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Digital per-oral cholangioscopy to diagnose and manage biliary duct disorders: a single-center retrospective study

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ABSTRACT

Background and study aims Digital, per-oral cholangioscopy (POCS) allows diagnosis of biliary ducts disorders and treatment for complicated stones. We aimed to determine the diagnostic accuracy of digital POCS systems for stricture lesions and the factors precluding complete biliary stone clearance.

Patients and methods We performed a retrospective analysis of a prospective database of 265 consecutive patients referred for POCS between December 2016 and July 2018. We first analyzed the diagnostic accuracy of digital POCS for malignant and benign stricture lesions in 147 patients. Then, we analyzed the factors associated with complete or partial biliary stone clearance achieved with electrohydraulic lithotripsy (EHL) delivered via POCS in 118 patients.

Results In the diagnostic group, digital POCS achieved 91 % visual-impression sensitivity, 99 % specificity, 99 % positive and 91 % negative predictive values, and 63.64 positive and 0.09 negative likelihood ratios for malignancy diagnosis. In the therapeutic group, complete biliary stone clearance was achieved by EHL in 94.9 % patients; the mean stone size was 20 mm (10–40 mm). In multivariable analyses, a stone size >20 mm (OR: 1.020, $P<0.001$) and the number of stones ≥ 3 (OR: 1.276, $P<001$) was associated with partial biliary stone clearance. Adverse events were reported in 3.3 % patients; no deaths were reported 30 days after the procedure.

Conclusions Digital POCS has excellent diagnostic efficacy for biliary lesions. EHL via POCS is effective for complicated biliary stone clearance. Stone size (>20 mm) and the number of stones (≥ 3) are associated with partial biliary stone clearance.

Introduction

Biliary diseases are frequently encountered in clinical practice. Currently, endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatoscopy (MRCP) are performed to delineate the biliary anatomy and establish a diagnosis in affected patients [1]. ERCP is also the treatment of choice for stone removal from the biliary duct system, but it is ineffective in up to 10 % of patients with complicated bile duct stones [2]. The results of these techniques are often suggestive but not diagnostic of the disease. Consequently, additional techniques are often applied to improve the diagnostic efficacy and therapeutic approach in affected patients.

Digital per-oral cholangioscopy (POCS) allows visualization of the bile and pancreatic ducts and assists therapeutic procedures, such as electrohydraulic lithotripsy (EHL), for complicated duct stones [3,4]. This system is easy to set up, requiring only a single plug-in into the combined light source and processor and a connection to suction and water pumps. Digital POCS can visualize the four bile duct quadrants by moving in four directions in the distal part of the device. This approach permits selective access to the intrahepatic bile ducts and enables target biopsies to be taken [5]. Indications for POCS include: diagnostic work-up of indeterminate biliary strictures; evaluation of post-liver transplantation and biliary and pancreatic intraductal tumors; selective placement of a guide-wire; treatment of complicated pancreatobiliary stones via EHL or laser lithotripsy; and removal of a migrated biliary stent [1].

Some frequently reported adverse events (AEs) include acute cholangitis, acute pancreatitis and rebleeding, which are similar to those reported for ERCP [6]. Here, we aimed to clarify the general outcomes and diagnostic accuracy for malignant and benign stricture lesions using digital POCS. We then aimed to critically analyze the factors affecting complete biliary stone clearance by digital POCS-guided EHL.

Patients and methods

Study design

A retrospective analysis of a prospectively collected database was performed from December 2016 to July 2018 at the Instituto Ecuatoriano de Enfermedades Digestivas (IECED), a tertiary center in Ecuador. The study protocol was approved by the institutional review board, and the study was conducted according to the Declaration of Helsinki and Strobe Statement. All participants provided written informed consent before any procedures were initiated.

Population selection

Consecutive patients aged > 18 years who required POCS were included. The indication of POCS was based on the results of cross-sectional imaging by ultrasonography, computed tomography (CT), MRCP, endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) or forceps biopsy and/or ERCP with negative brush cytology. Patients with suspicion of malignancy or indeterminate biliary strictures diagnosed with these techniques underwent a diagnostic POCS and were allocated into the diagnostic group. Biliary strictures were defined as indeterminate when the biliary strictures have no overt mass on noninvasive imaging (CT or MRCP) and cannot be distinguished as malignant or benign after ERCP fluoroscopic evaluations with standard brush cytology and/or forceps biopsy. Patients in whom biliary stones (> 20 mm) or had a previous failed lithotripsy and were referred to our unit by other medical center, were allocated into the therapeutic group.

Patients with < 6-month follow-up data available, who had uncontrolled coagulopathy, were pregnant and lactating, had contrast allergy, required a pancreatoscopy, had esophageal/gastric/duodenal stenosing tumors or a prior history of esophageal/gastric surgery with no possibility of scope passage were excluded from the analysis.

Patient demographics, procedure indication, number of prior ERCPs, tissue sampling, number of biopsies and histologic evaluation were extracted from the patient records. Information on sizes and locations of stones, size of the distal common bile duct, number of months between biliary plastic stent placement and POCS if EHL was performed, number of EHL sessions required for complete biliary stone clearance, and additional procedures during EHL was also collected from patient records. Complete biliary stone clearance was defined as absence of biliary stones in the bile duct observed during cholangioscopy, performed immediately after clearance (second look), and fluoroscopy. Clinical 6-month follow-up was performed by clinic visits.

Endoscopic technique

Enrolled patients were evaluated by standard duodenoscopy (Pentax ED 34-I10T; Pentax Medical, Hoya Corps., Tokyo, Japan), Pentax video processing (EPK-I7010) and digital POCS (Spyglass DS Boston Scientific, Marlborough, Massachusetts, United States).

All procedures were performed by three experienced endoscopists (C.R.-M, M.S.-A and M.V.) who had conducted more than 300 ERCP procedures per year and were experienced in POCS (> 140 cases). Patients were placed in a supine position under general anesthesia, and all participants received antibiotic prophylaxis (1 g ceftriaxone, intravenously). Endoscopic sphincterotomy was performed before the first cholangioscopy. Additional procedures, such as extension of sphincterotomy, balloon dilation or extension of sphincterotomy plus balloon dilation were performed in subsequent cholangioscopy sessions if required. Biliary cannulation was achieved with an over-the-wire approach. The cholangioscopy was passed proximally, suction was used to clear bile and contrast material, and sterile saline solution was infused to optimize imaging. Images were captured, and videos were recorded using a high-definition image capture system.

Cholangioscopic-guided tissue sampling of suspicious areas within the ductal system was performed using SpyBite forceps (Boston Scientific, Marlborough, Massachusetts, United States). Three or more biopsy samples were taken per suspected lesion.

EHL was performed in patients with complicated biliary stones refractory to conventional methods of extraction during ERCP. EHL was performed with a bipolar lithotripsy 1.9 Fr probe that discharged sparks with the aid of a charge generator (AUTOLITH Touch, Boston Scientific, Malborough, Massachusetts, United States) in a normal saline medium. The probe was positioned more than 5 mm from the tip of the scope and 1 to 2 mm from the stone. The sparks generate high-frequency hydraulic pressure waves, and the energy released from these high-frequency waves is absorbed by the stones, leading to fragmentation. Shock waves are delivered in brief pulses, ranging from a single discharge to continuous firing, until fragmentation. Then the stones were retrieved by conventional ERCP techniques.

Adverse events

AEs were defined in accordance with the American Society for Gastrointestinal Endoscopy criteria and were recorded up to 30 days after the procedure [6]. Abdominal pain with a 3-fold increase in serum amylase/lipase 24 h to 2 weeks after the procedure was defined as post-ERCP pancreatitis (PEP). Acute cholangitis was defined as the presence of fever (> 38 °C) and more than 24 hours with cholestasis. Bleeding was defined as hematemesis and/or melena, or a hemoglobin drop by > 2 g/dL. Perforation was defined as the presence of air or luminal content outside the gastrointestinal tract.

Outcome measurements

The overall visual impression was determined according to our previously reported proposed classification [7], and histological evaluation and/or 6-month follow-up were considered the gold standard. Univariable and multivariable analyses were performed to determine the risk factors associated with partial biliary stone clearance by EHL in patients with complicated biliary stones.

POCS macroscopic classification system

The POCS macroscopic classification was performed using the following new definitions: Non-neoplastic lesions were classified into three types. In type 1 "villous pattern", the lesions could have a) a micronodular pattern without vascularity or b) a villous pattern without vascularity. Type 2 "polypoid pattern", were considered a) adenoma or b) granuloma pattern without vascularity. Type 3 "inflammatory pattern" were regular or irregular fibrous and congestive pattern with regular vascularity [7].

Neoplastic lesions were classified into four types. A flat and smooth, or irregular surface with irregular or spider vascularity without ulceration was considered as type 1 "flat pattern". Type 2 "polypoid pattern" was a polypoid with fibrosis and irregular or spider vascularity. Type 3 "ulcerated pattern" were irregular ulcerated and infiltrative pattern with or without fibrosis and with irregular or spider vascularity. A fibrous honeycomb pattern with or without irregular or spider vascularity was considered as type 4 "honeycomb pattern" [7].

Statistical analyses

Baseline characteristics are described as frequency (percentage) and mean (standard deviation) or median (range) according to their statistical distribution (Kolmogorov-Smirnov or Shapiro-Wilk test). The relationship between history of previous ERCP and development of adverse events following diagnostic POCS was established by logistic regression (bivariable analysis). Quantitative variables were compared by Student's *t*-test or the Mann-Whitney U-test; qualitative variables were compared by Pearson's chi-squared or Fisher's exact test. The overall accuracy of diagnostic POCS for malignancy was defined in terms of sensitivity, specificity, positive predictive value and negative predictive value, and positive and negative likelihood ratio. The odds ratios (OR) were calculated after logistic regression (univariable and multivariable) analysis to determine the factors precluding complete biliary stone clearance in patients with biliary duct stones. For variables that achieved statistical significance, the OR was recalculated through a contingency table. Quantitative variables cut-off values were established using the ROC curve analysis and Youden's index, where necessary. $P < 0.05$ was considered statistically significant. Statistical analysis was performed with R v3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

▶ **Table 1** Patient demographics.

	(n = 265)
Age (years), median (range)	61.7 (19–93)
Sex, female (No., %)	151 (57.0)
Purpose of POCS, No. (%)	
Diagnostic	147 (55.5)
Therapeutic	118 (44.5)
Previous ERCP procedure, No. (%)	
▪ 0	85 (32.1)
▪ 1	134 (50.6)
▪ 2	32 (12.1)
▪ ≥ 3	14 (5.3)

POCS, per-oral cholangioscopy; ERCP, endoscopic retrograde cholangiopancreatography

Results

General baseline characteristics

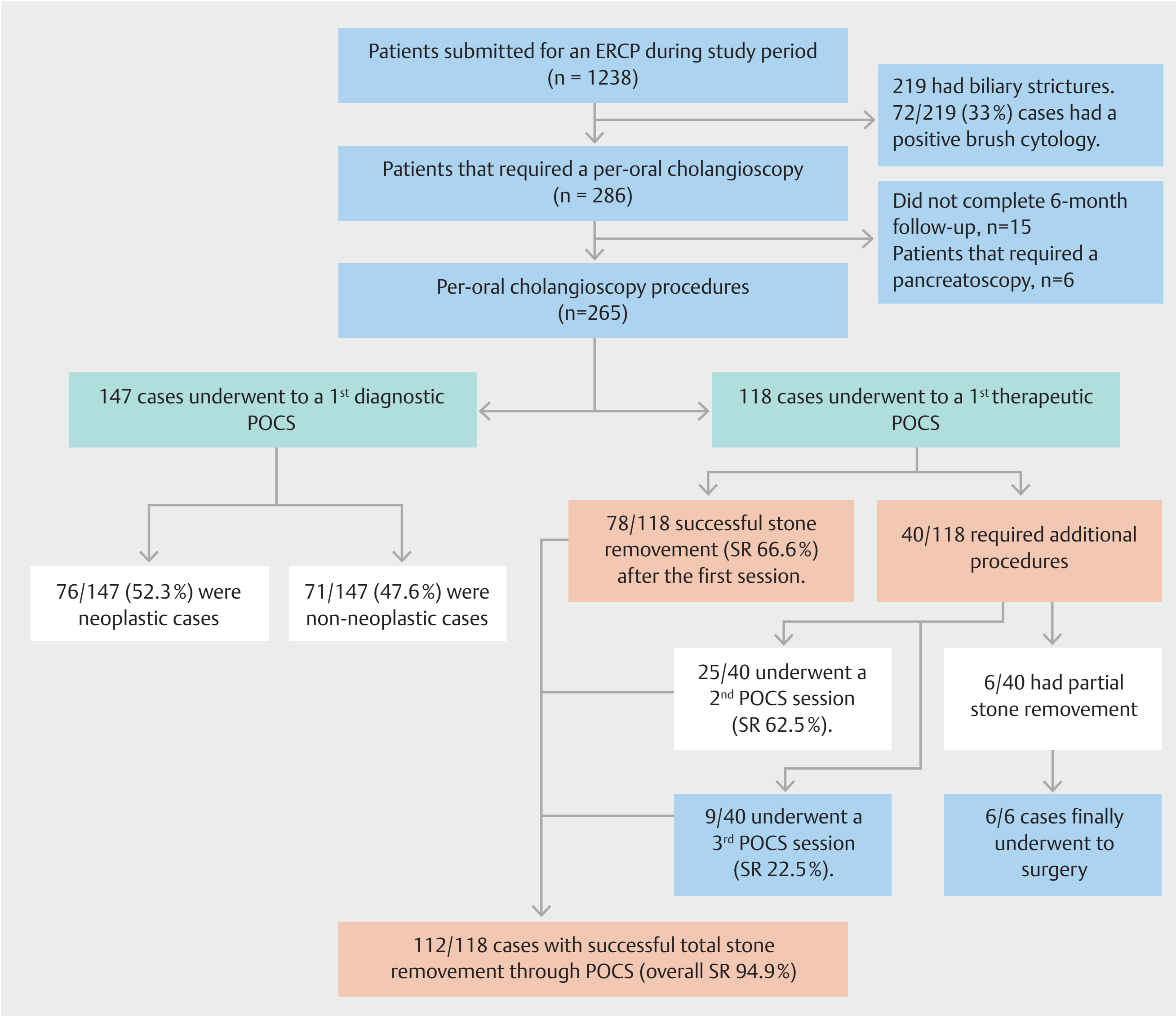
We performed 1238 ERCPs from December 2016 to July 2018 in our unit. 219 patients had biliary strictures, 72/219 (33 %) had a positive brush cytology and were excluded. A total of 286/1238 (23.1 %) patients were referred for digital POCS procedures, of which 15 did not complete the 6-month follow-up and 6 patients required a pancreatoscopy and were excluded. Of the remaining 265 patients (▶ **Table 1**), 147 were allocated to the diagnostic group and 118 to the therapeutic group (▶ **Fig. 1**).

Diagnostic POCS group

The mean age of included patients was 64 years (range: 19–93 years), and 56.1 % were female. All procedural data, the number of previous ERCPs, and histopathological diagnosis were recorded for each patient (▶ **Table 2**). The main indication for diagnostic POCS was undetermined bile duct stenosis (54.4 %). The main location of the lesions was the common bile duct (66.7 %). Two patients had extrinsic biliary compression secondary to an enlarged celiac ganglion (1.4 %), diagnosed using EUS. We captured representative images of all lesion types encountered in the diagnostic group for reference (▶ **Fig. 2**).

We classified the neoplastic lesions (76/147) and non-neoplastic lesions (71/147) using our POCS macroscopic classification system. Fifteen of 76 (19.7 %) had a type 1 "flat pattern" lesion, 29 of 76 (38.1 %) had type 2 "polypoid pattern," 28 of 76 (36.8 %) had type 3 "ulcerated pattern," and four of 76 (5.4 %) had type 4 "honeycomb pattern." Seventy-one patients had non-neoplastic lesions, 33/71 (46.5 %) had a type 1 "villous pattern" lesion, 17 of 71 (24.0 %) had type 2 "polypod pattern," and 21/71 (29.5 %) had a type 3 "inflammatory pattern" lesion (▶ **Table 2**).

We obtained biopsy samples (≥ 3 per patient) for 145 of 147 (98.6 %) patients using SpyBite forceps, except in two patients with biliary external compression, for whom a biopsy sample



▶ **Fig. 1** Patient recruitment and study flow.

was not obtained. The median number of biopsy samples was 3 (range: 3–7). We obtained an adequate tissue specimen for histological examination in 138/147 (93.9 %) patients. After a 6-month follow-up, 70 of 147 patients (47.7 %) had neoplastic lesions and 77 of 147 (52.3 %) had non-neoplastic lesions. From this information, we determined that the overall accuracy of diagnostic POCS was 94.5 %, with a 91 % sensitivity, 99 % specificity, 99 % positive predictive value, 91 % negative predictive value, with a positive likelihood ratio of 63.64 and a negative likelihood ratio of 0.09 (▶ **Table 3**).

Therapeutic POCS group

The median age of included patients was 59.5 years (range: 19.0–92.8 years), and 57.6 % were female (▶ **Table 4**). The main indication for a therapeutic POCS procedure was choledocholithiasis (89.8 %). A total of 61.9 % patients had one previous ERCP. Additionally, 88.1 % of patients had stones located in the common bile duct (▶ **Fig. 3**).

We detected more than three biliary stones in 28.8 % of patients. After the first EHL session, 78 of 118 (66.1 %) patients achieved complete biliary stone clearance; 40 of 118 (33.9 %) required additional procedures. In total, 25 of 40 (62.5 %) patients required a second EHL session and nine of 40 (22.5 %) patients required a third EHL session to achieve complete biliary stone clearance. The remaining six (15.0 %) patients achieved only partial stone clearance by EHL due to the size and location of stones and underwent surgery. Median stone size was 20 mm (range: 10–40 mm), based on EUS and MRCP evaluations.

Two devices were used during stone extraction: (1) balloon (98.3 %), and (2) balloon plus retrieval basket (1.7 %). The mean number of EHL shocks was 1,000 (range: 300–1,700 shocks). The median biliary stent permanence after POCS was 3 months (range: 0–22 months). A distal common bile duct

▶ **Table 2** Characteristics of the diagnostic POCS cohort.

(n = 147)	
Age (years), median (range)	64 (18–93)
Sex, female (%)	83 (56.5)
Previous ERCP procedures, no. (%)	
▪ 0	64 (43.5)
▪ 1	61 (41.5)
▪ 2	15 (10.2)
▪ ≥ 3	7 (4.8)
POCS indications, No. (%)	
▪ Undetermined bile duct stenosis	80 (54.4)
▪ Suspicion of biliary tumor	62 (42.2)
▪ Gallbladder tumor	2 (1.4)
▪ Cyst duct lesion	2 (1.4)
▪ Post-liver transplantation hepatic duct stricture	1 (0.6)
Endoscopic classification of lesions, no. (%)	
Neoplastic lesions (n = 76)	
▪ Type 1 "flat pattern"	15/76 (19.7)
▪ Type 2 "polypoid pattern"	29/76 (38.1)
▪ Type 3 "ulcerated pattern"	28/76 (36.8)
▪ Type 4 "honeycomb pattern"	4/76 (5.4)
Non-neoplastic lesions (n = 71)	
▪ Type 1 "villous pattern"	33/71 (46.5)
▪ Type 2 "polypoid pattern"	17/71 (24.0)
▪ Type 3 "inflammatory pattern"	21/71 (29.5)
Location of the lesions, no. (%)	
▪ Common bile duct	98 (66.7)
▪ Common hepatic duct	24 (16.3)
▪ Hepatic hilum	13 (8.8)
▪ Cystic duct	5 (3.4)
▪ Gallbladder	3 (2.0)
▪ Left intrahepatic duct	2 (1.4)
▪ Celiac ganglion	2 (1.4)
POCS biopsy diagnosis, no. (%)	
▪ Performed	145 (98.6)
▪ Not performed[1]	2 (1.4)
▪ Biopsy samples per suspected lesion, median (range)	3 (3–7)
▪ Tissue specimen adequate for histological examination, no. (%)	138/147 (93.9)
Histopathological diagnosis, no. (%)	
▪ Adenocarcinoma	12/138 (8.7)
▪ Adenoma	5/138 (3.6)
▪ Metastatic carcinoma	1/138 (0.7)
▪ Cholangiocarcinoma	43/138 (31.2)
▪ Chronic cholangitis	1/138 (0.7)
▪ Sclerosing cholangitis	2/138 (1.5)
▪ Fibroma	1/138 (0.7)
▪ Hepatocarcinoma	1/138 (0.7)
▪ Chronic lymphadenitis	1/138 (0.7)
▪ Acute inflammation	4/138 (2.9)
▪ Chronic inflammation	60/138 (43.5)
▪ Mycotic inflammation	3/138 (2.2)
▪ Parasitic inflammation	4/138 (2.9)
Final diagnosis according to follow-up or surgical specimen, no. (%)	
▪ Non-neoplastic lesions	77/147 (52.3 %)
▪ Neoplastic lesions	70/147 (47.7 %)
Adverse events, no. (%)	
▪ Post-procedural cholangitis	1/147 (0.7)
▪ Acute cholecystitis	1/147 (0.7)
▪ Mild acute pancreatitis	5/147 (3.4)

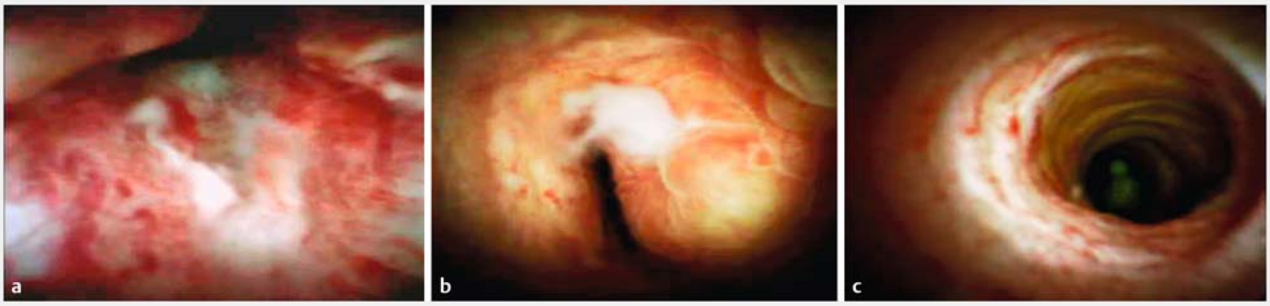
POCS, per-oral cholangioscopy
[1] Corresponded to external compression

diameter > 15 mm was found in 58.5 % of patients. A total of 38/118 patients required an additional procedure: 16 of 118 (13.5 %) patients required an additional extension of a previous sphincterotomy, 16 of 118 (13.5 %) underwent balloon sphincterotomy dilation, and 6/118 (5.3 %) required both procedures (▶ **Table 5**).

Adverse events

In the diagnostic group, seven of 147 (4.7 %) patients reported adverse events: one patient experienced post-procedure cholangitis (0.7 %), one patient developed acute cholecystitis (0.7 %) after the procedure, and five patients experienced mild-acute pancreatitis (3.4 %). Four additional patients showed papilla stigmata of bleeding that resolved with endoscopic management with no need for blood transfusion or a hemoglobin drop by more than 2 g/dL.

In the therapeutic group, two of 118 (1.6 %) patients reported major AEs. These two major AEs included one case of acute pancreatitis related to POCS secondary to biliary stones that



▶ **Fig. 2** Representative lesions in the diagnostic group. **a** Ulcerated and infiltrative lesion with irregular vascularity suggestive of cholangiocarcinoma. **b** Lesion with a ulcero-infiltrative pattern, suggestive of cholangiocarcinoma. **c** Primary sclerosing cholangitis during POCS.

▶ **Table 3** Overall diagnostic POCS accuracy.

Malignancy diagnosis	%	95 % CI
Disease prevalence	52	44–61
Sensitivity	91	82–96
Specificity	99	92–100
Positive predictive value	99	92–100
Negative predictive value	91	82–96
Positive likelihood ratio	63.64	9.08–446.0
Negative likelihood ratio	0.09	0.05–0.19

POCS, per-oral cholangioscopy

▶ **Table 4** Therapeutic group[1] patient characteristics.

(n = 118)	
Age (years), median (range)	59.5 (19–92)
Sex, Female (%)	68 (57.6)
Indication of therapeutic POCS, no. (%)	
▪ Choledocholithiasis	106 (89.8)
▪ Choledocholithiasis plus stenosis of the bile duct post-cholecystectomy	1 (0.8)
▪ Choledocholithiasis plus tumor lesion	11 (9.3 %)
Previous ERCP procedure, No. (%)	
▪ 0	21 (17.8)
▪ 1	73 (61.9)
▪ 2	17 (14.4)
▪ ≥ 3	7 (5.9)
Stone location in bile duct assessed by POCS, no. (%)	
▪ Cystic duct	3 (2.5)
▪ Common bile duct	104 (88.1)
▪ Common hepatic duct	9 (7.6)
▪ Left hepatic duct	2 (1.7)

ERCP, endoscopic retrograde cholangiopancreatography; POCS, per-oral cholangioscopy
[1] POCS, lithotripsy.

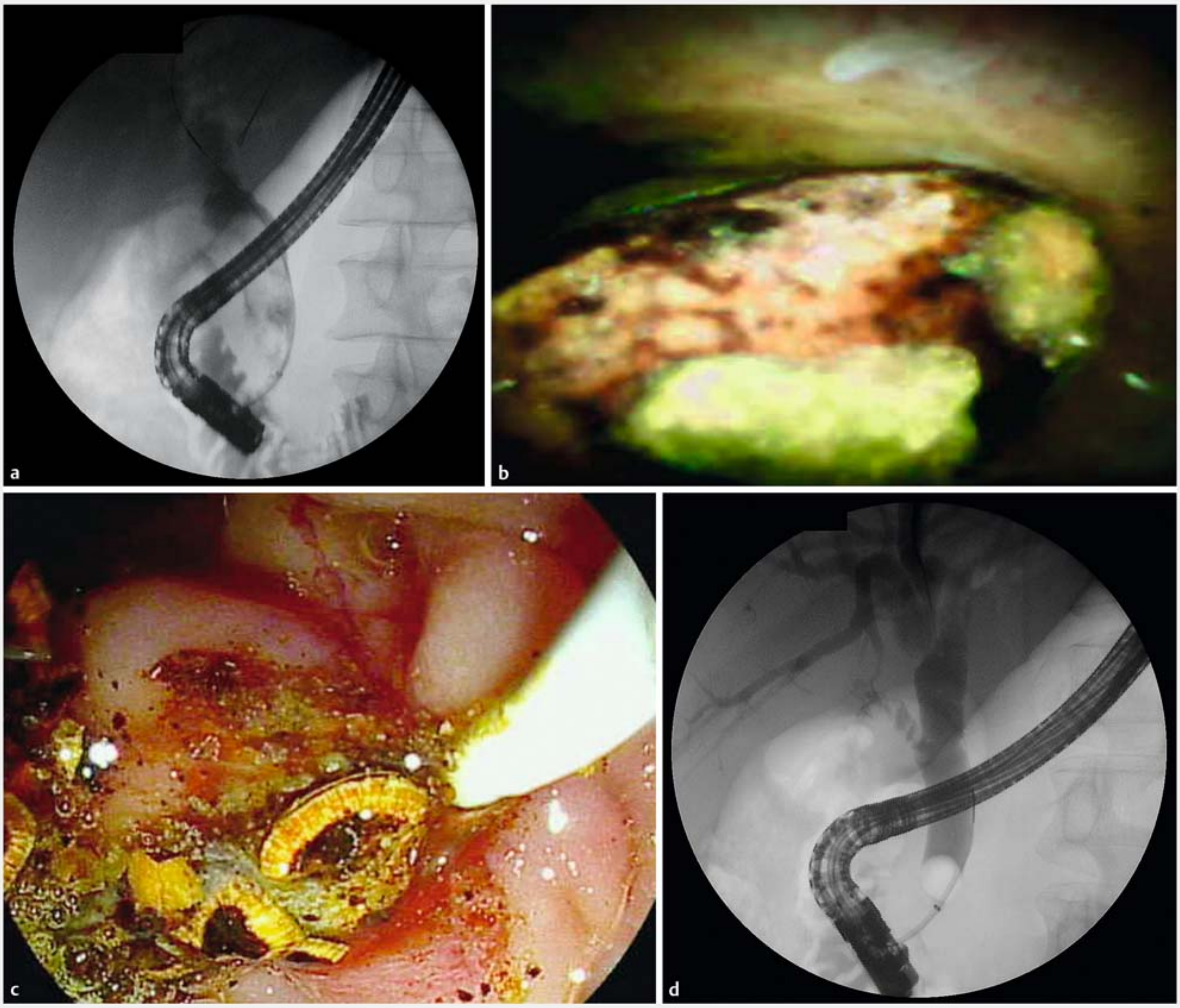
improved with clinical management and one case of acute cholangitis that improved upon antibiotic treatment. In addition, 10 of 118 patients showed papilla stigmata of bleeding that resolved with endoscopic management and did not require blood transfusion. The relationship between previous ERCPs and development of procedure-related AEs following a diagnostic or therapeutic POCS procedure was not statistically significant ($P = 0.524$).

Univariable and multivariable analyses

By univariable analysis, we found that the number of stones (≥ 3) and the stone size (> 20 mm) were significantly associated with partial biliary stone clearance. In the multivariable analysis, we found that the ORs for the number of stones (≥ 3) and the stone size (> 20 mm) were 1.276 (95 % CI: 1.176–1.385; $P < 0.001$) and 1.020 (95 % CI: 1.008–1.032; $P < 0.001$), respectively (▶ **Table 6**). These data indicate that the number of stones (≥ 3) and the stone size (> 20 mm) are risk factors associated with partial biliary stone clearance.

Discussion

The current study was performed in a large cohort (n = 265) to investigate the utility of digital POCS in the diagnosis of biliary duct lesions, its therapeutic approach and the risk factors precluding a complete biliary stone clearance. Use of POCS is expanding, especially as new indications emerge, such as cholangioscopy-guided gallbladder drainage (in poor surgical candidates), the management of complex biliary strictures with failed biliary drainage via ERCP, and detection of small stones not detected on cholangiograms [8–10]. A role for POCS in delineating biliopancreatic neoplasia before surgery was also recently evaluated in a cohort of 118 patients; here, the surgical plan changed as a result of POCS for 34 % patients [11]. We found that digital POCS have an excellent overall accuracy to detect malignant lesions. Also, the number and size of stones are risk factors associated to partial biliary stone clearance.



► **Fig. 3** Cholangioscopy laser lithotripsy. **a** ERCP showing a dilated common bile duct with large stones. **b** Cholangioscopic visualization of biliary stones. **c** Stone fragments after laser lithotripsy. **d** Fluoroscopic evaluation of the common bile duct after complete stone removal.

Digital POCS confers higher sensitivity and specificity for defining biliary strictures than histologic methods or other cholangioscopy approaches [7, 12, 13]. Shah et al. performed a retrospective analysis of 77 cases with indeterminate stricture or bile duct dilation. They found that tumoral vessels and infiltrative strictures were the most common characteristics of neoplasia, and that digital POCS exhibited 93.8 % accuracy, 97 % sensitivity, 93 % specificity, and 90 % positive and 98 % negative predictive values [14]. Navaneethan et al. performed a multicenter study that included 105 patients with biliary or pancreatic disorders. Here, they found that POCS exhibited 90 % sensitivity and 95.8 % specificity for malignancy diagnosis based on visual impression, relying primarily on the presence of tumor vessels characterized by dilated tortuous vasculature coursing in the epithelium accompanied by variable degrees of an exophytic mass protruding into the lumen of the bile duct [3]. Similar results were also obtained by Imanishi et al. for visual-impression diagnosis in 28 retrospective patients, with digital POCS achieving 93 % accuracy [15].

In the current study, we used a novel classification system to classify biliary lesions into neoplastic or non-neoplastic lesions [7]. This classification system achieved very good accuracy (90 %) in a cohort with 106 patients [7]. Here, we achieved similar results with regards to accuracy (94.5 %) when applying this classification to a much larger population (n = 147).

The study by Imanishi et al. also reported a complete biliary stone clearance rate of 91 % in cases treated via POCS-guided EHL; however, the size and number of the stones and an analysis of factors associated with complete biliary stone clearance was not reported [15]. In another study involving a large, multicenter cohort of 407 patients, Brewer et al. reported a complete stone clearance rate via POCS-guided EHL of 96.7 % and via laser lithotripsy of 99 % (P = 0.31), with a single session required in 77.4 % of cases (74.5 % for EHL and 86.1 % for laser li-

▶ **Table 5** Procedure characteristics of EHL via POCS.

(n = 118)	
No. of stones, no. (%)	
▪ 1	67 (56.8)
▪ 2	17 (14.4)
▪ ≥ 3	34 (28.8)
Size of stones (mm), median (range)	20 (10.0–40.0)
Devices used during stone therapy, no. (%)	
▪ Balloon	116 (98.3)
▪ Balloon and retrieval basket	2 (1.7)
Lithotripsy session, no. (%)	
▪ 1	84 (71.2)
▪ 2	25 (21.2)
▪ ≥ 3	9 (7.6)
▪ Stent permanence before POCS (months), median (range)	3 (0.0–22.0)
Size of distal common bile duct, no. (%)	
▪ < 15 mm	49 (41.5)
▪ > 15 mm	69 (58.5)
Additional procedures, no. (%)	
▪ None	80 (67.7)
▪ Extension of sphincterotomy	16 (13.5)
▪ Balloon dilation	16 (13.5)
▪ Extension of sphincterotomy plus balloon dilation	6 (5.3)
▪ Complete biliary stone clearance by total stone removal, no. (%)	112 (94.9)
Adverse events, no. (%)	
▪ None	116 (98.3)
▪ Mild acute pancreatitis	1 (0.8)
▪ Acute cholangitis	1 (0.8)

EHL, electrohydraulic lithotripsy; POCS, per-oral cholangioscopy

thotripsy, $P = 0.20$). Similarly, we obtained a total biliary duct clearance after a single session of 66.1 %. Brewer et al. also found that factors associated with the need for an additional lithotripsy session (≥ 2) were a difficult biliary anatomy or biliary cannulation and the duration of the index procedure (> 73.9 ±33.5 minutes). Finally, the median stone size in their study was 15.9 mm [16]. Conversely, we found a larger median stone size in our cohort of 20 mm (range: 10–40); a large stone size can affect the technical and clinical success rates described [16, 17].

Our study uniquely analyzed the effects of a stone size larger than 20 mm and three or more stones. Here we found that both factors were associated with partial biliary stone clearance during EHL via POCS.

In terms of the AEs found in this study, we identified seven cases of acute pancreatitis, two cases of cholangitis and one case of cholecystitis. The resulting total AE rate was 3.3 % (9/265), which was similar to that reported by Brewer et al., (3.7 %) [16]. All cases in this study required only conservative management. Lenze *et al.* reported similar data regarding the adverse event rate after digital POCS in a cohort of 67 patients: specifically, the researchers reported six cases of mild acute pancreatitis, five cases of acute cholangitis and one case of bleeding that required blood transfusion [18].

We found no statistically significant relationship between the number of previous ERCPs and the rate of AEs during POCS ($P = 0.524$). The rate of AEs was similar between those patients submitted to POCS for diagnostic and for therapeutic purposes (4.7 % vs 1.6 %). Regarding the bleeding rate described in our cohort, none of the patients had a 2 g/dL hemoglobin drop or required a transfusion. Acute cholangitis could be relatively more frequent with POCS because saline irrigation inside the bile duct is necessary to obtain good visualization; however, this effect might be reduced through the prophylactic administration of antibiotics. In addition, laser lithotripsy via POCS has a high efficacy, with the advantage of a low rate of adverse events, even in cases of impacted stones [6].

ERCP with brush cytology and intraductal biospies in the evaluation of biliary strictures in a recent meta-analysis showed a 45 % sensitivity for brush cytology and 48 % for intraductal biopsies, with combined procedures reaching a 59.4 % sensitivity [19]. In our unit, we performed 1238 ERCPs during the study period (December 2016 to July 2018), from which 219 had biliary strictures. 72 of 219 (33 %) cases had a positive brush cytology and were excluded. The remaining 147 cases were included in the study, and 91 % of cases were confirmed with POCS. In addition, in a recent economic analysis comparing ERCP with brush cytology versus POCS, the latter was associated with a lower number of procedures (–31 %), and inferior cost (€ 365 per patient) [20].

This study has limitations inherent with its retrospective and single-center nature; however, the large size of the cohort and the critical analysis of factors associated with complete biliary duct clearance are key milestones of the study. Prospective, multicenter studies are now required to validate these results. Studies that combine visual-impression diagnosis and the extension of the lesion through mapping via POCS are also required.

Conclusion

In conclusion, digital POCS has a high accuracy in the diagnosis of biliary lesions. EHL via POCS has high total and partial clinical success rates, with a low AE rate. A biliary stone size larger than 20 mm and three or more stones predispose patients to require more than one EHL session or to partial biliary duct clearance.

▶ **Table 6** Univariable and multivariable analyses of factors associated with lithotripsy and partial biliary stone clearance.

	Univariable analysis			Multivariable analysis		
	OR	95 % CI	*P* value	OR	95 % CI	*P* value
Age (years)	1.002	(0.959–1.045)	0.906	–	–	–
Sex (female)	1.382	(0.246–7.759)	0.699	–	–	–
Presence of tumor lesions	0.678	(0.012–1.277)	0.174	–	–	–
Previous ERCP	2.447	(0.332–13.506)	0.321	–	–	–
No. of stones (≥ 3)	4.116	(2.388–7.515)	< 0.001	1.276	(1.176–1.385)	< 0.001
Stone size (20 mm)	1.116	(1.036–1.209)	0.004	1.020	(1.008–1.032)	< 0.001
No. of lithotripsy sessions	0.175	(0.009–3.194)	0.239	–	–	–
Permanence of stent (months)	1.100	(0.857–1.559)	0.537	–	–	–
Distal common bile duct caliber (> 15 mm)	0.695	(0.121–3.933)	0.677	–	–	–

OR, odds ratio; CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography

Competing interests

Dr. Robles-Medranda is a key opinion leader and consultant for Pentax Medical, Boston Scientific, GTech Medical Supply and MD Consulting Group. The other authors have no conflicts of interest.

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