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EFFICACY AND SAFETY OF PRECUT SPHINCTEROTOMY FOR THERAPEUTIC ERCP:

A PROSPECTIVE STUDY IN A TERTIARY REFERRAL CENTER

S.S.D. MED/18

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ABSTRACT

BACKGROUND: Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) involves selective cannulation of the common bile and/or pancreatic ducts. If the cannulation fails, there is the choice whether to use more invasive procedures (i.d. precut papillotomy) or stop the esamination and proceed with alternative methods (i.d. percutaneous transhepatic biliary drainage - PTBD).

OBJECTIVES: To compare the success and complication rates of precut papillotomy and of standard endoscopic sphincterotomy (EST). In cases of ERCP failure, to identify treatments used and its complications.

METHODS: A prospective observational study was carried out on patients who underwent ERCP in a tertiary referral university hospital between January 2007 and April 2010.
Two groups were studied: a) all the patients who underwent precut papillotomy; b) a subgroup of patients who underwent a standard EST (consecutively selecting a patient every four). The success and complication rates associated to the various methods were considered the main outcome measurements.

RESULTS: A total of 783 ERCPs were performed, 755 with therapeutic intent.
A **precut papillotomy** was carried out in 17.3% of total therapeutic ERCP (131/755; 51.1% females; mean age 65.5±13.7). The overall success rate was 73.3% (96/131) with an intra-operator variability between 63.1% and 83.3%. The complication rate was 5.3% (7/131); there were no cases of death. In this group 46.6% of cases were classified as presenting a high grade of difficulty (grade 3 of Cotton's classification). The grade of difficulty was found to be inversely correlated with the success rate ($p<0.01$) but not with the complication rate.
Papillotomy failed in 35 patients who then underwent: PTBD in 18 cases (51.4%), medical treatment and radiological follow-up in 11 (31.4%), and surgery in 6 (17.2%). PTBD was associated to a 22.2% rate of complications (2 cholangitis and 2 bleeding requiring blood transfusion).
A **standard EST** was carried out in 151 cases (corresponding to 20% of the total therapeutic ERCPs): 56.3% female; mean age 63.5±17.6. The overall success rate was 92.7% (140/151) with an intra-operator variability between 88.8% and 97.2%. The complication rate was 7.3% (11/151). Twenty-five percent of standard EST were graded as presenting a high degree of difficulty (grade 3 of Cotton's classification).
If only severe complications are considered, there is only a slight prevalence in the precut group (2.3%) with respect to the standard EST group (1.3%) (p=ns).

CONCLUSION: In a consecutive series of patients with a high proportion of difficult cases, papilla precutting is an useful technique with an acceptable complication rate.

BACKGROUND: La colangiografia retrograda endoscopica (ERCP) con intento terapeutico richiede l'incannulazione selettiva della via biliare principale e/o del dotto pancreatico. Se tale incannulazione fallisce, si pone la scelta se utilizzare tecniche più invasive (es. precut della papilla) o interrompere l'esame e procedere con metodiche alternative (es. PTBD).

OBIETTIVI: Confrontare il tasso di successo e di complicanze della papillotomia-precut e della sfinterotomia endoscopica (EST) standard.
In caso di insuccesso dell'ERCP, valutare i trattamenti utilizzati e le complicanze ad essi correlate.

METODI: Nel nostro centro ospedaliero e universitario di riferimento per la patologia pancreatica, tra gennaio 2007 e aprile 2010 è stato condotto uno studio prospettico osservazionale sui pazienti sottoposti a ERCP. Sono stati considerati due gruppi: a) tutti i pazienti sottoposti a papillotomia precut; b) un sottogruppo di pazienti sottoposti a EST standard (selezionando consecutivamente un paziente ogni quattro). La misura di esito primaria è stata considerare il tasso di successo e di complicanze della varie metodiche.

RISULTATI: Sono state eseguite in totale 783 ERCP, delle quali 755 con intento terapeutico.
La **papillotomia precut** è stata praticata nel 17.3% di tutte le ERCP terapeutiche (131/755; 51.1% femmine; età media 65.5±13.7 anni). Il tasso di successo globale è stato del 73.3% (96/131) con una variabilità tra operatori che va dal 63.1% all'83.3%. Il tasso di complicanze è stato del 5.3% (7/131); non c'è stata mortalità correlata alla procedura. Le procedure endoscopiche, in questo gruppo, sono risultate essere ad elevato grado di difficoltà nel 46.6% dei casi (grado 3 sec. la classificazione di Cotton). Il grado di difficoltà era inversamente correlato al tasso di successo ($p<0.01$), ma non correlato al tasso di complicanze.
Il precut non è stato coronato da successo in 35 pazienti, che sono stati quindi sottoposti a: PTBD in 18 casi (51.4%), trattamento medico e follow-up radiologico in 11 casi (31.4%), trattamento chirurgico negli altri 6 (17.2%). Il PTBD ha registrato il 22.2% di complicanze (2 colangiti e 2 sanguinamenti con necessità di emotrasfusione).
La **EST standard** è stata eseguita in 151 casi (corrispondenti al 20% di tutte le ERCP terapeutiche): il 56.3% erano femmine; l'età media era 63.5±17.6 anni. Il tasso di successo globale è stato del 92.7% (140/151), con una variabilità tra operatori che va dall'88.8% al 97.2%. Il tasso di complicanze è stato del 7.3% (11/151). Le procedure endoscopiche, in questo gruppo, sono risultate essere ad elevato grado di difficoltà nel 25% dei casi (grado 3 sec. la classificazione di Cotton).
Se si considerano solamente le complicanze severe, si evidenzia una lieve prevalenza di casi nel gruppo dei precut (2.3%) rispetto al gruppo delle EST standard (1.3%) (p=ns).

CONCLUSIONI: in una serie consecutiva di pazienti, con un'alta proporzione di casi difficili, il precut della papilla risulta essere una tecnica efficace e associata ad un accettabile tasso di complicanze.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) was first described in 1968 by McCune et al[1]. By the introduction of endoscopic papillotomy, first reported by Classen et al [2] and Kawai et al[3] in 1974, it became possible to use ERCP for therapeutic purposes. While it is profitably employed in the minimally invasive management of biliary and pancreatic disorders, its use is challenged by a higher potential for serious complications. Complication rates, nevertheless, largely depend on the definition adopted and data collection methods[4].

The prerequisite for the success of therapeutic endoscopic procedures lies in deep cannulation of the bile or pancreatic duct. This maneuver proves difficult or impossible in 5-20% of patients[5-8]. Many centers use a precut papillotomy to facilitate the procedure: this is an umbrella term for a great variety of techniques giving access to the biliary (or pancreatic) duct, which is why some authors had proposed the term "access papillotomy"[9].

Regardless of the methods used, complications reportedly occur in 5-20% of patients[7, 10-17] and the safety of the procedure is still being debated with some Authors affirming that it is an independent risk factor for the onset of complications [4, 18-22]. Recent studies show that the precut *per se* is not responsible for the post-ERCP pancreatitis[23], but the reiterated failed attempts to cannulate the papilla that precede it [24, 25], especially in some types of patient with a history of pancreatitis or sphincter of Oddi dysfunction (SOD)[26]. A recent meta-analysis[27] suggested that early precutting reduces the risk of post-ERCP pancreatitis, but not the global rate of complications (hemorrhage, perforations and cholangitis).

The success and complication rates of precut papillotomy and standard sphincterotomy in patients with different pathologies were assessed by this prospective observational study.

In cases where ERCP was unsuccessful, the therapeutic methods adopted and their complication rates were also assessed.

The rationale behind this work was to answer the question if, in particularly difficult cases, it is opportune and safe to insist with precut papillotomy or if it is wiser to resort to alternative therapeutic procedures.

The results of this study indicate that precut papillotomy is an efficacious technique with an acceptable complication rate.

MATERIALS AND METHODS

All patients undergoing ERCP between January 2007 and April 2010 at the Pancreatic Endoscopy Unit of the Policlinico G.B. Rossi, Verona-Italy, were prospectively considered. This hospital is a national referral center for patients with neoplastic and flogistic pancreatic diseases.

We included patients with native papilla who had undergone therapeutic ERCP.

A first group included all the patients who underwent **precut papillotomy** in our center during the study period.

A second group of patients who underwent a **standard sphincterotomy** was considered the control group, composed by including every fourth consecutive patient: this number of patients was determined *a priori* evaluating that the precut papillotomy:standard sphincterotomy ratio in our center was about 1:5.

All endoscopic procedures were completed by two expert endoscopists [28] (GA and GT).

As this was an observational study, the type of procedure utilized was decided upon by the endoscopist on the basis of personal preference.

All of the **patients'** demographic details (gender, age), clinical records, indications for ERCP and clinical history (in particular the risk factors for acute pancreatitis: e.g. previous pancreatitis, SOD) [26, 29] , **operative reports**, and **clinical course** during and after the were collected and assessed. Data were collected prospectively in a specific database[4, 24].

With regard to the **procedure** itself, the success rate (at the first or second try and a global success) was registered. Success was defined as achieving deep biliary cannulation in accordance with the indication for the procedure or the successful completion of the operative procedure prescribed. Partial success, such as opacification of the duct without deep cannulation, or without successful completion of the treatment

procedure prescribed, were considered unsuccessful attempts. Clinical/surgical records were also assessed, separately but during the same time period, by a third clinician who was blinded to the name of the endoscopist and to patient characteristics.

The following variables regarding the technique were also registered:

1. If the procedure was an emergency or a scheduled one;
2. The degree of technical difficulty Cotton's classification[28, 30] (Table 1);
3. The presence of duodenal alterations (i.e. diverticula, neoplastic infiltration, sequelae of gastric resection);
4. The presence of prepapillary bulging;
5. Successful opacification of the duct;
6. The treatment carried out (stone removal, placement of biliary and/or pancreatic stent);
7. The final endoscopic diagnosis;
8. The type of sphincterotomy carried out: precut papillotomy or standard sphincterotomy;
9. The technique used (free-hand needle-knife or traction sphincterotome)

A **precut sphincterotomy** was performed using a traction sphincterotome or a needle-knife sphincterotome depending on the anatomical situation and/or the endoscopist's preferences. A traction sphincterotome was generally used for a biliary or pancreatic papillotomy: a) when accessing one of the ducts with a view to selectively cannulating the other; or b) when the tip of the catheter could only be inserted a few millimeters into the papilla without deep cannulation (infundibulotomy). In the vast majority of cases, a standard (20-30 mm) traction sphincterotome was used. A needle-knife sphincterotome was used, instead, to access ducts via an incision starting from the papillary pore or from a point cranial thereto (a so-called "fistulotomy")[7].

A **standard sphincterotomy** was carried out using a traction sphincterotome. One of the two endoscopists (GT) systematically cannulated using a guide wire.

Preliminary bile duct opacification was considered very useful but not indispensable for completing the endoscopic procedure, particularly when other imaging techniques showed a dilation of the terminal duct or when the papilla revealed specific anatomical features (e.g. prepapillary bulging). Precutting the major papilla was not used routinely if the papilla was flat and/or there was no opacification and/or dilation of the ducts on pre-ERCP imaging.

In accordance with Cotton's classification [28, 30], the difficulty of the ERCP was graded as: "standard", grade 1; "advanced", grade 2; or "tertiary", grade 3 (Table 1).

GRADE	DIAGNOSTIC	THERAPEUTIC
1° STANDARD	Selective deep cannulation, Diagnostic sampling	Biliary sphincterotomy, Stones < 10 mm, Stents for leaks and low tumors
2° ADVANCED	Billroth II diagnostic, Minor papilla cannulation	Stones > 10 mm, Hilar tumor stent placement, Benign biliary strictures
3° TERTIARY	manometry, Whipple, Roux-en-Y, Intraductal endoscopy	Billroth II therapeutics, Intrahepatic stones, Pancreatic therapies

Table 1. The difficulty degree of ERCP (Cotton's classification).

The patient's **clinical course** was monitored immediately after the ERCP by assessing blood chemistry values (hemoglobin, leukocyte count, bilirubin and amylasemia before the procedure and 24 hours afterwards) and by direct clinical examination. All clinical records were carefully assessed after each patient was discharged from the

hospital (the end of our observation period) and on the basis of these data the rate and severity of complications were graded.

Complications were defined as outlined in previous studies [31]. The severity of complications was graded considering the length of the hospital stay that was necessary and the measures entailed to treat them: mild complications entailed 2-3 days in the hospital; moderate complications 4-10 days; severe complications more than 10 days and requiring invasive surgical or radiological treatment. The term *post-ERCP pancreatitis* indicates persistent or worsening abdominal pain accompanied by an increase in serum pancreatic enzyme levels to at least three times normal maximum levels; pancreatitis was classified as mild-moderate or severe, in accordance with the Atlanta criteria[26, 32]. *Hemorrhage* was ascertained from clinical (not endoscopic) evidence of bleeding (e.g. melena or hematemesis) associated with a fall in hemoglobin levels >2 gr/dL or the need for blood transfusion. *Perforation* was detected either during the ERCP itself or subsequently, on the basis of clinical signs (persistent abdominal pain) and radiological evidence (computerized tomography - CT - scans showing pneumoperitoneum or retropneumoperitoneum).

PTBDs were carried out by the center's Interventional Radiology Department by expert radiologists.

Statistical analysis

Non-parametric tests (the Kruskal-Wallis, Mann-Whitney U and Spearman's correlation tests) were used to evaluate ordinal data, while the Chi-square test was used to analyze nominal data. In the two-way contingency tables, the Yates continuity correction was applied, or Fisher's exact test in the case of small expected frequencies.

Multivariate analysis was conducted using logistic regression analysis models. The backward method was used to select the predictive variables, adopting a variable elimination limit at $p>0.05$. The statistical package used was the SPSS, rel. 17.

RESULTS

A total of 875 attempts to perform ERCP were made between January 2007 and April 2010: in 57 cases (6.5%) it was impossible to access the papilla due to duodenal stenosis of neoplastic origin. In 35 cases (4%) the procedure was really a pseudocyst-gastroanastomosis (as a result of sequelae of acute pancreatitis or pancreatic surgery). Twenty-eight (3.4%) of the 783 ERCP had been prescribed for diagnostic purposes and were not considered (successfully completed).

Our population was made up, then, of 755 patients who underwent ERCP for therapeutic purposes.

The Precut Papillotomy Group

Our study group was made up of 131 subjects corresponding to 17.3% of all the therapeutic procedures (n=755): 64 were males (48.9%) and 67 females (51.1%); mean age was 65.5 ± 13.7 years (range 17-94 years).

The patients' clinical characteristics are summarized in Table 2.

VARIABLES	SUCCESS	FAILURE	TOTAL	p**
	n 96 (73.3%)	n 35 (26.7%)	n 131 (100%)	
Gender				ns (p=0.43)
Male	49/64 (76.6%)	15/64 (23.4%)	64/131 (48.9%)	
Female	47/67 (70.1%)	20/67 (29.9%)	67/131 (51.1%)	
Age (±SD)	65.9 ± 13.9	64.5 ± 13.4	65.5 ± 13.7	ns (p=0.6)
Indications*				ns (p=0.11)
benign diseases	**48/60 (80.0%)**	**12/60 (20.0%)**	**60/131 (45.8%)**	
gall stones	29/33 (87.9%)	4/33 (12.1%)	33/131 (25.2%)	
acute pancreatitis	12/17 (70.6%)	5/17 (29.4%)	17/131 (13.0%)	
chronic pancreatitis	3/5 (60.0%)	2/5 (40.0%)	5/131 (3.8%)	
pancreas divisum	1/2 (50.0%)	1/2 (50.0%)	2/131 (1.5%)	
biliary fistula	2/2 (100%)	0	2/131 (1.5%)	
echinococcosis	1/1 (100%)	0	1/131 (0.8%)	
neoplastic diseases	**48/71 (67.6%)**	**23/71 (32.4%)**	**71/131 (54.2%)**	
pancreas	39/56 (69.6%)	17/56 (30.4%)	56/131 (42.7%)	
bile duct	6/11 (54.5%)	5/11 (45.5%)	11/131 (8.4%)	
Papilla	3/4 (75.0%)	1/4 (25.0%)	4/131 (3.1%)	
Jaundice	66/89 (74.2%)	23/89 (25.8%)	89/131 (67.9%)	
Bile duct dilation				ns (p=0.9)
none/mild	32/44 (72.7%)	12/44 (27.3%)	44/131 (33.6%)	
Moderate	22/29 (75.9%)	7/29 (24.1%)	29/131 (22.1%)	
Severe	42/58 (72.4%)	16/58 (27.6%)	58/131 (44.3%)	
Urgent procedure	33/48 (68.8%)	15/48 (31.3%)	48/131 (36.6%)	ns (p=0.41)
Elective procedure	63/83 (75.9%)	20/83 (24.1%)	83/131 (63.4%)	
Prepapillary bulging	17/19 (89.5%)	2/19 (10.5%)	19/131 (14.5%)	ns (p=0.06)
Type of sphincterotome				ns (p=0.84)
Traction	41/57 (71.9%)	16/57 (28.1%)	57/131 (43.5%)	
needle-knife	55/74 (74.3%)	19/74 (25.7%)	74/131 (56.5%)	
Complications				ns (p=0.9)
None	90/124 (73.2%)	34/124 (27.4%)	124/131 (94.6%)	
mild acute pancreatitis	3/4 (75.0%)	1/4 (25.0%)	4/131 (3.1%)	
severe acute pancreatitis	1/1 (100%)	0	1/131 (0.8%)	
Perforation	2/2 (100%)	0	2/131 (1.5%)	
Operator				**p=0.01**
operator GA	41/65 (63.1%)	24/65 (36.9%)	65/131 (49.6%)	
operator GT	55/66 (83.3%)	11/66 (16.7%)	66/131 (50.4%)	

*A patient may have more than one indication

**Chi-square test or Fisher's exact test

Table 2. Patients' clinical characteristics in **precut papillotomy** group.

The procedures were equally distributed with regard to numerosity and indications between two endoscopists: endoscopist GA treated 65 cases (49.6%) including 38 neoplasms while endoscopist GT treated 66 patients (50.4%) including 33 neoplastic disorders (p=ns).

In accordance with Cotton's classification[28], the technical difficulty of the 783 ERCPs carried out was graded as follows: 46.7% (366 cases) were classified as grade 1 (standard); 17.3% (135 cases) grade 2 (advanced); and 36% (282 cases) grade 3 (tertiary). The 131 ERCPs involving a precut papillotomy were classified as follows: 42% (55 cases) grade 1; 11.5% (15 cases) grade 2; and 46.6% (61 cases) grade 3.

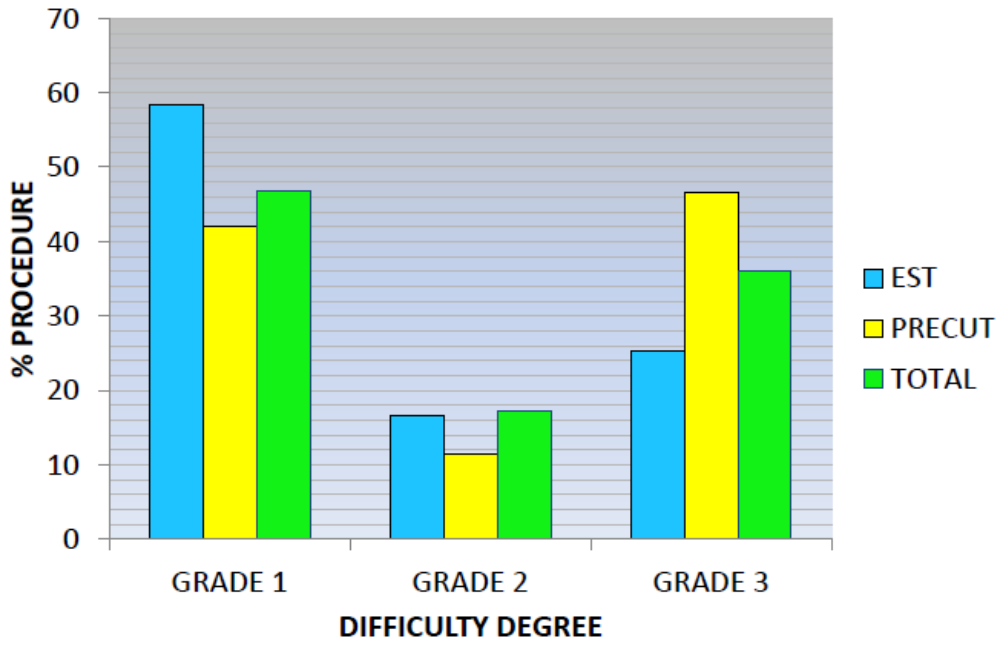

Figure 1. Difficulty degree in standard sphincterotomy, precut and total ERCP

The differences in the grades of difficulty between the ERCP with and without precut was statistically significant (Chi Square test $p<0.05$) (Table 3).

ERCP		1 - STANDARD	2 - ADVANCED	3 - TERTIARY
ST. EST	n=151	88/151 (58.3%)	25/151 (16.6%)	38/151 (25.2%)
				p=0,001
PRECUT	n=131	55/131 (42.0%)	15/131 (11.5%)	61/131 (46.6%)
				p<0,05
TOT ERCP	n=783	366/783 (46.7%)	135/783 (17.3%)	282/783 (36.0%)

Table 3. Difficulty degree in standard sphincterotomy, precut and total ERCP.

Endoscopist GA had more cases classified as tertiary with regard to the difficulty of the procedure (65.6% vs. 34.4% for endoscopist GT; p<0.01).

The **global success** rate of precut papillotomy procedures was 73.3% (96/131 cases); it was 63.1% (41/65) for endoscopist GA and 83.3% (55/66) for endoscopist GT (p=0.01). The procedure was successful at the first try in 83 cases. A second attempt was made in 17 patients proving successful in 13 of these (76.5%).

A **univariate analysis** was performed to identify the variables associated with the precut papillotomy success rate: gender, age, indication for the procedure, extent of dilation of the common bile duct (CBD) or pancreatic duct, emergency/elective procedures, prepapillary bulging and the type of sphincterotome. None of these variables proved statistically significant (Table 1).

There was a significant inverse correlation when the difficulty of the procedures was compared with the success rate (Spearman's correlation test r= - 0.23; p<0.01): i.e. a standard difficulty (grade 1) coincided with a higher success rate only for endoscopist GA (r=- 0.3; p=0.016) but not for endoscopist GT (r= - 0.01; p=0.94) (Figure 2).

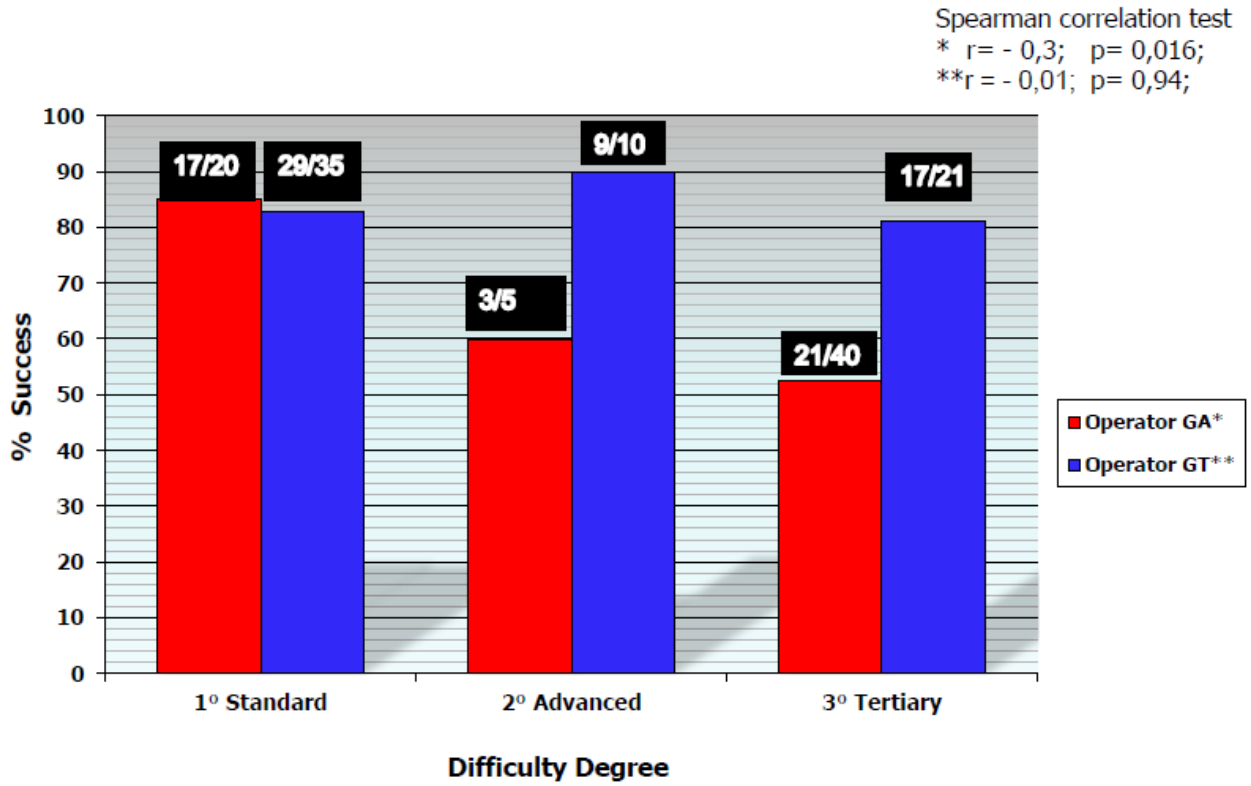

Figure 2. Success rate of precutting by grade of difficulty and by operator (the number of patients is indicated at the top of each column)

The two endoscopists differed in the type of sphincterotome each utilized most frequently: endoscopist GA used the traction-type sphincterotome in 63.1% of cases (41/65) involving the pancreatic duct in 29 patients and the biliary duct in 12. Endoscopist GT, instead, used the needle-knife sphincterotome in 75.8% of cases (50/66) involving the biliary duct in 46 patients and the minor papilla in 4. The difference was statistically significant ($p<0.001$).

In the **multivariate logistic regression analysis**, we considered the individual parameters potentially predictive of the success of precut papillotomy. Only the information available at the time the ERCP was carried out was considered: gender, age, indication for the test, biliary duct dilation, jaundice, emergency procedure, duodenal anatomical alterations. We also analyzed if there was any duct opacification prior to the precutting

procedure. With regard to all these variables, the only one found significantly associated with the success rate was the “endoscopist” (OR 2.9; 95%CI 1.3-6.6; p<0.01).

The overall **complication** rate after the precutting papillotomy was 5.3% (7/131 cases):

- 4 cases of mild acute pancreatitis (3%) in patients discharged within 7 days of the ERCP;
- 1 case of severe acute pancreatitis with retroperitoneal fluid collections (0.8%) amenable to medical treatment;
- 2 cases of duodenal perforation (1.5%):

  Case 1: A precut papillotomy was performed using a needle-knife sphincterotome in line with the biliary duct into the papilla, and after the bile duct was opacified and a guidewire was inserted, it was expanded using a traction sphincterotome in a patient with coledocholithiasis. A posterior duodenal perforation was diagnosed 3 days after the procedure by an abdominal CT scan prescribed for persistent abdominal pain and fever. During surgical treatment, an intraoperative cholangiography (with associated cholecystectomy) detected no interruptions in the biliary duct/duodenal wall.

  Case 2: A precut papillotomy was performed using a needle-knife sphincterotome in line with the biliary duct into the papilla, and after the duct was opacified and a guide wire was inserted, it was expanded with a traction sphincterotome in a patient with coledocholithiasis. A posterior duodenal perforation was identified during the endoscopic procedure and treated surgically (duodenorrhaphy with cholecystectomy).

The complications were moderate-severe in 3 cases (2.3%) (1 severe acute pancreatitis and 2 perforations) and mild in the other 4 (3.1%)[31]. Only one (mild) complication

occurred in a neoplastic patient (1.4%; 1/71 cases); mild complications were noted in 6 patients with benign disease (10.0%; 6/60 cases); (p=0.075). Endoscopist GA encountered 3 patients with mild complications and 1 case of severe acute pancreatitis; endoscopist GT treated 1 patient with mild complication and 2 with perforations (p=ns). No pancreatitis occurred in the two cases in which a “protective” pancreatic stent was placed. There were no episodes of precut papillotomy-related bleeding serious enough to cause a fall in hemoglobin >2 gr/dL and/or to require blood transfusion. There were no cases of cholangitis or procedure-related mortality.

The correlation between the difficulty of the procedure and the complications was not statistically significant.

Unsuccessful ERCP

The 35 patients whose ERCP was unsuccessful (at the first or second attempts) were treated as follows:

- a PTBD was placed in 18 patients (51.4%), 17 of these (94%) had neoplastic diseases (14 pancreatic and 3 bile duct cancers). The global complication rate after PTBD was placed was 22.2% (4/18 patients: 2 cases of acute cholangitis/cholecystitis and 2 of bleeding requiring blood transfusion);
- 11 were discharged (31.4%) requiring no further invasive procedures during their hospital stay. Medical treatment and/or radiological follow-up were prescribed. Seven of these patients had benign diseases (3 bile duct stones, 3 acute pancreatitis, 1 chronic pancreatitis) and neoplastic disease was suspected in 4 (involving the bile ducts in 2, the papilla in 1, and the pancreas in 1);
- 6 (17.2%) underwent surgery: 2 were cases of pancreatic cancer (one treated with duodenocephalopancreatectomy [DCP] and one with total splenopancreatectomy);

1 patient had acute pancreatitis and suspected pancreatic cancer (and underwent exploratory laparotomy); 1 had acute biliary pancreatitis (treated with cholecystectomy and intraoperative treatment of CBD lithiasis); 1 patient had chronic calcific pancreatitis and cholelithiasis (and underwent cholecystectomy); and 1 was a case of choledocholithiasis (requiring cholecystectomy and endoscopic rendezvous technique).

The Standard Sphincterotomy group

Patients with therapeutic indications for ERCP that were carried out after the study period by the same two endoscopists who performed the precut papillotomies were included in this group.

The control group was made up of 151 subjects, corresponding to 20% of the total therapeutic ERCPs (151/755): 66 were males (43,7%) and 85 females (56,3%); mean age was 63,5 ± 17,6 (range 15-97 years) (p=ns).

Patients'characteristics are outlined in Table 4.

VARIABLES	SUCCESS	FAILURE	TOTAL	p**
	n 140 (92.7%)	n 11 (7.3%)	n 151 (100%)	
Gender				ns (p=0,57)
Male	61/66 (92.4%)	5/66 (7.6%)	66/151 (43.7%)	
Female	79/85 (92.9%)	6/85 (7,1%)	85/151 (56.3%)	
Age (±SD)			63,5 ± 17,6	
Grade of difficulty				**p=0,001**
1 - standard	85/88 (96.6%)	3/88 (3.4%)	88/151 (58.3%)	
2 - advanced	25/25 (100%)	0	25/151 (16.6%)	
3 - tertiary	30/38 (78.9%)	8/38 (21.1%)	38/151 (25.2%)	
Indications*				ns (p=0,57)
benign diseases	**96/101 (95.0%)**	**5/101 (5.0%)**	**101/151 (66.9%)**	
gall stones	68/68 (100%)	0		
acute pancreatitis	12/14 (85.7%)	2/14 (14.3%)	14/151 (9.3%)	
chronic pancreatitis	4/5 (80.0%)	1/5 (20.0%)	5/151 (3.3%)	
pancreas divisum	0	0	0	
biliary fistula	0	4/4 (100%)	4/151 (2.6%)	
echinococcosis	8/10 (80.0%)	2/10 (20.0%)	10/151 (6.6%)	
neoplastic diseases	**44/50 (88.0%)**	**6/50 (12.0%)**	**50/151 (33.1%)**	
pancreas	26/32 (81.3%)	6/32 (18.8%)	32/151 (21.2%)	
bile duct	14/14 (100%)	0	14/151 (9.3%)	
Papilla	4/4 (100%)	0	4/151 (2.6%)	
Jaundice	101/108 (93.5%)	7/108 (6.5%)	108/151 (71.5%)	ns (p=0,38)
Bile duct dilation				ns (p=0,24)
none/mild	46/51 (90.2%)	5/51 (9.8%)	51/151 (35.2%)	
moderate/severe	89/94 (94.7%)	5/94 (5.3%)	94/151 (64.8%)	
Urgent procedure	37/39 (94.9%)	2/39 (5.1%)	39/151 (25.8%)	ns (p=0,42)
Elective procedure	103/112 (92.0%)	9/112 (8.0%)	112/151 (74.2%)	
Prepapillary bulging	7/8 (87.5%)	1/8 (12.5%)	8/151 (5.3%)	
Use of guidewire				ns (p=0,27)
no	83/88 (94.3%)	5/88 (5.7%)	88/151 (58.3%)	
yes	57/63 (90.5%)	6/63 (9.5%)	63/151 (41.7%)	
Complications				ns (p=0,19)
none	131/140 (93.6%)	9/140 (6.4%)	140/151 (92.7%)	
mild	7/9 (77.8%)	2/9 (22.2%)	9/151 (6.0%)	
moderate/severe	2/2 (100%)	0	2/151 (1.3%)	
Operator				**p=0,044**
operator GA	71/8 (88.8%)	9/80 (11.3%)	80/151 (53%)	
operator GT	69/71 (97.2%)	2/71 (2.8%)	71/151 (47%)	

*A patient may have more than one indication

**Chi-square test or Fisher's exact test

Table 4. Patients' clinical characteristics in **standard sphincterotomy** group

The procedures were equally distributed with regard to numerosity and indications between the two endoscopists: GA treated 80 procedure (53%) of which 28 (35%) were of a neoplastic origin; and endoscopist GT treated 71 procedures (47%) of which 22 (31%) were of a neoplastic origin (p=ns).

The degree of difficulty was classified as: “Grade 1” in 88 cases (58,3%), “Grade 2” in 25 cases (16,6%), “Grade 3” in 38 cases (25,2%) with the two endoscopists having overlapping percentiles (Table 4 and Figure 3).

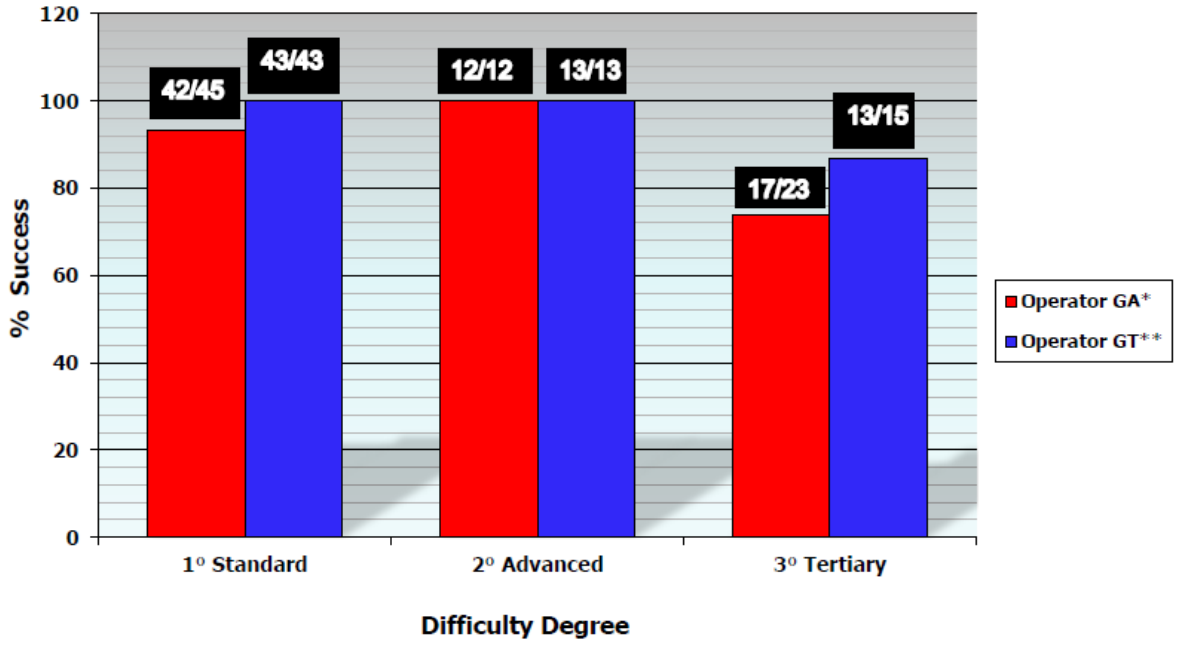

Figure 3. The success rate of standard EST by grade and by operator (the number of patients is indicated at the top of each column)

The **global success** rate was 92.7% (140 cases out of 151): 88.8% (71/80) for endoscopist GA e 97.2% (69/71) for endoscopist GT. The success rate at the first attempt at ERCP was 90.1% (136/151 cases) and 4 cases were successful at the second try.

The **complication** rate was 7.3% (11 cases out of 151). There were 9 cases of mild pancreatitis (6.0%) and 2 of severe pancreatitis (1,3%). Endoscopist GA performed 80

procedures out of which 7 (8.8%) were cases of mild pancreatitis e 2 (2.5%) of severe pancreatitis (9 total complications; 6.0%). Endoscopist GT performed a total of 71 procedures out of which 2 (2.8%) were cases of mild pancreatitis (p=ns). It should be noted that none of the 6 patients in whom a pancreatic prothesis was placed developed acute pancreatitis. There is a difference of complications between the operator who routinely used the guidewire and stent placement pancreatic protection, than those who did not use these techniques routinely. This difference, although not statistically significant, suggests a trend (Fisher exact test p=0.06).

No cases of perforation, cholangitis or haemorrhage were noted and no endoscopy-related deaths were reported.

Comparison between groups: precut vs. standard sphincterotomy

Homogeneous with regard to age and sex, the groups were statistically different with regard to some variables (global success rate, benign/neoplastic indication, prepapillary bulging, degree of difficulty, opacification of the ducts) (Table 5).

VARIABLES	PRECUT	STANDARD EST	p**
GENDER			ns (p=0,22)
MALE	64/131 (48,9%)	66/151 (43,7%)	
FEMALE	67/131 (51,1%)	85/151 (56,3%)	
AGE (±SD)	65,5 ± 13,7	63,5 ± 17,6	ns (p=0,29)
GRADE			**p=0,001**
1 - STANDARD	55/131 (42,0%)	88/151 (58,3%)	
2 - ADVANCED	15/131 (11,5%)	25/151 (16,6%)	
3 - TERTIARY	61/131 (46,6%)	38/151 (25,2%)	
INDICATIONS*			**p<0,001**
Benign diseases	**60/131 (45,8%)**	**101/151 (66,9%)**	
gall stones	33/131 (25,2%)	68/151 (45,0%)	
acute pancreatitis	17/131 (13,0%)	14/151 (9,3%)	
chronic pancreatitis	5/131 (3,8%)	5/151 (3,3%)	
pancreas divisum	2/131 (1,5%)	0	
biliary fistula	2/131(1,5%)	4/151 (2,6%)	
echinococcosis	1/131 (0,8%)	10/151 (6,6%)	
Neoplastic diseases	**71/131 (54,2%)**	**50/151 (33,1)**	
pancreas	56/131 (42,7%)	32/151 (21,2%)	
bile duct	11/131 (8,4%)	14/151 (9,3%)	
Papilla	4/131 (3,1%)	4/151 (2,6%)	
Jaundice	89/131 (67,9%)	108/151 (71,5%)	ns (p=0,30)
URGENT PROCEDURE	48/131 (36,6%)	39/151 (25,8%)	p=0,034
ELECTIVE PROCEDURE	83/131 (63,4%)	112/151 (74,2%)	
PREPAPILLARY BULGING	19/131 (14,5%)	8/151 (5,3%)	**p<0,001**
GLOBAL SUCCESS	96/131 (73,3%)	140/151 (92,7%)	**p<0,001**
COMPLICATIONS			ns (p=0,43)
None	124/131 (94,7%)	140/151 (92,7%)	
mild acute pancreatitis	4/131 (3,1%)	9/151 (6,0%)	
severe acute pancreatitis	1/131 (0,8%)	2/151 (1,3%)	
Perforation	2/131 (1,5%)	0	
OPERATOR			ns (p=0,32)
operator GA	65/131 (49,6%)	80/151 (53,0%)	
operator GT	66/131 (50,4%)	71/151 (47,0%)	

*A patient may have more than one indication

**Chi-square test or Fisher's exact test

Table 5. Comparison between groups: precut vs. standard sphicterotomy

The global success rate was higher in the standard EST vs. precut group (92.7% vs. 73.3%) (p<0,001).

A precut papillotomy was carried out more frequently in patients with neoplastic disorders: 54.2% (71/131) vs. 33.1% (50/151); while a standard EST was carried out more frequently in patients with benign disorders (66,9% vs. 45,8%), in particular with regard to choledocholithiasis (p<0.01).

Prepapillary bulging was present in 14.5% of the precut papillotomy group compared to 5.3% in the controls. The procedure was successful in 7 (89.5%) of the precut papillotomy group with prepapillary bulging (19 patients).

There was a lower rate of difficult grades (grade 3 “advanced”) in the standard EST vs precut group: 25.2% vs 46.6% (p=0.001).

Opacification of the duct, for which the exam was prescribed, was achieved in 146 of the controls (96.7%) vs. 92 patients in the precut papillotomy group (70.2%) (p<0,001).

No differences were registered instead with regard to the global complication rate and in the other variables considered (p=ns).

Total therapeutic ERCP population

All of the variables potentially predictive of the precut procedure were analyzed using a multivariate logistic regression model. It was found that a neoplastic indication (OR 2,32 C.I. 95% 1,54-4,17; p<0,001) and the presence of prepapillary bulging (OR 3,40 C.I. 95% 1,40-8,21; p<0,007) were directly correlated with the precut papillotomy procedure.

Jaundice at the time ERCP was carried out was inversely correlated to the risk of complications and to their severity; jaundice was, in fact, present in 190 (72%) patients without complications, in 6 (46%) with mild complications, and in 1 (20%) with medium-severe complications (p<0.01).

Even though the presence of jaundice and dilation of the bile ducts were two positively correlated variables ($r=0,35$ $p<0,001$), there was no association between the complication rate and dilation of the bile ducts.

DISCUSSION

A precut papillotomy technique was used in 17.3% of the ERCP patients assessed by this study, a figure falling in the middle range of values outlined in the literature which varied from 2.8% reported by Hattunen et al.[15] to 33% by Rabenstein et al. [13], also taking into consideration that it is not always attempted because considered excessively risky (Table 6).

The wide variability reported here could be due to the proportion of ERCPs carried out with a therapeutic intent. The advent of radiological methods, such as magnetic resonance (MR) cholangiopancreatography, has drastically reduced the role of endoscopy in diagnosis; in fact in our center only 3.4% of the procedures in the patients studied were carried out for diagnostic purposes.

AUTHOR	YEAR	PRECUT/ERCP	NEOPL DIS	SUCCESS	COMPL	PANCREAT	PERF	BLEED	CHOLANG	MORT
Goff[10]	1995	39/248 (15,7%)	not stated	89,70%	5 (12,8%)	4 (10,2%)	1 (2,5%)			0
Rabenstein [13]	1997	694/2105 (33%)	254 (43,9%)	85,20%	51 (7,3%)					0
°Mavrogiannis [14]	1999	103/772 13,3%)	0		20 (19,4%)	6 (5,8%)	4 (3,9%)	9 (8,7%)	1 (0,9%)	
		NKF* 74		90,50%						0
		NKPP** 79		88,60%						1
°Tang [43]	2005	32/642 (5%)	31%	97%	4 (13%)	2 (6%)	0	1 (3%)	1 (3%)	
Zhou [33]	2006	43/948 (4,5%)	19%	91%	2 (5%)	1 (2%)	0	1 (2%)	0	
°De Weerth [44]	2006	49,80%	58/145 (40%)	100%	3 (2,1%)	3 (2,1%)	0	0		
°Khatibian [45]	2008	106/242 (43,8%)	not stated	83%	3 (3%)	2 (1,9%)	1 (1%)	0	0	
§Halttunen [15]	2009	178/6209 (2,8%)	89 (56,6%)	71,30%	16 (10,2%)	8 (5,1%)	1 (0,6%)	6 (3,8%)	1 (0,6%)	1
°$Manes [24]	2009	80/1654 (4,8%)	33,70%	92,20%	11 (14,3%)	2 (2,6%)	0	5 (6,5%)	0	0
					Abdom pain 4 (5,2%)					
°Cennamo [46]	2009	36/1078 (3,3%)	12 (33%)	92%	3 (8%)	1 (3%)	1 (3%)	1 (3%)	0	
Colton [47]	2009	26/805 (3,2%)	not stated	not stated	3 (11,5%)					
Wang [12]	2010	216/3178 (6,8%)	86 (39,8%)	90%	35 (16,2%)	25 (11,8%)	1 (0,4%)	5 (2,3%)	4 (1,8%)	0
Bailey [25]	2010	12,80%	0	85%	14 (14,9%)	14 (14,9%)	0	0		
Testoni [48]	2011	170/2004 (8,5%)	0	95%	11 (6,5%)	11 (6,5%)	not stated	not stated	not stated	not stated

Table 6. Precutting rates and corresponding success and complication rates in the literature

(*NKF Needle-knife fistulotomy;**NKPP Needle-knife precut papillotomy; °Randomized study; §The patients evaluated for the study were 157; $The patients evaluated for the study were 77)

More than half of our patients in the precut papillotomy group (54%) had neoplastic disease and this figure is at the high end of the levels described in literature which vary from 19% reported by Zhou et al.[33] to 56.6% by Halttunen[15], some other studies have reported no cases of neoplastic disease[14].

The ERCPs carried out in our center using the precut papillotomy technique were classified as very difficult (grade 3[28]) in 46.6% of the patients studied – a high percentage in absolute terms. If ERCP's are considered as a whole, the percentage of procedures in grade 3 patients varied in a recent Italian multicenter study[26] from 4.3% (in a low volume center) to 10.1% (in a high volume one). At our center, 36% of all the ERCPs performed were considered difficult and there was a statistically signficant difference in relation to the 46.6% of ERCPs utilizing the precut technique, meaning that the latter may be a subgroup of more difficult cases. Another consideration supporting the hypothesis that the precut technique is used more frequently in difficult cases is the fact that the percent of neoplastic patients was almost double with respect to those who underwent standard sphincterotomy. The high number of difficult cases in our patients could be justified by the fact that ours is a referral center for pancreatic diseases often treating complex patients referred by other Italian health structures (referral bias).

In accordance with Schutz et al.[34], we found an inverse correlation between the difficulty of the procedure and the success rate, albeit only for one of the two operators (Figure 2), confirming the operator-dependent nature of ERCP. No corelation emerged with regard to the grade of difficulty and complication frequency, possibily because of the limited number of cases being treated. Although the correlation seems plausible, it is difficult to establish[30].

If deep cannulation of the ducts is unsuccessful other options may be pursued: attempting cannulation again a few days later; accessing the biliary ducts via a percutaneous transhepatic approach to achieve an endoscopic rendezvous or to place a biliary stent; attempting surgery if it is indicated; abandoning other invasive procedures. As compared to precut papillotomy, any of these options can lead to complications, higher costs and longer hospital stays. The patients in our study who underwent PTBD carried a 22% risk of hemorrhagic complications or cholangitis.

Since a second attempt at ERCP (a mean of 6 days after the first one) was successful in more than 76% of our patients, we agree this option should be pursued whenever clinically feasible before other therapeutic alternatives are considered.

The reports in the literature (Table 6) present a wide range of success and complication rates with regard to the precut papillotomy technique. The variability can probably be attributed to the different indications for the procedure, anatomical and other patient characteristics, timing of the technique, the endoscopist's experience (as indicated by Wang et al.[8]).

Considering the high percent of difficult procedures, the success rate of standard sphincterotomy is extremely good: 93% with an intra-operator variation from 89% to 97%. Our overall precut success rate was 73.3% (range between operators: 63.1% - 83.3%) which lies at the lower edge of the range outlined in the literature. These values are no doubt conditioned by the restrictive nature of the definiton given to success. In fact, success in achieving opacification of the ducts but without deep incannulation or without successful completion of the precedure prescribed was defined as unsuccess.

The variables available at the time ERCP was performed were studied using multivariate analysis. The only variable found to be significant was a statistically difference between the success rates of the two operators. In accordance with Cotton[28] and other Authors,

the outcome of precut papillotomy during the course of ERCP does indeed appear to be operator-dependent. In our study, we prospectively considered consecutive patients so any referral biases were presumably limited. On the other hand, cases were not randomly assigned to the two endoscopists and some bias could have been present as the older endoscopist handled a higher percentage of tertiary procedures. While both were expert endoscopists there was a statistical difference in their technical preferences (needle-knife or traction spincterotome). When the type of papillotomy was analyzed, the needle-knife papillotomy showed a 74.3% success rate compared to a 70% success rate for the transpancreatic traction spincterotomy (p=ns). Reports in the literature likewise indicate a variability with regard to the two techniques. Catalano[35] described a higher success rate using transpancreatic sphincterotomy, Kapetanos[36] found no differences in the success and complication rates of the two procedures and Halttunen[15] reported a higher success rate associated to the transpancreatic approach but noted no differences in the complication rate (pancreatitis) in relation to the needle-knife approach.

The complication rate found in our patients was 5.3% which is very low in comparison to that reported by other studies and comparable/lower to that associated to a standard sphincterotomy (7.3%). If only severe complications are considered, there is only a slight prevalance in the precut group (2.3%) with respect to the standard group (1.3%). Most of the complications associated to the precut technique were some cases of mild pancreatitis, two perforations and one case of severe pancretitis. In accordance with Bailey[25], we are convinced that precutting by needle-knife fistulotomy is not associated to pancreatic complications while precut papillotome involving the papillary pore can lead to episodes of pancreatitis.

The low percentage of cases of pancreatitis after ERCP could be explained by the early use of a guidewire to achieve cannulation. This finding is consistent with others in literature

although some Authors[22] did not obtain the same result using this method to prevent post-ERCP pancreatitis.

The two little perforations in the patients studied occurred during the expansion with a guidewire traction sphincterotome after a needle knife incision in an upper quadrant (fistulotomy). While this is routine practice, in the light of these data this methodology should be carried out with great caution particularly when there is no plan to place a biliary stent after sphincterotomy like in the case of biliary stones. Watchful waiting, providing appropriate medical therapy (placement of nasobiliary and nasogastric tubes, antibiotics) in cases of periampullary perforation makes it possible to avoid surgery in approximately 86% of these cases[37, 38]. In the first case of perforation observed in our patients (confirmed radiologically by a modest pneumoperitoneum) surgery on the third day revealed that there was no interruption in the biliary ducts or duodenum, indicating that perforation had probably regressed spontaneously.

There were no cases of clinically evident hemorrhage according to the criteria we utilized. The endoscopic technique generally used to control bleeding at the precut papillotome site was flushing with adrenaline at a dilution of 1:10000 in physiological solution. Less frequently a submucosal infiltration of that solution was used to prevent mechanical obstruction to the pancreatic outflow. In cases of partial thickness incisions of the circumflex artery of the papilla (an anatomical variant found in approximately 3% of patients), we completed the section of the vessel as was theoretically indicated and usually led to a good spontaneous hemostasis.

Nearly half of the patients in whom ERCP was not successful underwent PTBD with a fifth of those suffering from hemorrhagic-infective complications. Procedures alternative to endoscopy were associated to a not negligible complication rate.

In our opinion the complication rate after precut papillotomy is comparable to that reported by other studies [10, 39, 40]. Not only does the precutting technique have an acceptable risk rate but it also improves the success rate of therapeutic ERCP making it possible for some patients to avoid more invasive procedures such as PTBD or surgery [41, 42] which are accompanied by high rate of complications.

In conclusion, precut papillotomy is:

- an effective technique for deep cannulation of the ducts;
- accompanied by an acceptable complication rate;
- an operator-dependent method (just as ERCP in general);
- a useful technique permitting some patients to avoid more invasive procedures such as PTBD.

  After an unsuccessful precut papillotomy a second cannulation attempt often proves to be successful.

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