

Needle-knife fistulotomy vs. standard biliary sphincterotomy for choledocholithiasis: common bile duct stone recurrence and complication rate



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ABSTRACT

Background and study aims With common bile duct (CBD) stones, access to the CBD can be achieved through the papilla orifice followed by standard biliary sphincterotomy (SBS), or through precut fistulotomy (PF) in case of difficult cannulation. The two methods alter papilla anatomy

differently, potentially leading to a different rate of stone recurrence. No data have been published on stone recurrence after PF in patients with CBD stones. The aim of this study was to evaluate CBD stone recurrence, reintervention rate after PF versus SBS, and complications.

Patients and methods This was a retrospective single-center cohort study including patients undergoing for the first time endoscopic retrograde cholangiopancreatography (ERCP) for CBD stones with PF in case of failed repeated cannulation attempts, matched for sex/age to patients with SBS randomly extracted from our database. *T*-test and Fisher's tests were used for continuous and categorical variable comparison. Recurrence probability was calculated with Kaplan–Meier curve. Factors associated with ERCP repetition were evaluated with logistic regression through a Cox's proportional hazards model.

Results Eighty-five patients with PF were included, with 85 matched controls (mean age 68.7 years, 45.9% males). Overall, patients with PF had the same reintervention rate as those with SBS (14.1% vs. 12.9%) with a hazard ratio (HR) of 1.11 (95% CI 0.49–2.50; *P*=0.81), but mean time to reintervention was significantly lower (74.9±74.6 vs. 765.6±961.3 days; *P*<0.0001), with 100% of stones recurring within the first year in the PF group vs. 54.5% in the SBS group (*P*=0.01). The only factor associated with ERCP repetition risk was incomplete CBD clearing. Complications, including pancreatitis, did not differ significantly.

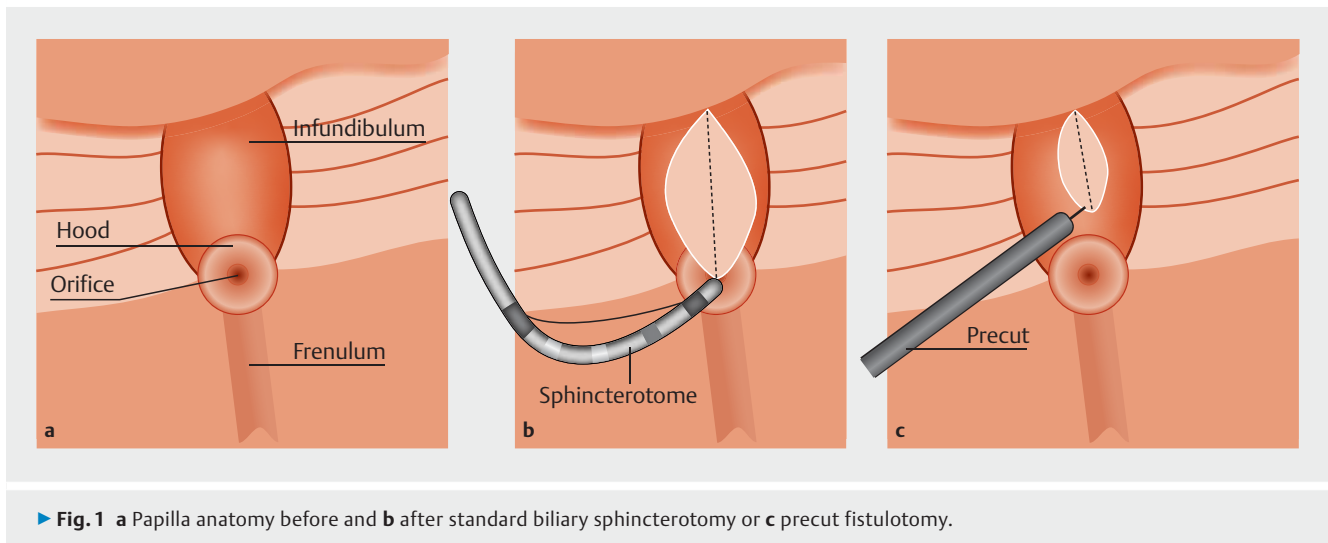
Conclusions The reintervention rate was significantly higher in the short term after PF. Therefore, closer follow-up in the first 6 to 12 months after ERCP might be appropriate for patients undergoing PF.

Introduction

Common bile duct (CBD) stones account for 8% to 20% of gallstone disease and are one of the main causes of hospitalization due to risk of jaundice, cholangitis or acute pancreatitis [1–3]. Standard treatment is endoscopic retrograde cholangiopan-

creatography (ERCP) with endoscopic sphincterotomy (EST) and stone extraction [1]. Recurrence of CBD stones is nevertheless a common event, with an overall incidence of 4% to 24% after ERCP with EST [4–6].

Access to the CBD can be achieved by advancing the sphincterotome or a cannulotome through the major papilla orifice



► **Fig. 1** a Papilla anatomy before and **b** after standard biliary sphincterotomy or **c** precut fistulotomy.

and afterwards performing standard biliary sphincterotomy (SBS) or, in case of failed standard cannulation, as suggested by the 2016 ESGE guidelines [7] by other techniques such as a precut. Precut fistulotomy (PF) is preferable to precut from the orifice in reducing trauma to the pancreatic orifice, and therefore, theoretically rates of post-ERCP pancreatitis (PEP) [7, 8]. Furthermore, intuitively, the two techniques alter the papilla anatomy differently (► **Fig. 1**), as SBS cuts the whole biliary sphincter from the papilla in an upward direction, while PF can leave the distal part of the sphincter intact, possibly leading to a reduced biliary outflow or higher risk of stone impact. Both techniques render the CBD more prone to backflow from the intestine of both bacteria and air, altering the chemical composition of the bile, leading to a crystallization of unconjugated bilirubin and therefore a higher risk of stone recurrence [9, 10].

Although the PF technique is part of the therapeutic algorithm to achieve access to the CBD in case of difficult cannulation [7], to the best of our knowledge, no data on risk of recurrence of CBD stones after PF have ever been published.

The primary aim of our study was, therefore, to evaluate the recurrence rate for CBD stones and reintervention rate in patients previously treated with PF as compared to those treated with SBS; the secondary aim was to evaluate the rate of perioperative complications in the same patient groups.

Patients and methods

This was a retrospective cohort study performed at a single tertiary referral center for bilio-pancreatic endoscopy. Data from all patients who had undergone therapeutic ERCP for documented biliary stone disease over a 9-year period (2008–2017) were retrieved from an electronic database in which the following variables were prospectively recorded: patient characteristics such as gender, age, comorbidities, drugs, indication for the procedure, technical details of the procedures including technique of cannulation (by contrast injection or the guide wire-assisted technique), type of papilla (small vs. normal vs. protruding or large) [11], diameter of the CBD, type of duct

cannulated (biliary or pancreatic, even if unintended) and number of cannulation attempts, final diagnoses, use of mechanical lithotripsy, positioning of biliary or pancreatic stent, perioperative procedure-related complications, blood test results. The same electronic database was used to retrieve patients' follow-up.

The study population was selected to include patients: 1) undergoing ERCP for CBD stones (native papilla) for the first time; 2) aged ≥ 18 ; 3) undergoing PF; 4) undergoing ERCP performed by expert endoscopists (A.M. and P.A.T., performing >250 ERCPs/year with precut rates being 5% to 15%); 5) who had normal size or protruding papilla; and 6) who had dilated CBD.

Exclusion criteria were: 1) patients undergoing, during the first ERCP, papillary balloon dilation; 2) patients undergoing PF and, later on, SBS from the natural orifice to re-gain access to CBD; 3) pregnancy; 4) contrast allergy 5) lack of requested data or follow-up information in the database.

All patients meeting inclusion criteria who received PF were extracted from the database and matched for same sex and age (± 1 year) to SBS patients extracted from the database after randomization.

Randomization and matching

Information on patients undergoing ERCP without PF was extracted from the database and inserted in a Microsoft Excel (Microsoft Corporation, Redmond, Washington, United States) spreadsheet. A random number was assigned through Microsoft Excel Randomization function and patients were therefore ordered based on this random number assigned. Matching was therefore carried out choosing as control for each PF case the first patient of same sex and age (± 1 year) who would meet inclusion and exclusion criteria with the characteristic of undergoing only SBS.

ERCP description

All procedures were performed under deep sedation with intravenous infusion of propofol (Diprivan, Zeneca, Germany), using a Pentax side-view endoscope (ED3470TK-ED34110T). Written,

informed consent was obtained from each included patient. Rectal Indometacin 100mg was administered perioperatively in all patients beginning in 2009, except in case of contraindications.

Deep biliary cannulation was achieved by either advancing a hydrophilic guidewire, preloaded into a triple lumen sphincterotome or, depending on either the operator's choice or study protocols carried out in the period of evaluation, through "delayed" or "early" precut fistulotomy.

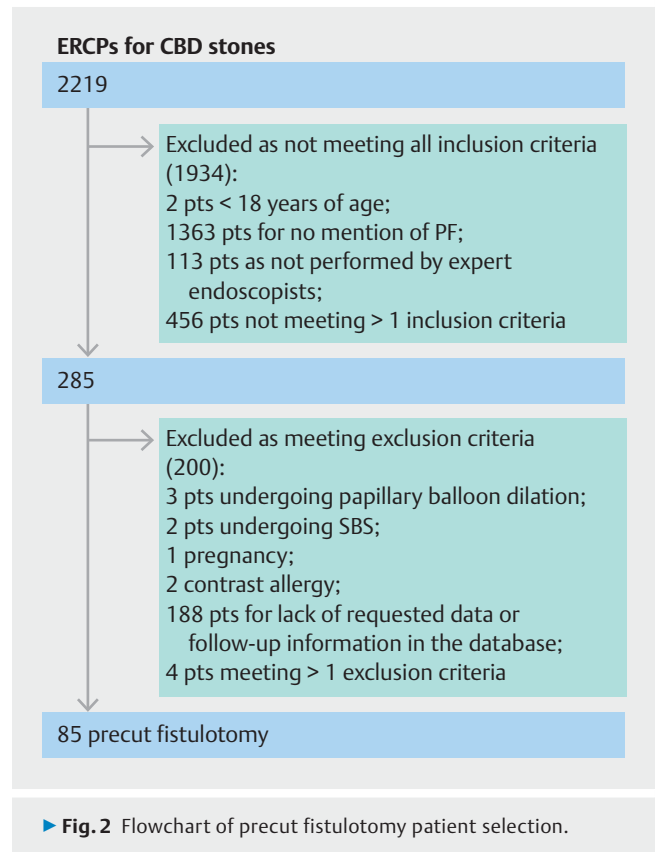
The precut was performed using the freehand technique, making a puncture onto the papilla approximately 3 to 5 mm above the orifice (fistulotomy), mainly with a bottom-up direction, until the biliary orifice was exposed, and once deep CBD cannulation with the guidewire was achieved, sphincterotomy was performed with a standard sphincterotome. A blended electrosurgical current with an ERBE generator (ICC 200; ERBE Electromedizin, Tübingen, Germany) was used, in endocut I mode. Precut fistulotomy was followed by deep biliary cannulation with a hydrophilic tip guidewire. In all cases, a low-osmolality non-ionic radiological contrast medium (Ultravist, Iopromide, Bayer Schering Pharma, Berlin, Germany) was injected for ductal opacification.

Once the CBD was cannulated, wire-guided sphincterotomy was performed for both cannulation techniques. In case of PF, it was done only partially as the distal part of the sphincter, near the pancreatic orifice, was left intact as expected with the technique. A pancreatic stent was positioned based on operator's choice.

Outcomes measured and definitions

Primary outcomes measured were: a) need to repeat unscheduled ERCP for any indication after a first ERCP with CBD stone clearance; when a CBD stone was retrieved at this ERCP repetition we considered the patient suffering from a stone recurrence; and b) access to the emergency room (ER) for cholangitis or abdominal pain associated with elevation of liver function test without cholangitis, treated conservatively. At discharge after ERCP, patients referred to our center for biliary stones are given information on check-up blood tests at defined timepoints, which is to be shown to their general practitioner. Results are to be emailed to us, and if they have any abdominal symptoms, patients are instructed to call our ward phone number, write to our institutional email addresses, or if they have moderate-severe upper quadrant abdominal pain, jaundice, fever with chills or abnormality of liver function tests, to go to the ER.

The secondary outcome was post-ERCP complications defined according to the 1991 consensus guidelines [12]. Accordingly, PEP was defined as onset of new abdominal pain with at least a threefold elevation in serum amylase persisting more than 24 hours after the procedure. Bleeding was defined as having clinical evidence of bleeding with a decrease in hemoglobin greater than 3g/dL and need for endoscopic treatment or interventional radiology. Cholangitis was defined as an elevation in temperature to more than 38°C that was thought to have a biliary cause, without evidence of other concomitant infections. Perforation included retroperitoneal or bowel-wall perforation visualized using any imaging modality.



"Delayed" precut fistulotomy was defined as execution of precut fistulotomy after unsuccessful CBD cannulation for more than 15 minutes or more than six passes of the guidewire into the pancreatic duct [13]. Difficult stones were defined as being ≥ 1.5 cm, more than three stones, unusually shaped stones (barrel-shaped) or intrahepatic location of the stones or proximal to strictures [14].

Statistical analysis

Continuous variables are expressed as means and standard deviation (SD), categorical variables as number and percentage. *T*-test was used for comparison of continuous variables, Fisher's test was used for comparison of categorical variables. Overall recurrence probability was calculated with Kaplan-Meier method, and the results were compared by using a log-rank test. Risk factors for ERCP repetition were expressed as hazard ratio (HR; 95% confidence interval [CI]), and the analysis was performed using a univariate and multivariate logistic regression through Cox's proportional hazards model (Enter method). Risk factors for post-ERCP pancreatitis (PEP) were evaluated by logistic regression analysis and expressed as odds ratio (OR, 95% CI). Tests of statistical significance and CIs were two-sided; $P < 0.05$ was considered statistically significant.

Results

As shown in ► **Fig. 2**, among 2219 ERCPs performed between 2008 and 2017 for biliary stones, a total of 85 patients meeting inclusion criteria received PF and were included as the study

population. Patients excluded and reasons for exclusion are reported in ► **Fig. 2**.

Eighty-five matched patients with SBS who met inclusion and exclusion criteria as PF patients except for having performed SBS instead of PF were then included as controls, for a total population of 170 patients.

Baseline patient data

Mean age for both PF and SBS groups was 68.7 years, with 45.9% being males.

No significant intergroup difference was seen in terms of presence of difficult stones and complete clearance of CBD after first ERCP or presence of CBD-associated stone stenosis. Patients undergoing SBS had a significantly higher rate of duodenal diverticulum (23.5% vs. 8.3% in the PF group; $P=0.01$), a lower rate of type III papilla (8.2% vs. 51.8% in the PF group; $P<0.0001$), and lower rate of unintended Wirsung cannulation (21.2% vs. 36.5% in the PF group; $P=0.04$) (► **Table 1**). Precut fistulotomy was considered “delayed” in 75 (88.2%) PF group cases.

Mean follow-up period for PF patients was significantly longer compared to SBS patients (1740,34 ± 194,06 vs. 1510,42 ± 875,27 days; $P=0.019$).

Short- and long-term recurrence rate

In terms of need to repeat an unscheduled ERCP, overall there was no difference between patients undergoing PF or SBS (14.1% for the PF group vs. 12.9% for the SBS group; $P=1$) but patients with PF had a significantly lower time to reintervention (74.9 ± 74.6 days vs. 765.6 ± 961.3 days; $P<0.0001$). There was no difference in terms of recurrences treated conservatively between the two groups (► **Table 2**).

At survival probability analysis, no differences were seen in the long run between PF and SBS techniques in terms of ERCP repetition probability (► **Fig. 3**). However, most recurrences were seen in a short time in the PF group, in which 100% of stones recurrence occurred within the first 365 days, compared to 54.5% in the SBS group ($P=0.01$) (► **Table 3**). During the ERCP repetition session, six of 12 patients who had recurrence after PF (50%) underwent an extension of the sphincterotomy or balloon dilation of the fistulotomy, while only three of 11 patients with a recurrence after SBS (27.3%) underwent such procedures ($P=0.4$).

Risk factors for CBD stone recurrence

At multivariate logistic regression through Cox’s proportional hazards model (► **Table 4**), adjusted for sex and age, the only factor associated with ERCP repetition was complete clearing of the bile duct, with an HR of 0.04 and 95% CI 0.01–0.14 ($P<0.0001$). Use of PF technique, presence of difficult stones, CBD diameter, use of mechanical lithotripsy, previous or subsequent cholecystectomy, presence of diverticulum, of CBD stenosis and type III papilla were not associated to an increased or reduced risk of ERCP repetition.

► **Table 1** Baseline characteristics of the study patients and ERCP features.

	PF (85)	SBS (85)	P
Age (years), mean ± SD	68.7 ± 15.3	68.7 ± 15.2	1
Sex (M)	39 (45.9%)	39 (45.9%)	1
Papilla morphology			
▪ Type I	0	28 (32.3%)	<0.0001
▪ Type II	41 (48.2%)	50 (58.8%)	0.21
▪ Type III	44 (51.8%)	7 (8.2%)	<0.0001
CBD stenosis	8 (9.4%)	3 (3.5%)	0.21
CBD diameter (mm), mean ± SD	11.1 ± 4.6	10.9 ± 4.2	0.79
Difficult stones	14 (16.5%)	15 (17.6%)	1
Mechanical lithotripsy	3 (3.5%)	1 (1.2%)	0.62
Biliary stent positioning	9 (11.1%)	7 (8.2%)	0.6
Diverticulum	7 (8.3%)	20 (23.5%)	0.01
Wirsung cannulation	31 (36.5%)	18 (21.2%)	0.04
Wirsung injection	12 (14.1%)	6 (7.1%)	0.21
Pancreatic stent positioning	17 (20%)	11 (12.9%)	0.08
Complete clearance of CBD at first ERCP	76 (93.8%)	78 (91.8%)	0.77
Cholecystectomy (pre-ERCP or peri-ERCP)	54 (98.1%)	50 (87.7%)	0.06

PF, precut fistulotomy; SBS, standard biliary sphincterotomy; SD, standard deviation; m, male; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography

Post-ERCP complications

There were no significant differences in terms of post-procedural complications (► **Table 5**). However, although these differences were not statistically significant, patients with PF had a higher rate of perforation (3.6% vs. 1.2%; $P=0.37$) and post-ERCP pancreatitis (12.9% vs. 7.1%; $P=0.3$). In a subanalysis for type of PF, 13.3% of “delayed” PF cases had PEP, versus 10% of “early” PF cases ($P=1$). In a logistic regression for PEP occurrence, among procedure-related factors, only cannulation of Wirsung duct was associated to PEP occurrence, while PF technique was not (► **Supplementary Table 1**). On the contrary, PF patients had a lower rate of bleeding (2.3% vs. 5.9%; $P=0.44$) (► **Table 5**).

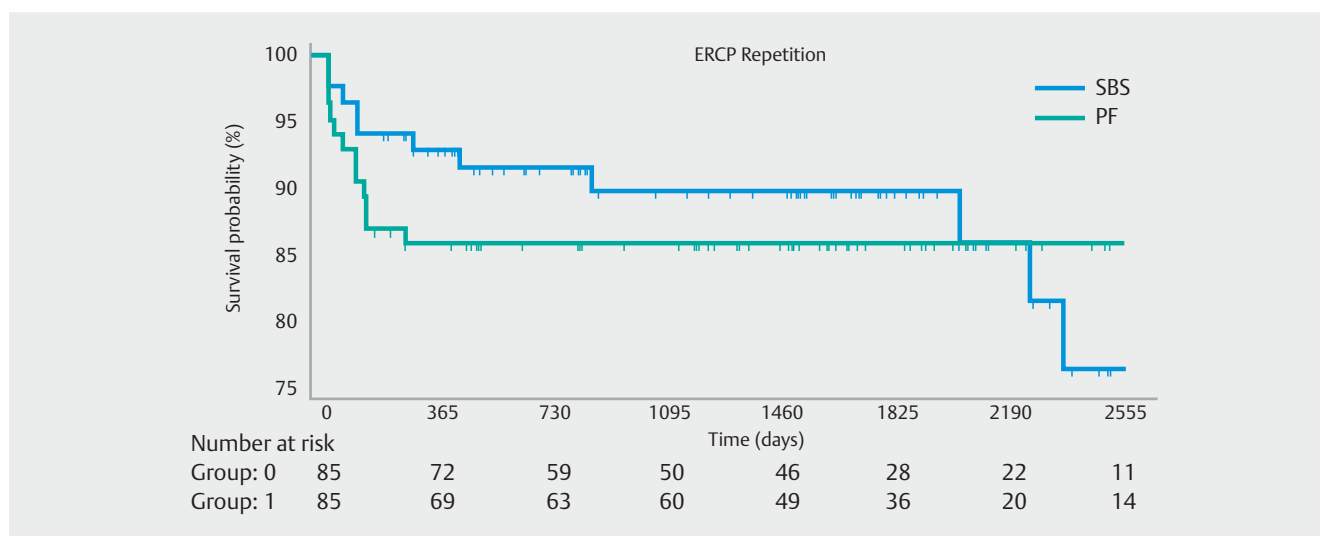
Discussion

CBD stones are a highly incident disease, and ERCP is the mainstay of their treatment [1]. Access to the CBD can be achieved through different techniques based on the difficulty of biliary cannulation and the morphology of the papilla, with PF being one of the employed techniques. Nevertheless, this technique

► **Table 2** Postoperative and follow-up clinical characteristics of the patients.

	PF (85)	SBS (85)	P
ERCP repetition (overall)	12 (14.1%)	11 (12.9%)	1
Time to reintervention (days) mean ± SD	74.9 ± 74.6	765.6 ± 961.3	<0.0001
Number of ERCP sessions to achieve CBD clearance (if not complete at first ERCP), mean ± SD	3 ± 1.4	3.2 ± 0.8	0.79
Recurrence, treated conservatively	0	3 (3.5%)	0.24
Recurrence free survival (days) mean ± SD	1505.2 ± 938.9	1414.0 ± 915.9	0.5
Follow-up (days) mean ± SD	1740.34 ± 194.06	1510.42 ± 875.27	0.019

PF, precut fistulotomy; SBS, standard biliary sphincterotomy; SD, standard deviation; ERCP, endoscopic retrograde cholangiopancreatography



► **Fig. 3** Kaplan-Meier curves showing the cumulative incidence of ERCP repetition (time expressed in days). PF, precut fistulotomy; SBS, standard biliary sphincterotomy

► **Table 3** Need for ERCP repetition due to CBD stones recurrence at different time points.

Days	Number of events within timepoints/cases			Number of events within timepoints/total events		
	PF	SBS	P	PF	SBS	P
30	5/85 (5.9%)	2/85 (2.3%)	0.44	5/12 (41.7%)	2/11 (18.2%)	0.37
60	6/85 (7.1%)	3/85 (3.5%)	0.49	6/12 (50%)	3/11 (27.3%)	0.4
180	11/83 (13.3%)	5/85 (5.8%)	0.12	11/12 (91.7%)	5/11 (45.5%)	0.03
365	12/81 (14.8%)	6/78 (7.7%)	0.21	12/12 (100%)	6/11 (54.5%)	0.01

ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; PF, precut fistulotomy; SBS, standard biliary sphincterotomy

alters the papilla anatomy differently than does SBS, therefore possibly impacting on the recurrence rate of CBD stones, but this has never been explored. Also, PF is not a widespread technique as it is considered risky, with a high rate of peri-procedural complications.

In the current study, PF was associated with the same overall risk of CBD stone recurrence and need for ERCP repetition when compared to patients treated with SBS, but a higher risk in the

short term, with mean time to reintervention in the PF group being significantly shorter (74.9 vs. 765 days). In fact, 100% of stones recurred within the first year in the PF group while only 54.5% in the SBS group ($P=0.01$), but a significant difference was already seen at 180 days, (91.7% vs. 45.5%; $P=0.03$). These data are novel, as this issue was previously unexplored. The explanation for this phenomenon is not clear, and it might be related to two things. The first is a recurrence due to a smaller

► **Table 4** Factors associated with ERCP repetition due to CBD stone recurrence.

	Univariate ¹ (HR 95%CI)	P	Multivariate ¹ (HR 95%CI)	P
Use of PF technique	1.11 (0.49–2.49)	0.82	/	/
Difficult stones	3.51 (1.48–8.33)	0.005	0.82 (0.27–2.57)	0.74
Diameter of CBD	1.09 (1.00–1.20)	0.05	1.01 (0.91–1.12)	0.79
Mechanical lithotripsy	3.44 (0.78–15.05)	0.10	/	/
Complete clearing	0.05 (0.02–0.12)	<0.0001	0.04 (0.01–0.14)	<0.0001
Pre/Peri-ERCP Cholecystectomy	0.58 (0.12–2.78)	0.49	/	/
Diverticulum	1.02 (0.34–3.09)	0.97	/	/
Type II papilla	0.71 (0.32–1.62)	0.42	/	/
Type III papilla	1.59 (0.69–3.67)	0.28	/	/
CBD stenosis	1.29 (0.30–5.56)	0.73	/	/

HR, hazard ratio; PF, precut fistulotomy; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct

¹ Analysis adjusted for age and sex

► **Table 5** Incidence of periprocedural complications.

	PF (85)	SBS (85)	P
Periprocedural complications (overall)	5 (5.9%)	6 (7.1%)	1
Bleeding	2 (2.3%)	5 (5.9%)	0.44
Mild	2 (2.3%)	5 (5.9%)	0.44
Moderate-severe	0	0	/
Perforation	3 (3.6%)	1 (1.2%)	0.37
Cholangitis	0	0	/
Post-ERCP pancreatitis	11 (12.9%)	6 (7.1%)	0.3
Mild	9	5	0.4
Moderate	2	1	1
Severe	0	0	/
Deaths	0	0	/

PF, precut fistulotomy; SBS, standard biliary sphincterotomy; ERCP, endoscopic retrograde cholangiopancreatography

biliary orifice in terms of width after PF compared to SBS. Concerning this first point, it is interesting how, in our cohort, patients who had recurrence after PF underwent an extension of the sphincterotomy or a dilation of the fistulotomy orifice more frequently compared to patients recurring after SBS. In such cases, a careful extension of the sphincterotomy during the first ERCP session could help reduce the recurrence of stones. That possibility is that a residual stone was not seen during the first ERCP and therefore was left in place. Indeed, it is well known how cholangiography performed during ERCP has a low sensitivity, which can range between 67% and 94% for stones [15], but could be even lower for residual fragments or

sludges and, in case of PF, the cholangiography might not be able to point out smaller residual stones behind the papilla. In that case, it might not be correct to call these episodes a “recurrence” but a case of missed stones.

At any rate, findings in the current study might suggest that patients undergoing ERCP for CBD treatment with a PF technique might benefit from a wider sphincterotomy after PF or more careful handling of the CBD during the ERCP session to prevent recurrence due to residual stones, such as saline irrigation as recently suggested by Ahn et al. [16], or closer follow-up in the first 6 to 12 months after the first ERCP.

In terms of adverse events, interestingly, in the current study the overall rate of peri-procedural complications did not differ significantly between the two groups. However, the specific complications seemed to occur differently in the two groups, although these differences did not reach a statistically significance, possibly due to a low statistical power. In more detail, patients treated with ERCP+PF, as expected, showed a higher rate of perforation and PEP, but interestingly a lower rate of bleeding. The higher rate of perforation and PEP are in line with the previous literature [17–20]. Notably, it is difficult to define the actual cause-effect association between PF and PEP, as this is most likely due to the very high rate of “delayed” precut fistulotomy in the current cohort and not to PF itself [7, 13]; this seems to be corroborated by the fact that in the “early” precut group the rate of PEP was lower, although not statistically significant, likely due to the low sample size. Indeed, when cannulation is difficult, repeated attempts may cause papillary edema, and delayed PF is usually attempted after repeated Wirsung cannulation and/or contrast injection, which are well known risk factors for PEP [21]. It is therefore not surprising that both multiple Wirsung cannulation and contrast injection were more frequent in the PF group (► **Table 1**).

The current study has some strengths. It is the first of its kind, exploring a specific hypothesis that might result in clinical

relevance. The population has been observed and treated homogeneously in a tertiary center by expert endoscopists, and the two groups were matched for sex and age, which are well known risk factors for CBD stone onset and recurrence [22]. Data were recorded in a well-defined electronic database and inclusion and exclusion criteria were respected.

Nevertheless, our study presents some limitations. The sample size was relatively small, and as the possible difference between these two groups for the primary outcomes was difficult to be hypothesized as there are no published data on this topic, no power calculation was performed. Concerning this point, we performed a post hoc analysis of the power. Considering the observed rate of stone recurrence-free survival of 87% in patients treated with PF and 94% in patients treated with SBS at 180 days (► **Table 3**), allowing an alpha error of 0.05 and beta error of 0.20 with a 1:1 ratio of the two groups, 280 patients per group would be needed to observe a significant difference in the survival analysis. Therefore, as patients undergoing PF are a great minority of patients undergoing ERCP, the possible lack of adequate power might only be resolved by a large study in a multicenter setting.

Also, evaluation of completeness of CBD clearance was performed by fluoroscopy at the end of any ERCP, and it is not known whether that can be a reliable method for patients with PF, considering the possible suboptimal evaluation of the distal portion of the CBD right behind the major papilla. Therefore, whether ERCPs were repeated for a real recurrence of stones or for presence of residual stones undetected at first ERCP is uncertain. In addition, other recently proposed risk factors for recurrence of CBD stones, such as type of stone and CBD angulation [23], were not analyzed in the current study.

Furthermore, these data derive from a 10-year timeframe, and therefore may be biased by the possible different diagnostic and therapeutic approaches that might have changed throughout the years. Finally, our data report the practice in a tertiary center, which are possibly not generalizable.

Conclusion

In conclusion, the current study suggests no overall increased risk of recurrence in patients undergoing PF as a CBD access technique in case of stones, but that finding is limited to the first 6 to 12 months after ERCP. Interestingly, the rate of complications did not differ significantly from SBS, although the observed higher rate of PEP and perforation in the PF group support the policy of an “early” precut, which has already been advocated in previous studies.

Competing interests

None

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► **Supplementary Table 1** Factors associated with post-ERCP pancreatitis.

	Univariate¹ (OR 95%CI)	P
Use of PF technique	2.02 (0.70 – 5.91)	0.2
Use of “delayed” PF	0.85 (0.09 – 8.29)	0.89
Wirsung cannulation ≥ 1	3.17 (1.09 – 9.17)	0.03
Wirsung injection ≥ 1	3.14 (0.86 – 11.55)	0.08
Pancreatic stent positioning	1.96 (0.21 – 18.30)	0.55

OR, odds ratio; PF, precut fistulotomy; CBD, common bile duct
¹ Analysis adjusted for age and sex