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### Title

Peroral cholangioscopy: Update on the state-of-the-art

### Permalink

<https://escholarship.org/uc/item/8xq6t2c3>

### Journal

World Journal of Gastrointestinal Endoscopy, 14(2)

### ISSN

1948-5190

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### Publication Date

2022-02-16

### DOI

10.4253/wjge.v14.i2.63

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Peer reviewed



## Peroral cholangioscopy: Update on the state-of-the-art

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**Author contributions:** Subhash A, Buxbaum JL, and Tabibian JH have all been involved in drafting the manuscript and/or making critical revisions; Subhash A, Buxbaum JL, and Tabibian JH meet the criteria for authorship established by the International Committee of Medical Journal Editors and approve the final manuscript for publication.

**Conflict-of-interest statement:**

There are no conflicts of interest to disclose.

**Country/Territory of origin:** United States

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): 0  
Grade C (Good): C  
Grade D (Fair): 0  
Grade E (Poor): 0

**Open-Access:** This article is an

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### Abstract

Peroral cholangioscopy (POC) is an endoscopic procedure that allows direct intraductal visualization of the biliary tract. POC has emerged as a vital tool for indeterminate biliary stricture evaluation and treatment of difficult biliary stones. Over several generations of devices, POC has fulfilled additional clinical needs where other diagnostic or therapeutic modalities have been inadequate. With adverse event rates comparable to standard endoscopic retrograde cholangioscopy and unique technical attributes, the role of POC is likely to continue expand. In this frontiers article, we highlight the existing and growing clinical applications of POC as well as areas of ongoing research.

**Key Words:** Peroral cholangioscopy; SpyGlass™; Difficult bile duct stones; Indeterminate biliary strictures; Cholangioscope-guided biopsy; Cholangioscope-guided lithotripsy

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**Core Tip:** Cholangioscopy is an endoscopic technique that was first developed in the 1970s as a minimally-invasive modality for the evaluation of various biliopancreatic pathologies. Since the advent of the digital single-operator cholangioscopy (D-SOC) in 2015 as well as other, complementary advancements in the field, diagnostic and therapeutic applications have further expanded. Herein, we discuss the various current

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**Received:** June 30, 2021

**Peer-review started:** June 30, 2021

**First decision:** July 29, 2021

**Revised:** August 25, 2021

**Accepted:** January 17, 2022

**Article in press:** January 17, 2022

**Published online:** February 16, 2022

**P-Reviewer:** Maetani I

**S-Editor:** Fan JR

**L-Editor:** A

**P-Editor:** Fan JR



applications of cholangioscopy, with a focus on D-SOC, and areas of ongoing research to better understand potential future directions.

**Citation:** Subhash A, Buxbaum JL, Tabibian JH. Peroral cholangioscopy: Update on the state-of-the-art. *World J Gastrointest Endosc* 2022; 14(2): 63-76

**URL:** <https://www.wjgnet.com/1948-5190/full/v14/i2/63.htm>

**DOI:** <https://dx.doi.org/10.4253/wjge.v14.i2.63>

## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) was first reported in 1968 as a method to cannulate the major duodenal papilla[1]. It is now widely utilized as the primary interventional modality for many biliopancreatic disorders. Despite its vast utility, ERCP technique relies on indirect visualization of the biliary tree *via* fluoroscopy; this can be limiting for certain diagnostic and/or therapeutic applications (*e.g.* evaluation of biliary strictures, mapping of intraductal tumors for operative planning, tumor-directed ablative therapy, *etc.*).

In order to provide direct visualization of the biliopancreatic tree, peroral cholangioscopy (POC) was introduced in the 1970s[2,3]. POC was originally designed as a “mother-baby” system that required two endoscopists to operate the “mother” duodenoscope and “baby” cholangioscope[2]. In addition to the multi-operator requirement, there was a notable deficiency in this setup in the ability to acquire tissue following visualization, thus further limiting its use. Moreover, the initial scopes provided only two-way tip deflection, were fragile, and costly[4].

Over the past several decades, technologic improvements in the equipment utilized for POC has led to more widespread adoption and a growing number of applications (Figure 1). In the early 2000s, a new single-operator duodenoscope-assisted cholangioscopy technique utilizing a Pentax cholangioscope (FCP-8P/FCP-9P, Pentax Precision Instruments, Orangeburg, New York, United States) was introduced. However, this technique required the use of an endoscopist-worn breastplate to mount the cholangioscope, which allowed for manipulation of the duodenoscope with the left hand and the cholangioscope with the right hand[5]. In 2005, Boston Scientific released the first commercially available single-operator cholangioscopy (SOC) system (SpyGlass™, Boston Scientific Corporation, Natick, MA, United States), a catheter-based system that utilizes an optical probe inserted through the duodenoscope working channel[6]. Ten years later, a digital SOC (D-SOC) system was introduced (SpyGlass™ DS, Boston Scientific Corporation)[6]; this updated digital system brought improvements in image size and quality, a wider field of view, and a redesigned working channel allowing for larger diameter cholangioscopic accessories, among other changes[4,7]. In 2018, a third generation SpyScope™ DSII Catheter (Boston Scientific Corporation) featuring increased resolution and improved lighting was introduced alongside new cholangioscopic accessories. Alternatively, direct POC (DPOC) can be performed utilizing a modern ultraslim upper endoscope that can be advanced into the biliary tree following endoscopic sphincterotomy, a technique first published in a pilot study in 2006[8-10]; however, this setup is primarily used outside the United States and available in only select markets[7].

Given the recent technologic advancements in POC, its array of accessories (Figure 2), and improved training of advanced endoscopists, there has been wide propagation of this technique across most large medical centers. In this *Frontiers* article, we aim to underscore the major developments in the growing body of literature on POC, with particular emphasis on SOC and D-SOC, including diagnostic and therapeutic applications as well as established and investigational indications.

## COMMON APPLICATIONS OF CHOLANGIOSCOPY

### **Management of difficult biliary stones**

Approximately 10%-18% of patients with symptomatic cholelithiasis will have concomitant choledocholithiasis[11]. The standard of care for these patients is ERCP

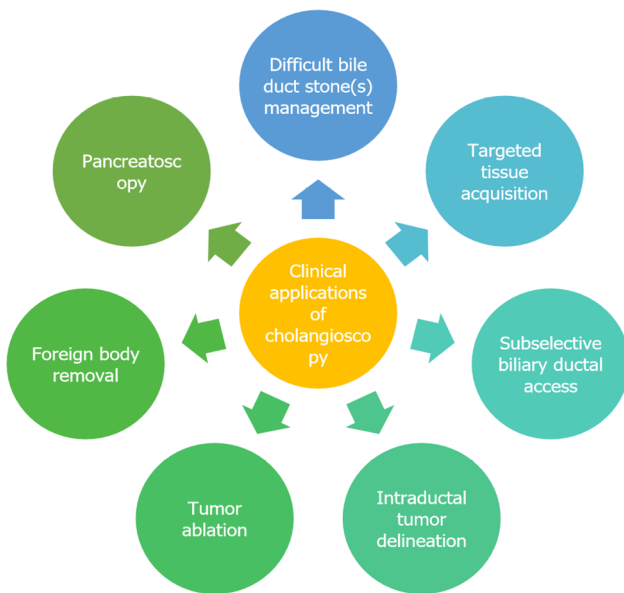


Figure 1 Common diagnostic and therapeutic applications of cholangioscopy.



Figure 2 SpyGlass™ DS accessories including: Autolith™ Touch biliary electrohydraulic lithotripsy probe, Lumenis SlimLine™ SIS GI™ holmium laser lithotripsy probe, SpyBite™ Max biopsy forceps, SpyGlass retrieval snare, and SpyGlass retrieval basket (left to right). Additional accessories are expected to be developed over time[83]. Image adapted with permission from Dr. Isaac Rajiman and Boston Scientific. Citation: **Boston Scientific Corporation**. An Expanding Suite of Compatible Accessories and Applications. [cited June 23, 2021]. Available from: <https://www.bostonscientific.com/en-EU/products/direct-visualization-systems/spyglass-ds-direct-visualization-system/accessories-and-applications.html>. Copyright© 2022. Published by SpyGlass™ DS.

with endoscopic sphincterotomy followed by stone extraction with a balloon or basket [4,11]. In a minority of cases, bile duct stones may be more difficult to extract, requiring additional measures[12]. Difficult bile duct stones have been previously defined as large size (> 1.5 cm in diameter), impacted stones in the bile or cystic duct, intrahepatic location, hard stone consistency, stricture distal to stones, and/or anatomical variants (*e.g.* unusual size/shape of bile duct) posing technical challenges [12,13].

POC allows for direct visualization and decreased risk of bile duct injury and is a vital addition to the ERCP armamentarium for stone disease. Indeed, a recent meta-analysis found the estimated success rate for difficult bile duct stone clearance to be 88% [95% confidence interval (CI): 85%-91%] across 820 patients ( $n = 31$  studies)[14]. Furthermore, POC was found to have a low adverse event (AE) rate of 7% (95% CI: 6%-95%), comparable to ERCP[14,15]. Thus, POC is a valuable modality in addition to or in lieu of conventional ERCP methods such as mechanical lithotripsy (ML) and endoscopic papillary large balloon dilation (EPLBD).

Since the time of publication of the aforementioned meta-analysis, three randomized controlled trials (RCTs) comparing POC-guided electrohydraulic lithotripsy (EHL) or holmium laser lithotripsy (LL) *vs* conventional therapy (*i.e.* ML,

EPLBD, and balloon extraction) have been published. In the first study, the investigators randomized patients with bile duct stones > 1 cm in diameter in a 2:1 ratio to SOC-guided LL *vs* conventional therapy. Stone clearance was achieved in 39 of 42 (93%) patients treated with SOC-guided LL compared to 12 of 18 (67%) treated with conventional therapy ( $P = 0.009$ ). AE rates were similar in the two treatment groups [16]. In the second study, successful stone removal did not differ in the SOC-guided EHL arm (37 of 48) *vs* conventional therapy arm (36 of 50) ( $P > 0.05$ ); similarly, crossover yielded non-statistically significant differences in the two groups (successful stone removal in 40 of 47 patients *vs* 42 of 44 patients,  $P > 0.05$ ) [17]. In the final study, the investigators randomized 32 patients with large CBD stones in whom sphincterotomy and/or EPLBD had failed into ML or D-SOC-guided LL treatment arms. Crossover was permitted as a rescue treatment if the primarily assigned technique failed to achieve stone clearance. Stone clearance rates for ML and D-SOC-guided LL groups were 63% and 100%, respectively ( $P < 0.01$ ). In six patients, ML was considered a failure; when crossed over to LL, four of these patients achieved stone clearance in the same session, and the remaining two patients achieved stone clearance in subsequent LL sessions. AEs were reported at similar rates, 13% in the ML group and 6% in the LL group ( $P = 0.76$ ). The median length of hospital stay following the respective procedures was 1 d in both groups ( $P = 0.27$ ). At six months follow-up, neither group had recurrent cholangitis or evidence of recurrent CBD stones [18]. While the RCT data presented above may appear mixed or only partially in favor of POC in the management of difficult bile duct stones, it is important to note that only the last of the three studies discussed above utilized the newer generation of D-SOC. Thus, additional RCT data using the contemporary D-SOC system is needed.

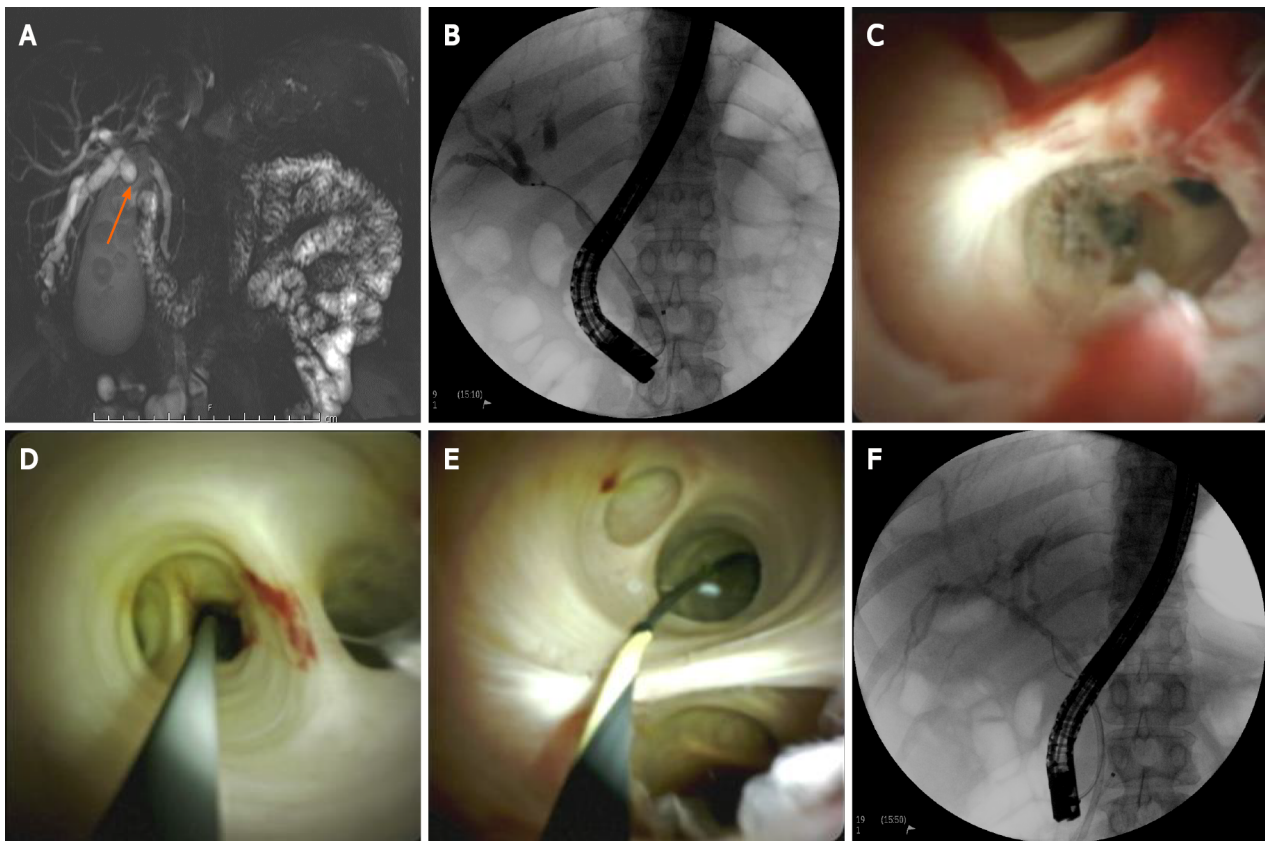
POC can also be utilized to confirm stone clearance in cases of choledocholithiasis. In a retrospective study of 36 patients who underwent ERCP with EPLBD for difficult biliary stones, DPOC was performed immediately after a negative balloon-occluded cholangiography [19]. In 31 of 36 patients (86%), technical success was achieved with hepatic hilum visualization. Residual stones were found in 7 of these 31 patients (22.5%) upon DPOC, among which 4 patients underwent successful stone extraction during the same DPOC session. The remaining 3 patients underwent secondary ERCP for residual stone removal. There were no reported AEs in the study.

### **Indeterminate biliary strictures**

**Visual evaluation:** Another major indication for POC is the evaluation of indeterminate biliary strictures (IDBSs). IDBSs are defined as biliary strictures of persistent unclear etiology following cross-sectional imaging and evaluation by ERCP with brush cytology or intraductal biopsies [20]. In a meta-analysis of 16 studies including 1556 patients, the overall sensitivity of conventional cytology from ERCP was found to be 41.6% (99%CI: 38.4%-44.8%), with a negative predictive value of 58.0% (99%CI: 54.8%-61.2%) [21]. This study and others, as well as widespread clinical experience, attest to the need for improved diagnostic capability for IDBSs.

The visual diagnosis of intraductal lesions can be aided by direct visualization during POC (Figure 3). Currently, there is no widely accepted classification system for visual diagnosis; however, some cholangioscopic findings are highly suggestive of malignancy in the appropriate clinical context. These findings include the presence of neovascularization, mucosal changes and projections, and intraductal nodules, among others [22-24]. Historically, neovascularization, also termed “tumor vessels,” has had the most consensus regarding its description and malignant implications [24]. It has been described as irregularly dilated, tortuous, and abnormally proliferating vessels on the mucosa adjacent to a stricture.

In a recent systematic review and meta-analysis of 21 studies examining the diagnostic performance characteristics of POC-based visual assessments of IDBSs, the pooled sensitivity and specificity for establishing a malignancy diagnosis were 88% (95%CI: 83%-91%) and 95% (95%CI: 89-98%), respectively [25]. Subgroup analysis of studies that utilized D-SOC found a higher sensitivity for visual diagnosis [94% (95%CI: 89%-97%)] compared to D-SOC-guided biopsy [79% (95%CI: 72%-84%),  $P < 0.001$ ] while also showing a higher specificity for D-SOC-guided biopsy [100% (95%CI: 97%-100%)] compared to D-SOC visual impression [86% (95%CI: 76%-92%),  $P < 0.001$ ] [25]. Subgroup analysis of studies that utilized DPOC did not reveal statistically significant differences in performance characteristics of visual impression *vs* DPOC-guided biopsy (possibly suggesting superior optical performance of DPOC compared to D-SOC), though power was limited [25]. Overall, performance characteristics of visual impression utilizing modern POC (both D-SOC and DPOC) appears promising.



**Figure 3** Example of an indeterminate biliary stricture further evaluated by cholangioscopy, initially thought to be Mirizzi syndrome secondary to chronic choledocholithiasis. A: Magnetic resonance cholangiopancreatography (T2 HASTE, coronal projection) demonstrating cholelithiasis, choledocholithiasis, and right hepatic ductal dilation as well as possible common hepatic duct (CHD) obstruction (arrow); B: Endoscopic retrograde cholangiopancreatography (ERCP) showing 1.5 cm CHD stricture suspicious for perihilar cholangiocarcinoma (CCA); C: Frond-like growth and neovascularization suggestive of neoplasm involving the CHD, later confirmed as perihilar CCA following SpyBite™ Max biopsy (previously with negative cytology on initial ERCP); D and E: Multiple views of the hepatic ducts that demonstrate scant reactive changes (from prior plastic biliary stent) and proximal limit of disease extension/tumor mapping; F: ERCP confirming successful deployment of plastic biliary stent across CHD stricture and subsequent decompression of right hepatic duct.

A recent group of researchers have produced a new schema, the “Monaco Classification,” in order to attempt to standardize visual criteria in evaluating IDBSs as malignant *vs* benign. Twelve expert biliary endoscopists from around the world reviewed 40 video clips (13 benign pathology, 27 malignant) in order to consolidate visual criteria into the following: (1) Presence of stricture (symmetric or asymmetric); (2) Presence of lesion (with associated mass, nodule, or polypoid in appearance); (3) Smooth or granular mucosal features; (4) Papillary projections; (5) Ulceration; (6) Abnormal vessels; (7) Scarring (local or diffuse); and (8) Pronounced pit pattern[26]. Thereafter, 21 D-SOC video clips were reviewed by 14 interventional endoscopists utilizing these criteria, ranging from slight to moderate in interobserver agreement [26]. Diagnostic accuracy of visual interpretation of malignant *vs* benign pathology was 70% based on the new criteria, compared to an average accuracy less than 50% on prior attempts to establish visual criteria[26,27]. While the Monaco Classification has taken a crucial step in a forward direction, it would benefit from further refinement and validation.

**Cytopathologic evaluation:** In addition to the visual diagnosis of IDBSs, POC-guided biopsy can provide further histopathologic interpretation of IDBSs. In a systematic review with meta-analysis of 10 studies evaluating the use of SOC-guided biopsy for the diagnosis of malignant biliary strictures, the overall pooled sensitivity and specificity were 60.1% (95%CI: 54.9%-65.2%) and 98.0% (95%CI: 96.0%-99.0%), respectively[28]. In a subset of four studies, patients ( $n = 148$ ) had previously undergone ERCP with benign or non-diagnostic brushing/biopsy results (with strong suspicion for malignancy); in this specific cohort, the pooled sensitivity and specificity of SOC-guided biopsy were 74.7% (95%CI: 63.3%-84.0%) and 93.3% (95%CI: 85.1%-97.8%), respectively[28]. More recently, a systematic review with meta-analysis of 11 studies examined the use of D-SOC-guided biopsy for evaluation of IDBSs. The pooled

sensitivity and specificity were 74% (95%CI: 67%-80%) and 98% (95%CI: 95%-100%), respectively[29]. These data suggest that POC-guided biopsy, in particular D-SOC-guided biopsy, yields improved diagnostic sensitivity when evaluating IDBSs.

POC-guided biopsies can be useful in cases where prior ERCP biopsies/brushings return benign or non-diagnostic results (when a strong suspicion for malignancy nevertheless remains) (Figure 3). In addition, a retrospective study of 40 patients found that biliary lavage cytology can be combined with POC-guided biopsy to further improve diagnostic sensitivity and accuracy when compared to POC-guided biopsy alone (sensitivity 88% *vs* 70% and accuracy 90% *vs* 75%, respectively)[30]. Of note, the data presented above predates the advent of the SpyBite™ Max biopsy forceps, which has increased tissue capacity compared to the first-generation SpyBite (legacy) forceps. This, along with other improvements, is expected to further improve the diagnostic performance of POC-guided intraductal biopsy.

One limiting factor that has been thought to potentially hamper the utility of SOC-guided biopsy is the absence of on-site cytopathology for real-time tissue processing, a concern recently addressed by the SOCRATES (single-operator cholangioscopy randomized trial evaluating specimens) trial[31]. In this RCT, patients ( $n = 62$ ) with IDBSs were randomized to an off-site tissue processing cohort ( $n = 30$ ) and an on-site cohort ( $n = 32$ ) in order to compare diagnostic accuracy. The study found a diagnostic accuracy of 90% (95%CI: 73.5%-97.9%) versus 84.4% (95%CI: 67.2%-94.7%) when comparing off-site tissue processing *vs* on-site, respectively ( $P = 0.86$ ). Additionally, the overall treatment costs of D-SOC based on the Medicare reimbursement fee structure (including anesthesia, hospital fees, laboratory fees, medications, supplies, and radiologic fees) was found to be \$14423 for the off-site cohort compared to \$13015 for the on-site cohort ( $P = 0.60$ ). Thus, this RCT suggests that D-SOC is a cost-effective option for the evaluation of IDBSs, even in centers without on-site cytopathology.

### Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic, progressive disease that causes inflammation and fibrosis of the biliary tract, often leading to end-stage liver disease and/or cholangiocarcinoma (CCA)[32]. Patients with PSC can develop “dominant strictures,” or focal narrowing defined at ERCP as stenosis with diameter  $\leq 1.5$  mm in the CBD and/or  $\leq 1.0$  mm in a hepatic duct within 2 cm of the ductal confluence[20,32-34]. Dominant strictures are clinically significant in light of their higher propensity for bacterial cholangitis and for underlying dysplasia or carcinoma[32,35]. A recent systematic review and meta-analysis of 21 studies found that the pooled sensitivity and specificity of POC for diagnosis of CCA was 65% (95%CI: 35%-87%) and 97% (95%CI: 87%-99%), respectively[36]. POC-guided biopsy also had the highest diagnostic accuracy (96%), compared to bile duct brushings (87%), fluorescence *in situ* hybridization (FISH) (69% for polysomy and 47% for trisomy), and probe-based confocal laser endomicroscopy (75%)[36].

However, not all data to date support the use of POC in patients with PSC. For example, a prospective study of 47 patients with PSC evaluating the use of POC-guided biopsy of strictures found a significantly lower sensitivity (33%) than previously reported[37]. Additionally, a retrospective study of 92 patients, both with ( $n = 36$ ) and without ( $n = 56$ ) PSC, examined the performance characteristics of ERCP with brush cytology, FISH, POC-guided biopsy, transpapillary biopsy and each possible combination of the aforementioned for the detection of CCA. When combining all diagnostic modalities, patients without PSC showed a trend towards improved sensitivity compared to brush cytology alone (75% *vs* 40.9%,  $P = 0.06$ )[38]. However, the PSC group did not show a similar trend towards improved sensitivity when comparing all four diagnostic modalities to cytology alone (60% *vs* 50%,  $P = 1$ ) [38].

Overall, the precise role of POC in the diagnostic evaluation of dominant strictures in PSC remains unclear. POC can potentially play an important role in studying the natural history and progression of PSC and in general facilitate better characterization and sampling of dominant strictures. For instance, with the newly proposed cholangioscopy-based “Edmonton Classification” system for phenotypic classification, dominant strictures can be classified into one of the three following phenotypes: Inflammatory, fibro-stenotic, or nodular or mass-forming. One theory is that these and other POC findings may differ by disease stage/pathobiological involvement (*e.g.* nodular or mass forming may be indicative of developing or nascent CCA)[39]. It is proposed that combining phenotypic data with histopathology, biochemical markers, and cholangiography scores over time could lead to improved management algorithms[40]. For now, validation of this classification system remains the initial step

prior to determining its ultimate clinical utility.

### **Evaluation of intraductal neoplasms**

POC is becoming increasingly useful in the mapping of biliopancreatic neoplasms such as CCA and intraductal papillary mucinous neoplasms (IPMNs). With improved visual delineation of neoplastic margins in the biliary tree and pancreatic ducts, staging can be more precise, and thus a better-informed therapeutic plan can be formulated (Figure 3). A multicenter prospective cohort study of 118 patients evaluated the impact of cholangiopancreatography on preoperative assessment of biliopancreatic neoplasms. Following cholangiopancreatography, the initial therapeutic plan was altered in 34% of patients[41]. Of these patients, more extensive surgery was required in 10%, less extensive surgery was required in 65%, and surgery was avoided in the remaining 25%[41]. Additionally, the study reported a 88% correlation in histology between the surgical specimens and cholangiopancreatography specimens [41].

Cholangiopancreatography is also being utilized to directly examine pancreatic duct abnormalities, such as distinguishing between pancreatic duct dilation secondary to chronic pancreatitis *vs* IPMNs[42]. When used in conjunction with non-invasive imaging, POC/cholangiopancreatography improves diagnostic and therapeutic ability. As has been discussed in prior sections, this is mainly from direct visual tissue inspection and the ability to obtain targeted biopsies. Simultaneously, it also offers the opportunity for facilitate therapeutic intervention (*e.g.* management of pancreatolithiasis).

### **Selective guidewire placement**

Numerous case reports, series, and a retrospective study have all demonstrated the potential benefits of POC-guided guidewire placement across strictures of varying causes (malignant, post-OLT, PSC, *etc.*) [43-45]. In the retrospective study, a total of 23 patients with known biliary strictures in whom endoscopic guidewire placement had previously failed underwent 30 procedures; technical success (guidewire placement) was achieved in 70% [43]. Subgroup analysis demonstrated a higher technical success rate among benign biliary strictures *vs* malignant strictures (88% *vs* 46%,  $P = 0.02$ ). Of the 23 patients, 7 underwent repeat procedures, both in patients with previous failure of guidewire placement ( $n = 3$ ) and prior success of guidewire placement ( $n = 4$ ). A higher technical success rate was demonstrated on initial exam compared to subsequent exams (78% *vs* 43%,  $P = 0.15$ ) [43]. While data are limited, POC-guided guidewire placement can be an effective alternative option, though traditional ERCP approaches should be attempted primarily given the significantly higher costs associated with POC and the ability to potentially troubleshoot successfully with varying guidewire diameters, tip designs, tip core materials, *etc.* during ERCP.

### **Biliary tumor ablation**

The use of POC-guided radiofrequency ablation (RFA) to provide locoregional cancer-directed therapy for the management of extrahepatic CCA or other intraductal malignancies has been presented in various case reports[46,47]. Historically, percutaneous RFA has been well studied, though this technique has demonstrated an association with various AEs[48]. ERCP-RFA (without POC) has thus been explored as a possible alternative in porcine models, yielding similar concerns for high AE rates [49]. In a review article, the pooled data from 12 studies evaluating endoscopic RFA treatment for the management of patients with unresectable malignant biliary strictures showed similarly high AE rates (16%) across 318 total patients[50]. In a retrospective study of 12 patients, POC-guided RFA was both technically (RFA probe insertion into stricture site) and clinically successful (tumor ablation with POC imaging) while demonstrating safety (1 AE in study population) and efficacy in maintaining stent patency (median of 154 d) following POC-guided RFA. Though data are limited, POC-guided RFA could be explored in further studies as a potentially viable, safer (compared to percutaneous RFA and endoscopic RFA) palliative treatment option for select patients with unresectable malignant biliary strictures.

POC-guided photodynamic therapy (PDT) has also been suggested to improve symptoms and prolong survival in cases of unresectable biliary tumors, with relatively few complications[51]. PDT begins with the administration of intravenous photosensitizer, which is preferentially retained by malignant tissue, approximately 24 h prior to POC. Subsequently, light energy can be delivered under POC guidance to the target tissue at a photoactivating wavelength, resulting in a photochemical reaction inducing ischemia and necrosis of tumor cells[52]. RCT data is limited to ERCP-based studies, in which PDT plus endoscopic stenting ( $n = 20$ ) *vs* endoscopic stenting alone

( $n = 19$ ) found improvement in median survival (493 d *vs* 98 d,  $P < 0.0001$ )[53]. However, a retrospective case series ( $n = 45$ ) demonstrated similar absolute increases in median survival time when comparing SOC-guided PDT *vs* PDT-only, though not statistically significant (386 d *vs* 200 d,  $P = 0.45$ )[51]. This may suggest that larger cohorts need to be studied to better understand whether the effect of SOC-guided PDT truly plays an essential role compared to PDT therapy alone.

### **Post-liver transplant biliary complications**

One AE orthotopic liver transplantation (OLT) patients face is the development of biliary strictures, either anastomotic (more common) or nonanastomotic (less common). Biliary strictures affect up to nearly 40% of post-OLT patients[54]. In these cases, POC can be utilized for visual assessment of the biliary epithelium and/or targeted biopsy, if needed[55]. Additionally, some strictures are not amenable to guidewire insertion or cannulation with standard ERCP (*e.g.* angulated strictures)[56]; the addition of POC can facilitate guidewire insertion and possibly obviate the need for biliary drainage or surgical intervention[55,56].

In a recent observational study of 26 patients who underwent ERCP followed by POC for suspected biliary complications post-OLT, 33 biliary complications were found in 22 patients. The remaining 4 patients were found to have normal bile ducts. Of the biliary complications, anastomotic strictures were the most common (14), followed by nonanastomotic strictures (7), biliary stones (6), and lastly biliary casts (3). In 12 patients (46%), POC demonstrated a clear benefit: Selective guidewire placement, identification of biliary cast and/or stones not previously found on ERCP, or epithelial changes (*e.g.* ulceration or inflammation) secondary to infection[44]. Additional case series have shown the potential benefits of POC-guided steroid injections for management of anastomotic strictures and POC-guided guidewire placement across strictures (previously failed under fluoroscopic guidance)[56,57]. All of these observational studies suggest low rates of AEs, even in the post-OLT population[44,56,57]. Of note, in immunocompromised post-OLT patients, it is important to provide a prophylactic course of antibiotics given the potential increased risk of bacterial translocation with POC[58].

### **Radiation-free management**

One of the disadvantages of conventional ERCP therapy is radiation exposure to patients and medical staff from the use of fluoroscopy. In particular, there can be teratogenic risk posed to pregnant patients in the first trimester[59]. While ERCP remains the standard of care and every effort should be made to use fluoroscopy selectively and with proper safety measures, POC can be utilized as an alternative management strategy to minimize or obviate the use of radiation[60]. A recent retrospective, multicenter study demonstrated 100% success rate in achieving bile duct cannulation without the use of fluoroscopy in the study population of pregnant patients ( $n = 10$ ) with a mean gestational age of 23 wk. Indications for intervention included: Choledocholithiasis (7), stent removal (1), biliary stricture (1), and combined choledocholithiasis/stent removal (1). Fifty-percent of patients were able to undergo a completely radiation-free procedure, while an additional 30% received a dose minimized below the recommended amount. AEs (pancreatitis[1], mild bleeding[1]) occurred in two patients (20%)[61]. The data remain limited in this cohort, but this application of POC can certainly be considered as a possibly safer alternative in select cases[61-63].

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## **EMERGING AND MISCELLANEOUS APPLICATIONS OF CHOLANGIOSCOPY**

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Novel applications of POC continue to emerge. One area of demonstrated utility has been in the removal of migrated stents and other foreign bodies. Following failed retrieval attempts with ERCP, POC can provide better visualization and/or access for successful extraction, thereby avoiding more invasive procedures[64-67]. Additionally, POC can aid in the evaluation and management of hemobilia. After magnetic resonance cholangiopancreatography (MRCP) or ERCP demonstrates the presence of blood in the bile duct, POC can facilitate determining the source and etiology of bleeding. In one case report, POC was utilized to confirm hemobilia arising from the gallbladder, and ultimately a diagnosis of diffusely infiltrative gallbladder cancer was made[68]. Another case report describes the detection of biliary angiodysplasia during

POC following an unrevealing MRCP[69]. There have also been reports of the use of POC in select cases of cholecystitis, where patients may not otherwise be surgical candidates and/or in the presence of anatomical challenges. In these instances, POC can be utilized to access and traverse the cystic duct with subsequent deployment of metal or plastic stents as a means of minimally-invasive management[70-72]. Finally, there has been a reported case of POC-guided EHL for the removal of a calcified stool bezoar in an elderly patient with chronic, severe constipation[73].

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## DRAWBACKS OF CHOLANGIOSCOPY: ECONOMIC CONSIDERATIONS AND AEs

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Though the clinical applications of POC continue to expand, several factors hinder further widespread use. In particular, the financial implications of POC *vs* conventional ERCP, owing to the high cumulative costs of the POC processor, cholangioscopes, and cholangioscopic accessories, are major hindering factors. Overall, start-up costs have been estimated to range between 50000 to \$90000, though they can vary substantially by institutional contract[74]. Additionally, cholangioscopes (D-SOC) and their accessories are both single-use, and each one costs on the order of thousands and hundreds of dollars, respectively. Based on a micro-costing approach, one European study suggested that POC could be cost-effective for both treatment of difficult bile duct stones and diagnosis of IDBSs when compared to conventional ERCP[75]. However, robust economic data are lacking in the United States. Moreover, procedure times are often longer with POC when compared to conventional ERCP; thus, this may deter performance of POC due to the ability to generate more revenue with conventional ERCP *per* unit of time.

The overall AE rate associated with POC has been reported to be between 4% and 22%[76]. The major AEs include: Cholangitis, bacteremia, liver abscess, pancreatitis, and bleeding[77]. In a nationwide study in Sweden analyzing 36352 ERCP procedures and 408 cholangioscopy procedures between 2007 and 2012, reported post-procedural AEs were higher with POC when compared to ERCP (19.1% *vs* 14.0%)[78]. Pancreatitis (7.4% *vs* 3.9%) and cholangitis (4.4% *vs* 2.7%) showed similar increases, though multivariate analysis did not demonstrate a statistically significant difference when adjusted for confounders[78]. While higher rates of AEs with POC remain a concern, one group found that administration of peri-interventional antibiotics can substantially reduce rates of cholangitis[79]. With ongoing evolution of POC technology, its safety profile when directly compared to conventional ERCP will need continued assessment.

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## RECENT AND FUTURE DEVICE DEVELOPMENT

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In May 2019, a next generation “mother-baby” videocholangioscope system (CHF-B290, Olympus Medical Systems Corporation, Tokyo, Japan) was introduced[80,81]. Despite being a newer iteration with notable improvements, some previously known limitations (*e.g.* two endoscopist operators and two equipment towers) remain, while others, such as scope fragility and accessory channel diameter, have been reported to be improved[80]. Currently, this system is only available for use in certain markets in Asia and Europe[80].

In July 2020, Ambu Inc. received FDA approval for the Ambu® aScope™ (Ambu Inc, Columbia, MD United States) Duodeno, a single-use duodenoscope. It is anticipated that a single-use cholangioscope and additional accessories will follow in the next 1-2 years, with the potential for new clinical applications. It will be interesting to compare these developments to existing scopes and accessories.

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## CONCLUSION

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With growing evidence to support its use, POC has evolved into an important tool in the biliopancreatic armamentarium. It is an important therapeutic option for difficult biliary stones and a core part of the evaluation of indeterminate strictures. Outcomes from the use of D-SOC for other ongoing and investigational indications (*e.g.* radiation-free intervention in pregnant patients, migrated stent/foreign body extraction, post-OLT biliary complication management, and selective guidewire

placement) appear promising. Still, as discussed in this review, there are constraining factors and limitations to consider, *e.g.* device costs, paucity of standardized cholangioscopic visual classification systems, anatomical challenges, *etc.* [82].

In the future, further research and data are needed to solidify the evidence for POC and clarify the outcomes of its investigational applications. For now, endoscopists may continue to explore additional frontiers of clinical application, particularly with the advent of new accessories and further technologic enhancements that may be on the horizon.

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