, one possible explanation for the higher rates of pancreatitis for EC, may result from the technique of cannulation employed. EC confirmed the duct through injection of contrast, while the other two inserted the wire deep in the duct before injection. This could increase the proportion of patients with inadvertent injection of contrast to the main pancreatic duct, which is per se a risk factor for post-ERCP pancreatitis, not specifically related to the NKF technique. The results from other studies are diverse, Harewood *et al.*. report that the complications did not diminish over time and Fukatsu *et al.*. report an increase from 10% to 16%[11,15]. Contrarily Robinson *et al.*. report a decrease in the complications over time, which may be explained by the increased use of pancreatic stents in the latter groups[17]. One may argue that the inexistence of a clear decline in the complication rates results from the use of precut only after a difficult biliary cannulation. It is interesting to note that the precut procedures applied to all of the patients encompassed in the precut training reports, were only performed following a difficult biliary cannulation. As this procedure is in itself a risk factor for post-ERCP complications, in particular pancreatitis, it could partially offset the positive effect of experience[28]. Another possible explanation is an inherent baseline complication rate associated with the precut that cannot be diminished by experience, as Harewood *et al.*. suggest[11].

Our study, similar to others, indicates that a skilled endoscopist with the proper cognitive skills may safely and effectively learn the needle knife precut technique without supervision. Nonetheless it must be emphasized that these endoscopists are not a sample representing the average endoscopists, but rather a specific group of professionals who perform a large volume of ERCPs

per year (>200/ year). Although all endoscopists from the published studies initiated the technique without previous hands-on training, it is strongly advised that, given the potential medical legal implications, a fellowship should be setup in an ERCP center with a liberal use of the technique. The studies published often suggest 40 to 50 NKF as the adequate number of precuts for training, given most endoscopists after this threshold report a needle-knife precut success above 70%[5,11,14,16,17]. Although suggesting a minimum number of precuts for accessing the proficiency in NKF is problematic, we propose 20 NKFs (and not 40 or 50) for the first moment of assessment. This number takes into consideration the existence of some endoscopists that become skillful in the technique in an earlier phase of their learning curve, as demonstrated in our study by EA and EC. Given that few centers in the world perform more than 40 precuts per year, a full-time or part-time half program is required. Obviously, the training in NKF should only be offered to endoscopists that achieve a selective biliary cannulation above 80% using a standard approach. During the training period, the trainee should be able to master the more complex aspects of the precut, such as the identification of the correct axis of the incision and the recognition of the CBD duct after unroofing the papilla[1,16].

The insights from the presented data together with the existing studies could contribute towards the establishment of evidence-based recommendations and the design of prospective studies addressing the issue.

In summary, precut with few complications is easily learned by a skillful endoscopist with the proper cognitive skills performing a high number of ERCPs. While some endoscopists could begin on their own because of their innate skills, the vast majority should have a formal training period to speed up their learning curve. However, as the focus of ERCP in the twenty first century should be on quality, the precut procedure should be an obligatory issue in the ERCP training curriculum for all future interventional endoscopists. We propose a minimum of twenty NKF precuts to first attest a trainee's competence in this procedure.

Table 1- Demographics and clinical indications

	A			B			C			
	Group 1	**Group 2**	**Group 3**	**Group 1**	**Group 2**	**Group 3**	**Group 1**	**Group 2**	**Group 3**	**P**
	n(%)	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	
Sex [% female)	25 (62,5)	23 (57,5)	22 (55)	24 (60)	21 (52,5)	23 (57,5)	23 (57,5)	24 (60)	21 (52,5)	0,88
Age [*mean(SD)]*	68,5 (13,9)	66,4 (15,4)	65,9 (17)	69,2 (14,1)	68,2 (17)	66,8 (14)	69,5 (15,9)	64,4 (18,4)	69,9 (17,2)	0,89
No. ERCPs (% NKF)	220 (18,2)	201 (19,9)	212 (18,87)	265 (15,1)	198 (20,2)	220 (16,67)	298 (13,42)	232 (17,24)	240 (16,67)	0,46
Indications										
Jaundice	13 (32,5)	15 (37,5)	14 (35)	14 (35)	12 (30)	12 (30)	18 (45)	16 (40)	15 (37,5)	
Choledocholithiasis	15 (37,5)	12 (30)	13 (32,5)	17 (42,5)	12 (30)	13 (32,5)	12 (30)	14 (35)	16 (40)	
Biliary/pancreatic cancer	5 (12,5)	3 (7,5)	4 (10)	1 (2,5)	5 (12,5)	4 (10)	5 (12,5)	4 (10)	4 (10)	
Dilated CBD	3 (7,5)	8 (20)	3 (7,5)	3 (7,5)	4 (10)	6 (15)	3 (7,5)	2 (5)	1 (2,5)	
Injuries	3 (7,5)	2 (5)	2 (5)	2 (5)	2 (5)	2 (5)	1 (2,5)	2 (5)	2 (5)	
Others	1 (7,5)	2 (5)	2 (5)	3 (7,5)	5 (12,5)	3 (7,5)	1 (2,5)	2 (5)	2 (5)	

Table 2- NKF cannulation rates and adverse events

		Group 1 n(%)	Group 2 n(%)	Group 3 n(%)	p
Cannulation					
A	First Attempt	34 (85)	35 (87,5)	35 (87,5)	0,95
	Global	37 (92,5)	38 (95)	38 (95)	0,47
B	First Attempt	24 (60)	33 (82,5)	34 (85)	0,03
	Global	33 (82,5)	35 (87,5)	36(90)	0,68
C	First Attempt	34 (85)	35 (87,5)	36 (90)	0,42
	Global	38 (95)	36 (90)	37 (92,5)	0,76
Complications					
A	Overall	4 (10)	2 (5)	4 (10)	0,79
	Pancreatitis	4 (10)	2 (5)	2 (5)	0,43
	Bleeding	0 (0)	0 (0)	2(5)	0,26
B	Overall	2(5)	4 (10)	3 (7,5)	0,32
	Pancreatitis	2 (5)	3 (7,5)	2 (5)	0,68
	Bleeding	0 (0)	1(2,5)	0 (0)	0,81
C	Overall	4 (10)	4 (10)	5 (12,5)	0,56
	Pancreatitis	3 (7,5)	4 (10)	4 (10)	0,58
	Bleeding	1 (2,5)	0 (0)	1 (2,5)	0,68

Figure 1- NKF learning curve

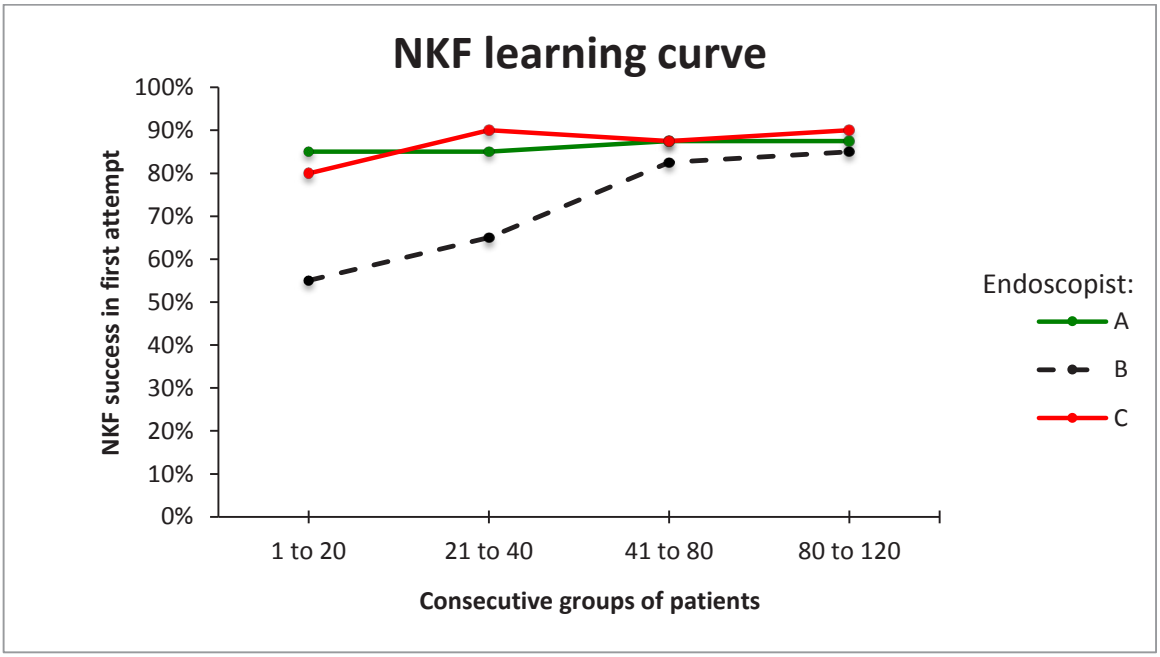

Table 3- Published series about needle-knife precut learning curve *(all single endoscopist)*

Author	NKF (n)	Groups of Patients (n)	Cannulation rate (first attempt) (%)	Cannulation rate (global) (%)	Complications (%)	NKF rate by group (%)
Harewood *et al* [11]	253	4 of 50 and the last with 53	*na*	88-89-90-88-98↑	12-18-20-12-14⊘	13-12-10-10-9↓
Rollhauser *et al* [14]	68	22 and 46	64-74 *↑↑	86-98↑	*na*	4,7-6,3 ↑
Fukatsu *et al* [15]	104***	41 and 63	80-95 *↑↑	90-98↑	10-16↑	15-20↑
Akaraviputh *et al* [16]	200**	4 of 50	88-86-94-82⊘	94-96-94-92⊘	*na*	*na*
Robinson et al [17]	*150*	*6 of 25*	*64-68-76-80-76-84*↑↑	*84-84-88-88-88-92*↑	*8-8-16-4-0-4*↓	*na*

na: non available; p<0,05;** NKF and classic precut; *** classic precut/// ⊘:no trend; ↑↑:positive trend and p<0,05; ↑:positive trend; ↓:negative trend*

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PART III

Discussion and conclusions

7
General Discussion

ERCP has revolutionized the diagnosis and therapy of biliary and pancreatic disorders (Cohen *et al.* 2002; Cha *et al.* 2013). However, its benefits in the minimally invasive management of these disorders are compromised by a higher potential for serious complications than in most of the other endoscopic techniques (Loperfido *et al.* 1998; Cohen *et al.* 2002).

As previously described, precut sphincterotomy is a controversial technique, and according to published reports, the use of cutting techniques varies between centers from 0% to 50% of the cannulations attempted (Hogan 1988; Jowell *et al.* 1996; Vandervoort & Tham 2006; Parlak *et al.* 2007; Verma *et al.* 2007; Fukatsu *et al.* 2009).

The willingness to investigate this issue came from our perception that most of the criticisms were biased and unfounded. The successful use of NKF in our unit to overcome situations of difficult biliary cannulation coupled to the difficulties observed in other centers in achieving biliary cannulation were the main reasons to embark on this research project.

In prospective multicenter studies involving academic and community practices with endoscopists with varying levels of experience, the needle-knife precut has been shown to be an independent risk factor for post-ERCP complications, with an adjusted odds ratio of 3.61 in a study from Freeman *et al.* (Freeman *et al.* 1996) and a relative risk of 1.87 in a study from Loperfido *et al.* (Loperfido *et al.* 1998). More recently, Glomsaker *et al.* published a prospective study involving 11 Norwegian hospitals and 2808 ERCPs, in which precut was a predictive factor for the development of severe complications (Glomsaker *et al.* 2012).

In general, studies involving endoscopists with varied experience have demonstrated that a precut papillotomy significantly increased the risk of

complications, whereas those from tertiary centers have not (Freeman *et al.* 1996; Loperfido *et al.* 1998; Harewood & Baron 2002). There is a lack of large series studies on NKF from general hospitals aimed at assessing if the results from tertiary centers are reproducible in other settings (Loperfido *et al.* 1998; Abu-Hamda *et al.* 2005; Ang *et al.* 2010).

Convinced of the benefits associated with needle knife fistulotomy, we decided to review our series of patients submitted to NKF between November 2006 and December 2010. The main advantage of this retrospective analysis was that all procedural data, including the first 24 hour follow-up, was prospectively collected and registered in a predefined form, put into practise since ERCP was implemented in the department. An independent investigator blinded to the intervention performed the collection of post-procedural complications in the 30 days after discharge. With 204 patients, this is the third largest series reported to date from a single center, and the largest in a general hospital setting (Harewood & Baron 2002; Donnellan *et al.* 2010). The outcomes were analyzed on an intention-to-treat basis. The patients included in this study represent an unselected consecutive group, in all of whom the standard biliary cannulation failed. During the study period, all ERCPs were performed by two experienced endoscopists, who followed a standardized cannulation protocol. A difficult biliary cannulation was assumed as a failure if a selective biliary wire-guided access was not achieved after 12-15 minutes of attempts. The definition of a difficult biliary cannulation in the literature, as previously described in the introduction (Part I, chapter 1.3), is diverse, arbitrary and depends largely on the judgment of the endoscopist (Akaraviputh *et al.* 2008; Udd *et al.* 2010). A standardized definition of a difficult biliary cannulation would be a major advance in this field for comparative purposes.

Our NKF rate of 18.7%, i.e. the NKF as a percentage of total number of ERCPs, is comparable to other high-volume centers in which needle-knife precut is the first rescue option (O'Connor *et al.* 1997; Akaraviputh *et al.* 2008). Bruins Slot *et al.* reported a NKF use of 17% (180/1071) and Lim *et al.* performed 72 NKFs over 218 ERCPs (33%) (Bruins Slot *et al.* 1996; Lim *et al.* 2012). Although some authors argue that a NKP is only necessary in a maximum of 5% of biliary cannulations, we strongly disagree with this opinion (Shakoor & Geenen 1992; Vandervoort & Carr-Locke 1996; Cotton 2010; Ang *et al.* 2011). We share the view of Rabenstein *et al.*, in that the frequency of NKP implementation is not a suitable measure of the skill and experience of the endoscopist in a high-volume center, but more a reflection

of the personal preference of the endoscopist (Rabenstein *et al.* 1997).

The success rate of NKF in the first attempt varies between 69% to 90%, significantly increasing the overall cholangiography success rate to over 90% (Kasmin *et al.* 1996; Harewood & Baron 2002; Donnellan *et al.* 2010). In our series, the use of NKF in the first ERCP increased the biliary cannulation from 81% to 96%; the fistulotomy success in the first ERCP was 81%. If cannulation failed in the first attempt despite NKF, a biliary cannulation was successful in the second NKF in 72%, increasing the overall cannulation rate to 98%. Our study supports the strategy of referring patients to a second ERCP, instead of immediately contemplating other more invasive techniques. Few studies have directly investigated the outcome of repeating an ERCP after the failed use of a needle knife (Rollhauser *et al.* 1998; Fukatsu *et al.* 2009; Kevans *et al.* 2010; Donnellan *et al.* 2012; Kim *et al.* 2012). Donnelan *et al.* reported a successful repeated cannulation rate of 75% in a retrospective series of 51 patients, following an initial NKF failure (Donnellan *et al.* 2012).

The overall complications following NKF, from several studies, varied from 5% to 20-30%. There are also reports from tertiary centers stating that the course of precutting is no different from standard cannulation, which highlights the importance of experience (Foutch 1995; Gholson & Favrot 1996; Rabenstein *et al.* 1997; Cennamo *et al.* 2010; Swan *et al.* 2013). The average rate of complications, if patients with SOD are excluded, is lower than 12% (Kahaleh *et al.* 2004; Robison *et al.* 2007; Lynch & Evans 2010). Complication rates are difficult to interpret due to varying patient populations, NKP techniques, different timings and procedure duration. Particular attention was paid to safety factors in the cannulation algorithm design for our unit. Cannulation was initially attempted with a sphincterotome preloaded with a guide wire, as this approach is more successful and safer than other standard approaches (Cortas *et al.* 1999; Schwacha *et al.* 2000; Fukatsu *et al.* 2009). The precut technique chosen was NKF, as there are studies that suggests a trend toward a lower incidence of pancreatitis with this technique (Harewood & Baron 2002; Abu-Hamda *et al.* 2005; Choudhary *et al.* 2014). Although technically more demanding, it is thought that as the pancreatic duct is not injured, the normal pancreatic flow is not compromised (Fazel *et al.* 2003; Bailey *et al.* 2010; Dumonceau *et al.* 2010; Testoni *et al.* 2011; Baillie 2012).

In our series, complications occurred in 16 patients (7.9%), which is comparable to other studies performed at high-volume centers with

experience in performing precut. The pancreatitis rate was 6.4% (n=13), which is equivalent to commonly quoted rates. In a large multicenter study performed in the United States pancreatitis occurred in 6.7% of 1,693 procedures (Freeman *et al.* 2001). Merely one patient had a severe complication (pancreatitis) and there were no fatalities, which emphasizes the safety of the procedure, although we must interpret this zero death rate with caution, taking into account the small number of patients enrolled. An interesting finding was the low incidence of bleeding (1%) when compared to 5.5% reported by Bruins Slot *et al.* or 8.6% reported by Kaffes *et al.* (Bruins Slot *et al.* 1996; Kaffes *et al.* 2005). A possible explanation may result from the settings used in the endocut current, with a relative high coagulation effect. A small bile duct diameter, often found in younger patients, has been emphasized as a risk factor for post-ERCP complications in studies from referral centers on biliary sphincterotomy (Sherman *et al.* 1991; Boender *et al.* 1994; Chen *et al.* 1994; Ang *et al.* 2010; Dumonceau *et al.* 2010). Freeman *et al.* found however that a small bile duct diameter increased the risk of pancreatitis only in the subgroup of patients with suspected SOD (Freeman *et al.* 1996). Pancreatitis occurred in 12% of patients in whom the diameter of the duct was large (>10 mm), 18% of those in whom it was normal (6-10 mm), and 31% of those in whom it was small (≤5 mm). Loperfido *et al.* recognized a small bile duct as an independent risk factor for major overall complications in ERCP (Loperfido *et al.* 1998). The notion that patients with smaller ducts and especially those with smaller ducts and SOD, are likely to have an increased incidence of pancreatitis is further supported by other studies (Laasch *et al.* 2003; Williams *et al.* 2007). The majority of the published studies have assessed potential risk factors for post-ERCP complications, but have not specifically for a precut procedure. Kasmin *et al.* did however observe that patients with small duct diameter had an increased complication rate after NKF (Kasmin *et al.* 1996). Unlike previous studies, the vast majority of complications were hemorrhage and perforation, instead of pancreatitis and all patients who developed complications had the presumptive diagnosis of SOD. In our study an association between CBD diameter and post-NKF complications was also detected, but surprisingly, it occurred in patients with no SOD. It was clear that the overall risk of complications was higher in the smaller than 4 mm group (13.9%), *versus* the remaining patients (4.5%). The risk of pancreatitis in the less-than-4-mm group was also higher (9.7%) than for the remaining patients (4.5%), although not statistically significant. The probability of

developing a complication after NKF was 3.4 times higher in patients with a thin CBD. We postulate that this risk is related to the technical difficulty in performing the fistulotomy, as the recognition of the duct is more difficult, the precision of the cut is reduced and consequently the probability of injuring the papillary base and the pancreatic duct is higher.

During the study period pancreatic duct stents or pharmacologic prophylaxis were not employed, which reinforces the results obtained. As our overall experience yielded a low pancreatitis rate, these prophylactic measures were seldom performed at that time. Patients in this study were largely enrolled before the emergence of the current evidence for prophylactic stent placement in preventing PEP. There is now a good body of literature, namely the European Society of Gastrointestinal Endoscopy (ESGE) guidelines on prophylaxis of post-ERCP pancreatitis published in 2010: for low-risk ERCPs, periprocedural rectal administration of non-steroidal anti-inflamatory drugs is recommended; for high-risk ERCPs, prophylactic pancreatic stent placement are strongly recommended (Lee *et al.* 2011; Dumonceau *et al.* 2010). In a randomized controlled trial by Cha *et al.* it was demonstrated that placing and maintaining a PD stent for NKP reduced the frequency and severity of post procedure pancreatitis (Cha *et al.* 2013). However, in a recent survey conducted by Hanna *et al.* in the United Kingdom less than 53% of ERCP endoscopists used pancreatic stenting or NSAIDs (Hanna *et al.* 2014).

We demonstrated that NKF is a safe and effective procedure in a difficult cannulation, increasing the biliary cannulation rate to above 90% in the first ERCP. The results published from tertiary centers are attainable in other settings by experienced endoscopists. The results of this study demonstrate that a thin bile duct is a patient-related risk factor for complications after NKF. In this subgroup of patients, extra-caution is required and pancreatic stents are probably recommended **(Aim 1 - Chapter 4)**.

Subsequent to attesting the safety and efficacy of NKF after a difficult biliary cannulation, the next logical step was to address the NKF timing in the cannulation algorithm. Managing a failed biliary cannulation is found to be confusing and contradictory, even among the experts (Vandervoort & Carr-Locke 1996). Should we persist with standard cannulation attempts, and use the needle knife as a late resort, or should we perform a precut early on? When is the optimal moment? Although NKP is a very useful tool in achieving biliary-ductal access when cannulation of the bile duct is not possible, it is not a simple process (Misra & Dwivedi 2008). Accepting the argument that experts will achieve a cannulation success above 95% with

or without precut techniques, the question that remains is which algorithm is the safest and most cost-effective to achieve the same success rate. It is controversial whether performing precut sphincterotomy to gain bile duct access adds to the risk of pancreatitis or merely reflects the prolonged cannulation attempts that precede its use (Freeman 1997). Since precutting generally follows a number of failed cannulation attempts, it is hard to clarify whether precutting as such or repeated cannulation is the prime culprit in post-procedure pancreatitis (Freeman 2003b; Espinel Diez *et al.* 2005; Testoni *et al.* 2011). A difficult cannulation is a well-known risk factor for post-ERCP complications, namely pancreatitis (Cheng *et al.* 2006; Williams *et al.* 2007). Trauma to the papilla and the pancreatic sphincter resulting from repeated attempts at biliary cannulation has been proven to be a risk factor for the development of PEP (Loperfido *et al.* 1998; Sherman *et al.* 1991; Freeman 2002); therefore the ESGE guidelines on post-ERCP prophylaxis recommends that the number of cannulation attempts should be minimized (Dumonceau *et al.* 2010). In a prospective multicenter study, Freeman *et al.* demonstrated several patient-related and procedure-related risk factors for PEP (Freeman *et al.* 2001). A difficult biliary cannulation was, by itself, significantly associated with pancreatitis by univariate and multivariate analysis. The odds ratio for a moderate-to-difficult cannulation was 3.41 (95% CI 2.13-5.47). The number of pancreatic injections was also associated with an increased risk of complications. Two or more injections into the pancreatic duct increased the risk to 2.72 (95% CI 1.43-5.17).

There are few prospective studies evaluating the early implementation of precut and most are single-arm studies (Kaffes *et al.* 2005; Parlak *et al.* 2007; Lim *et al.* 2012). Kaffes *et al.* reported that the early use of a needle knife precut (both classic precut and NKF), within 10 minutes of a failed biliary cannulation, was a safe and effective technique (Kaffes *et al.* 2005). Lim *et al.* performed an early NKF if selective cannulation was not achieved after five biliary attempts (Lim *et al.* 2012). The NKF improved the overall cannulation rate from 67% to 98%; the overall complications rate was 12.5%, with 4.2% of PEP. A very small number of randomized (Tang *et al.* 2005; Zhou *et al.* 2006; de Weerth *et al.* 2006; Khatibian *et al.* 2008; Manes *et al.* 2009; Cennamo *et al.* 2009; Swan *et al.* 2013) and non-randomized studies with small sample sizes have evaluated the role of early precut *versus* persistent attempts. In only 2 of the studies, NKF was the precut technique employed (Khatibian *et al.* 2008; Manes *et al.* 2009). The comparability is limited by major differences between studies, such as

differences in early precut definition, precut techniques, duration of precut and persistent attempts (Dumonceau *et al.* 2010). Cennamo *et al.* did not consider mild pancreatitis as a post-ERCP complication. Tang *et al.* reported the overall success of the persistent arm, but however included patients submitted to precut after a failed persistent cannulation in his results. When comparing two cannulation algorithms, the limited published studies on this topic have primarily compared an early precut strategy *versus* a persistent attempt strategy. None were designed to specifically test an early precut strategy *versus* the traditional late precut strategy, which is in reality the pertinent question that endoscopists want answered.

Certain of the safety of an earlier precut approach, we decided to test the hypothesis that a clearly defined early NKF strategy would be superior to the current practice of a precut after a difficult biliary cannulation. Comparable biliary cannulation success was expected, although with fewer complications (especially pancreatitis) and a much shorter ERCP procedure. This was the first study to evaluate two NKF strategies, addressing their practice impact, namely the effect in the overall ERCP duration. A well-designed prospective study has been conducted, which in multiple dimensions emulates a randomized controlled trial. Patients were assigned to each endoscopist according to available schedule (each endoscopist performed ERCP in a different day of the week) by an administrative assistant blinded to the study, as per standard process for the unit. In this way, there was a proper allocation sequence, with allocation concealment. On average each endoscopist usually received the same number of patients per week. In order to ensure patient safety, each endoscopist kept his preferred cannulation strategy throughout the study: endoscopist A, opted for an early NKF, while endoscopist B kept the unit's policy of a standard late NKF strategy. In fact, this was an obligatory requirement from the institutional ethics committee in order to guarantee patients would receive the best ERCP management. Furthermore, it could minimize the potential for a confirmation bias towards the proponent strategy. Another aspect that should be stressed is the timing chosen for the early precut strategy. In order to assess the real safety profile of NKF all the procedure-related risk factors were minimized in the early precut arm. The criteria for early timing are the most restrictive ever published (5 minutes; 5 biliary attempts; 1 MPD cannulation/ injection), thereby enabling to assess the risk potential of NKF, as the issue of papillary trauma was overcome. The definition of an easy cannulation was based on the criteria published by Freeman et *et al.* and Udd *et al.* (Freeman *et al.*

2001; Udd *et al.* 2010).

In the study, the rate of biliary cannulation was similar in the two strategies. In the first ERCP, successful cannulation increased after NKF from 73% to 96% in early NKF strategy and from 80% to 94% in late NKF strategy. These results are comparable with reports from other high-volume centers (Kasmin *et al.* 1996; Bruins Slot *et al.* 1996; Lim *et al.* 2012). Cennamo *et al.* reported a 74% cannulation rate achieved in less than 5 minutes following a standard biliary cannulation(Cennamo *et al.* 2009).

Although the overall complication rate is comparable, the evolution of PEP is different between strategies. In the early NKF arm, the rate of pancreatitis remained at 4% even after NKF was performed, while in the late NKF strategy, the rate of pancreatitis increased from 4% to 9% after the NKF in patients with difficult biliary cannulation. These observations not only support the notion that NKF *per se* is not a risk factor for PEP, but it is in fact the difficult biliary cannulation (15 minutes or 10 biliary attempts), as suggested in some earlier publications (Cennamo *et al.* 2010; Gong *et al.* 2010; Choudhary *et al.* 2014). In a recent meta-analysis Choudhary *et al.* reported a significant decrease in PEP when precut was performed within 5-10 minutes of a failed cannulation (Choudhary *et al.* 2014). The results from our study reinforce these findings, as the pancreatitis rate from patients submitted to NKF was similar to the patients with a successful standard cannulation within five minutes in the early precut arm.

The optimal timing of an early NKF is one in which there is a significant decrease in the overall ERCP duration, while ensuring safety and success. The success in biliary cannulation is high in the first few minutes with just a couple of standard biliary attempts (Udd *et al.* 2010; Davee *et al.* 2012); after this time frame the biliary cannulation success is progressively more difficult to achieve (Cennamo *et al.* 2009; Lim *et al.* 2012). An early precut strategy, applied at this optimal timing, accelerates again biliary cannulation and therefore dramatically decreases the ERCP duration. Gong *et al.* suggested that precut might not be the quicker method for biliary cannulation (Tang *et al.* 2005; Zhou *et al.* 2006; de Weerth *et al.* 2006; Gong *et al.* 2010). However these studies did not specifically address the optimal timing of the precut. In our study NKF was performed within the first five minutes if the biliary cannulation was not successful. This arbitrarily defined optimal timing had a tremendous impact on the overall duration of the ERCP. After 10 min, 96% of patients have been successfully cannulated through an early NKF strategy, while within the same time frame less

than 80% had been cannulated in the late NKF strategy. This significant reduction in time can be very important in areas related to sedation safety and operational efficiency (Kaushal *et al.* 2014). Providing the appropriate anesthesia for ERCP cases is challenging, especially for high risk patients, such as the elderly (≥80 years) and patients with ASA ≥III (Riphaus *et al.* 2005; Barnett *et al.* 2013). A prolonged ERCP procedure is a risk factor for cardiopulmonary complications during sedation, entailing a longer recovery period (Sharma *et al.* 2007). Given that a significant number of patients who undergo ERCP are high-risk patients (26% in our study), the strategy of an early NKF not only reduce the procedure time, but also helps to reduce the possible risks resulting from sedation.

One limitation of this study, which is common to most published studies on the topic, is the huge number of patients required to detect differences in rates of outcomes (i.e. success and complications) below 5%. A *post hoc* analysis using the proportions for pancreatitis reported in our study would require (at a 5% level of significance) a minimum sample size of about 964 patients (and an initial enrollment of at least 3,574 patients), to achieve 80% statistical power. Cennamo *et al.* and Tang *et al.* claim that only a large multicenter study, with many participating centers, could achieve the elevated number of patients required to compare two cannulation strategies involving precut (Tang *et al.* 2005; Cennamo *et al.* 2009). One must not however forget that one of the largest prospective multicenter studies to date on ERCP enrolled a maximum of 2,769 patients (Freeman *et al.* 1996; Loperfido *et al.* 1998).

We conclude that an early precut strategy significantly decreases the duration of an ERCP, while being at least as safe and effective as the late fistulotomy approach. Moreover, results suggest that the risk of post-ERCP pancreatitis may originate from the difficult biliary cannulation and not the fistulotomy itself. If the endoscopist is experienced in ERCP and NKF, a fistulotomy should be the first choice if a successful biliary cannulation is not achieved within the first 5 minutes. **(Aim 2 - Chapter 5).**

Given the tremendous potential demonstrated by NKF in the two previous studies, the last aim addressed the issue of training and competency. Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most technically demanding and high-risk procedures performed by gastrointestinal endoscopists (Cohen *et al.* 2002; Cheng *et al.* 2006; Williams *et al.* 2007). Hence, it requires significant focused training and experience to maximize success and safety. The close relationship between

success and complications of ERCP with endoscopic training, expertise, case volume and practice setting have been extensively reviewed elsewhere (Sherman *et al.* 1991; Loperfido *et al.* 1998; Freeman 2002; Petersen 2002; Freeman 2003a; Freeman & Guda 2005). Studies have established that a learning curve exists for attaining technical expertise in performing ERCP (Jowell *et al.* 1996; Hogan 1988; Verma *et al.* 2007). Although the exact number of ERCPs required to achieve competency is unknown, both Jowell and Hogan have suggested that at least between 180-200 ERCPs should be performed under supervision (Hogan 1988; Jowell *et al.* 1996). The American Society of Gastrointestinal Endoscopy (ASGE) ERCP core curriculum requires 200 cases, with at least half of these therapeutic (Chutkan *et al.* 2006). The target for achievement of competency is set above 80% successful cannulation rate for native papilla (Harewood & Baron 2002; Kaffes *et al.* 2005; Parlak *et al.* 2007; Lim *et al.* 2012). NKP has become the method of choice for achieving CBD cannulation during ERCP when all other techniques fail. Although it is considered unsafe when performed by inexperienced endoscopists, uncertainty exists regarding the nature of the learning curve associated with the procedure (Harewood & Baron 2002; Kaffes *et al.* 2005).

It is however essential for the novice endoscopist committed to a career in advanced biliary endoscopy to be trained in this technique (Abu-Hamda *et al.* 2005; Lim *et al.* 2012), as it is now considered the ultimate tool to endoscopically access the bile duct during ERCP when all else fails (Abu-Hamda *et al.* 2005; Khatibian *et al.* 2008; Manes *et al.* 2009). Failure to complete the ERCP not only leaves the disease untreated but also increases the cost-effectiveness of the overall management of the patients (Akaraviputh *et al.* 2008; Dumonceau *et al.* 2010) The impact of failure at attempted ERCP is striking: prolonged hospital stay for a mean of five days, due to repeat ERCP or alternative procedures (Freeman 1997).

Currently, there are no guidelines for either the training required by endoscopists or the assessment of competency (Freeman *et al.* 2001; Akaraviputh *et al.* 2008; Udd *et al.* 2010). Only a few published studies, all single endoscopists, have addressed the correlation between the cumulative NKF experience and outcomes (Rollhauser *et al.* 1998; Harewood & Baron 2002; Robison *et al.* 2007; Akaraviputh *et al.* 2008; Fukatsu *et al.* 2009). In fact to date, all publications concerning the learning curve were written by endoscopists who had not undergone formal hands-on training (Ang *et al.* 2011). In our study the learning curve of three endoscopists was analyzed and

described with a sample of 360 consecutive patients undergoing NKF. In order to assess the learning curve, 120 NKFs procedures performed by each of the three endoscopists in the study were divided arbitrarily in chronological order into three groups, 40 patients in each. The data is unique as it includes the use, success, and complications, from the very first NKF performed, continuing over an extended period of time.

Harewood *et al.* suggests a decreased need for precut sphincterotomy with increasing ERCP experience (Harewood & Baron 2002). In his study involving 253 NKF over 2,385 ERCPs, the rate of NKF decreased from 13% in the first 385 patients to 9% in the last 583 patients. It suggests that as experience increases the success of a standard biliary cannulation improves, therefore diminishing the need for a precut rescue technique. Through this perspective, we could argue that the frequency of precut could be used as a surrogate index for assessing the skill and experience in cannulation of the papilla. Other authors reported distinct conclusions, such as Rollhauser *et al.* and Fukatsu *et al.* who reported an increase of precut with ERCP experience (Rollhauser *et al.* 1998; Fukatsu *et al.* 2009). Our results demonstrated that NKF use did not significantly change as experience was gained. As the timing of the precut in the cannulation algorithm is key in determining the rate of precut use, we argue that the non-decline in the NKF use, reported in some of the studies (Rollhauser *et al.* 1998; Fukatsu *et al.* 2009) resulted from lowering the threshold of the precut over time (Udd *et al.* 2010; Cennamo *et al.* 2010; Swan *et al.* 2013). Rabenstein *et al.* claim that the precut implementation should not be used as a suitable measure of skill and experience in cannulation of the papilla, as it more properly reflects the endoscopist's personal preferences about the precut timing in the biliary cannulation algorithm (Rabenstein *et al.* 1997).

The importance of experience in the NKF success rate is influenced decisively by innate endoscopic skills of the endoscopists (Robison *et al.* 2007). Our results demonstrate that some degree of improvement exists in the cannulation success rate with NKF as procedural experience increases, although this effect might be greater for some operators and smaller or minimal for others. By combining our results with the results from other studies, we suggest that technical experience is an important determinant of procedural success, for endoscopists with average skill in ERCP who present sub-optimal precut cannulation rates (below 70%) soon after beginning to perform NKF. On the other hand, for those who start with cannulation success rates of 80% or higher, cumulative volume seems to be

a less significant influencing factor and innate technical skills probably play an important role.

As experience is accumulated in a technique one would expect a decrease in the complications reported. However, the majority of the reports published do not support this logical prognosis. Fukatsu *et al.* report an increase from 10% to 16% over time while Harewood *et al.* noticed that the complications did not change with experience (Harewood & Baron 2002; Fukatsu *et al.* 2009). Our results are similar to those of Harewood *et al.* The only exception is the report by Robinson *et al.* in which the number of complications decreased throughout the study (Robison *et al.* 2007). However, as the use of pancreatic stents increased in the latter part of his study, it is not possible to establish firm conclusions. The inability to reduce complication rates despite experience could result from an inherent risk factor associated with the technique itself, as proposed by Harewood *et al.*, or with the actual timing of the NKP in the cannulation algorithm. In the published reports which analyze experience, this procedure was performed after a difficult biliary cannulation, thus the positive effect of experience could be partially offset, as the risk of PEP is already escalating rapidly, by the time NKP is performed (Sharma *et al.* 2007; Bailey *et al.* 2010; Testoni *et al.* 2011; Baillie 2012).

The issue of who should perform NKF, as well as the training requirements remains controversial (Tang *et al.* 2005; Robison *et al.* 2007; Cennamo *et al.* 2009; Cotton 2010). In addition, there is a need to establish indicators and targets for attesting competency in the technique. The insights from published reports, describe the learning curve of endoscopists who began the technique unsupervised, without previous formal hands-on training, achieving mastery through repeated practice in high-volume settings. The results from endoscopists from low volume centers are inferior; Figueiredo *et al.* reported a complication rate of 19%, a mean ERCP duration of 67 min and a successful standard cannulation of 70.5% within 10-15 min (Figueiredo *et al.* 2010). Although not assessed in previous studies, the mean procedure duration is expected to decrease as the number of procedures performed by the endoscopist increases. Lee *et al.* reports a decrease in the total duration of the NKF from 8.6 min to 5.1 min in their last 53 patients (Lee *et al.* 2011). In the twenty first century as ERCP is now a mainstream therapeutic procedure, formal training ought to be a prerequisite in order to speed up competency and enhance patient safety (Freeman 1997; Cotton *et al.* 1991; Ang *et al.* 2011; Debenedet *et al.* 2013). Ang *et al.* claim that NKF

should only be performed by endoscopists with experience and expertise in performing ERCP (Ang *et al.* 2010). Although certain reports suggest that the NKF technique could easily be mastered alone without prior training, due to innate skills and exposure to a high ERCP volume, for quality and legal reasons a formalized training period is strongly recommended (Robison *et al.* 2007; Cotton 2010). It is proposed that the NKF success rate at first attempt ERCP be the major indicator of the competence in the technique, with a minimum target of 70% (Leung *et al.* 1990; Khatibian *et al.* 2008; Donnellan *et al.* 2010). This hurdle rate, in conjunction with a standard biliary cannulation above 80% assures a cannulation rate above 90%. Given some endoscopists achieve this quote quicker than others, an initial competency assessment after 20 NKFs is recommended. Until further studies on this issue are published, it is suggested that this advanced training period should be performed in high-volume centers (>200 ERCPs/year) as the results from low-volume centers tend to be inferior (Williams *et al.* 2007).

The results from this study demonstrate that precut with few complications is easily learned by a skillful endoscopist with the proper cognitive skills performing a high number of ERCPs. While some endoscopists could begin on their own due to innate skills, the vast majority should have a formal training period to speed up their learning curve. Moreover, this should be integrated in the ERCP curriculum for all future interventional endoscopists. **(Aim 3 - Chapter 6).**

8
Future Directions

The promising results, which were achieved through the performance of a fistulotomy immediately within the first five minutes of an unsuccessful cannulation, need validation by other ERCP endoscopists with experience in NKF from high-volume centers. A large-scale multicenter study or a multicenter registry for prospective data collection is warranted to assess this new standardized algorithm protocol.

As results indicate that the risk of PEP does not increase when NKF is performed within an early timing, the benefits of using pancreatic stents in patients submitted to a precut biliary fistulotomy should be reweighted. As a consequence, studies are needed to re-evaluate the recommendations set by the ESGE guidelines for prophylaxis of post-ERCP pancreatitis (Dumonceau *et al.* 2010).

Another key topic in ERCP research is to ensure that everyone uses the same terminology (Cotton 1989). Freeman *et al.* claim that one of the major advances in ERCP was the establishment of standardized outcome-based definitions for post-ERCP complications (Freeman 1997). There is an urgent need to follow this quality path in the definition of a difficult biliary cannulation and in a standardized nomenclature for the different precut techniques (Abu-Hamda *et al.* 2005; Udd *et al.* 2010). It would be a major step forward as results between studies could be compared facilitating the design of future projects.

NKF can be learned and mastered through cumulative experience in high-volume ERCP centers. More comprehensive studies are needed to determine the usefulness of our evidence-based recommendations for training programs.

9
Main conclusions

Since its introduction in 1986, and despite several other new techniques of cannulation access, the use of needle knife precut, and particularly NKF, still remains the primary and ultimately choice for the vast majority of expert endoscopists in a difficult biliary cannulation (Bourke *et al.* 2009; Udd *et al.* 2010; Testoni *et al.* 2011). The studies presented in this thesis have greatly contributed to improving the recognition of this valuable technique in its proper setting.

NKF is a safe and effective technique when performed by skilled endoscopists from high volume ERCP centers. The same excellent results reported by tertiary centers are also possible in general hospitals.

An early NKF strategy is at least as safe and effective as the current practice of a late NKF after multiple biliary attempts. The first five minutes of a standard cannulation could be considered an optimal timing for NKF.

While innate skills may determine that some endoscopists easily learn NKF begining on their own, the vast majority must have formal training. The precut procedure should be obligatory in the ERCP training curriculum for all future interventional endoscopists, and a minimum of twenty NKF precuts are suggested to first attest a trainee's competence, with a NKF success rate above 70% as minimal goal.

These recommendations are not applicable outside high-volume centers, experienced in NKF. Therefore we advise against unwarranted application of these recommendations by inexperienced endoscopists or low-volume centers.

PART IV

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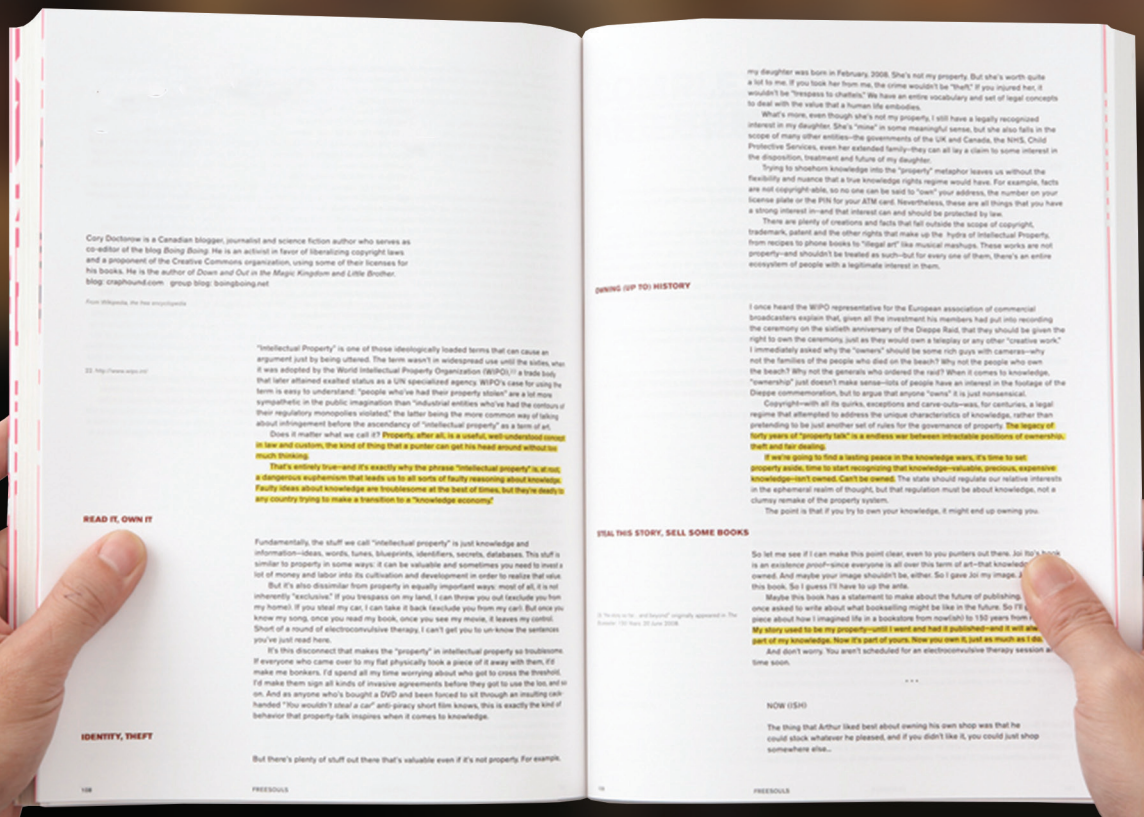

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