Applications, Limitations, and Expansion of Cholangioscopy in Clinical Practice

Amith Subhash, MD,[1] Alexander Abadir, MD,[2] John M. Iskander, MD,[3] and James H. Tabibian, MD, PhD[4,5]

[1]Department of Internal Medicine, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California

[2]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

[3]Department of Gastroenterology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California

[4]Division of Gastroenterology, Olive View-UCLA Medical Center, Sylmar, California

[5]Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, California

Corresponding author:
Dr James H. Tabibian
Olive View-UCLA Medical Center
14445 Olive View Drive, 2B-182
Sylmar, CA 91342
Tel: (747) 210-3205
Fax: (747) 210-4573
E-mail: jtabibian@dhs.lacounty.gov

Abstract: Peroral cholangioscopy (POC) provides minimally invasive, direct endoscopic visualization of the biliary ductal system for both diagnostic and therapeutic purposes. POC has benefited from a number of technologic advances since its first introduction several decades ago. These advances have led to improved utility and expanded functionality, making POC an integral part of managing various bile duct diseases and disorders. Over time, the clinical role of POC has expanded. Novel applications and capabilities are being increasingly appreciated and developed. This article provides an overview of the current state of POC, with a particular focus on digital single-operator cholangioscopy and its strengths, limitations, advances, and emerging applications.

Keywords
Peroral cholangioscopy, difficult bile duct stones, indeterminate biliary strictures, dominant strictures, cholangioscopic biopsies, electrohydraulic lithotripsy, bile duct diseases

Peroral cholangioscopy (POC) was introduced in the 1970s to permit direct visualization of the biliopancreatic tree for the diagnosis and treatment of intraductal disorders.[1,2] The original cholangioscope used for POC required 2 endoscopists to handle the "mother-baby scope" setup, which was composed of a "mother" duodenoscope and a "baby" cholangioscope. Numerous other technical limitations were associated with POC.[1] However, POC has undergone significant transformation across multiple generations of devices. In 2005, the first single-operator cholangioscopy (SOC) system was introduced followed by a digital single-operator cholangioscopy (D-SOC) system in 2015.[3] Improvements, including dramatically higher image resolution, wider field of view, brighter light source, tapered tip, increased therapeutic channel lumen diameter, and 4-way tip deflection, have all further revolutionized modern POC.[4,5]

In parallel with technical improvements, clinical applications of POC (Table 1) have expanded over time, as evidenced, in part, by the growing number of publications on the topic of cholangioscopy (Figure 1).[6] Nevertheless, data in support of the role of POC in these applications, while generally favorable, have been variable, as has been the level of evidence on which to guide management. Thus, amid the enthusiasm and promise surrounding this modality, objectivity and further research remain essential.

The goal of this article is to provide a critical overview of the current state of POC, focusing on D-SOC and its applications, strengths, limitations, recent developments, and future directions. This article aims to provide clinically useful information not only for advanced endoscopists, but also for general gastroenterologists, hepatologists, and other practitioners involved in the management of bile duct disorders.

Current Applications of Cholangioscopy

Array of Cholangioscopic Accessories

The current generation of D-SOC, termed SpyGlass DS (Boston Scientific), uses a 10-Fr catheter containing

Table 1. Clinical Applications of Cholangioscopy

Diagnostic Applications[a]
Choledocholithiasis (and other intraductal filling defects)
Indeterminate bile duct strictures
Dominant strictures in primary sclerosing cholangitis
Intraductal tumor mapping of cholangiocarcinoma for staging
Post–liver transplant bile duct disorders
Therapeutic Applications[a]
Lithotripsy for choledocholithiasis
Biliary tumor ablative therapy
Selective biliary duct wire cannulation
Extraction of migrated stents

[a]In some of these diagnostic and therapeutic applications, cholangioscopy is not a first-line procedure but rather is reserved for instances in which conventional endoscopic retrograde cholangiopancreatography techniques are insufficient. However, emerging data appear to support earlier implementation of cholangioscopy in the management algorithm for a growing number of indications.

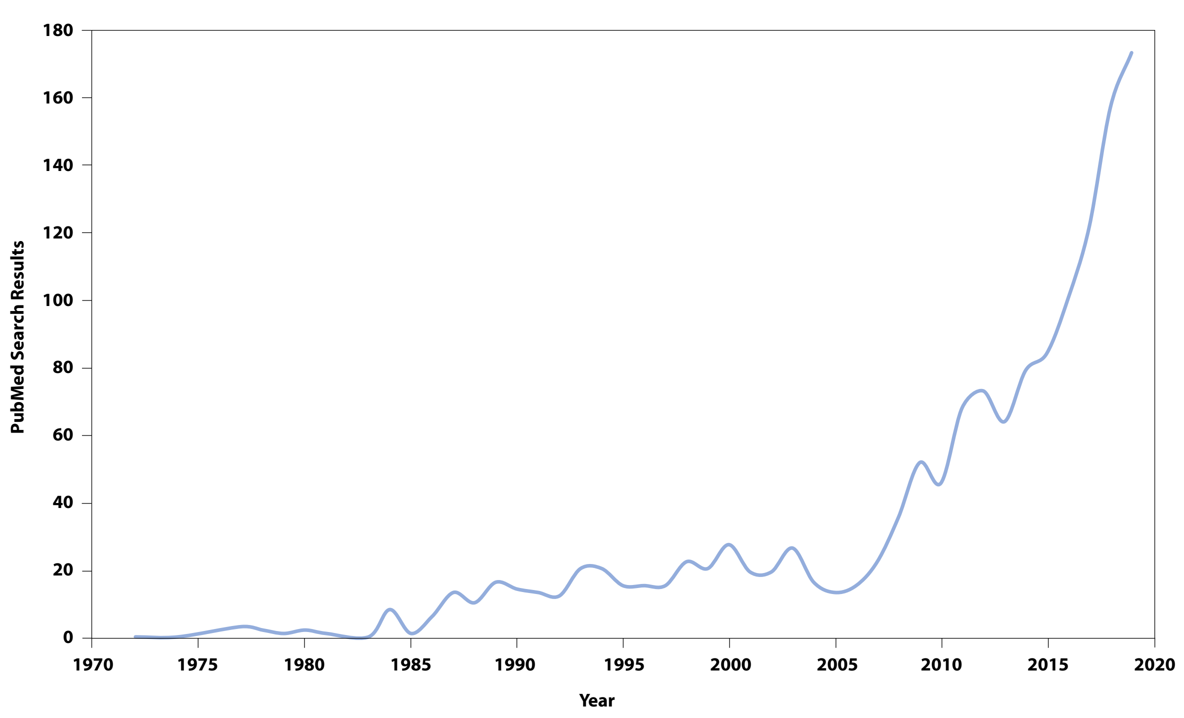

Figure 1. The growing number of annual publications related to cholangioscopy, pancreatoscopy, and SpyGlass indexed in PubMed over time.

Figure 2. From left to right, accessories for electrohydraulic lithotripsy, holmium laser lithotripsy, SpyBite Max, the SpyGlass retrieval snare, and the SpyGlass retrieval basket for the SpyGlass DS system.

Adapted from Boston Scientific.[9]

a fiber-optic probe that passes through the endoscopic retrograde cholangiopancreatography (ERCP) scope. The catheter has a dedicated 1.2-mm working channel through which a variety of accessories can be passed (Figure 2).[7] For tissue acquisition, SpyBite biopsy forceps, or the newly available SpyBite Max biopsy forceps, can be used.[8] For biliary stones, the working channel of the SpyGlass DS system accommodates the Autolith Touch Electrohydraulic Lithotripsy Generator (Northgate Technologies) for electrohydraulic lithotripsy and the Lumenis Pulse and the VersaPulse PowerSuite Holmium Laser Generator (Lumenis) for holmium laser lithotripsy.[7] Additionally, the SpyGlass retrieval snare and retrieval basket can be used for the removal of stone fragments or foreign bodies.[9] Finally, the SpyGlass system is compatible with the Habib EndoHPB Bipolar Radiofrequency Catheter (Boston Scientific).[9] These accessories and their applications will be discussed in subsequent sections.

Treatment of Difficult Bile Duct Stones

Choledocholithiasis can be seen in approximately 10% to 18% of patients with symptomatic cholelithiasis.[10] ERCP with endoscopic sphincterotomy and extraction of stones is an established treatment for common bile duct stones, with a success rate of 84%.[10] Difficult bile duct stones have been variably defined as including large bile stones (>1.5 cm in diameter), stone impaction in the bile or cystic duct, intrahepatic location, stricture distal to stones, and/or anatomic variants causing challenging access to the biliary duct (eg, surgically altered anatomy).[11,12] Conventional ERCP approaches to difficult common bile duct stones include mechanical lithotripsy and endoscopic papillary large balloon dilation.

A meta-analysis of 49 studies examined the efficacy of POC for the treatment of difficult bile duct stones and the evaluation of indeterminate strictures. Difficult bile duct stones were defined as stones that could not be removed by conventional methods (eg, ERCP with standard extraction balloons, baskets, or lithotripters). Common methods of extraction included POC-guided electrohydraulic lithotripsy, laser lithotripsy, and/or basket or balloon catheter retrieval (Figure 3). Of the 49 studies evaluated in the meta-analysis, 33 included data on difficult bile duct stones. The overall estimated stone clearance rate was 88% (95% CI, 85%-91%) across 820 patients (n=31 studies).[13] In the treatment of difficult bile duct stones, POC can significantly improve procedural success.

Three recent randomized, controlled trials have compared SOC-guided lithotripsy to conventional therapy (such as mechanical lithotripsy, endoscopic papillary balloon dilation, and balloon extraction). In 2 studies, stone clearance was achieved in more than 90% of patients in the SOC-guided treatment arms, with similar adverse event (AE) rates compared with conventional therapy.[14,15] In the remaining study, successful stone

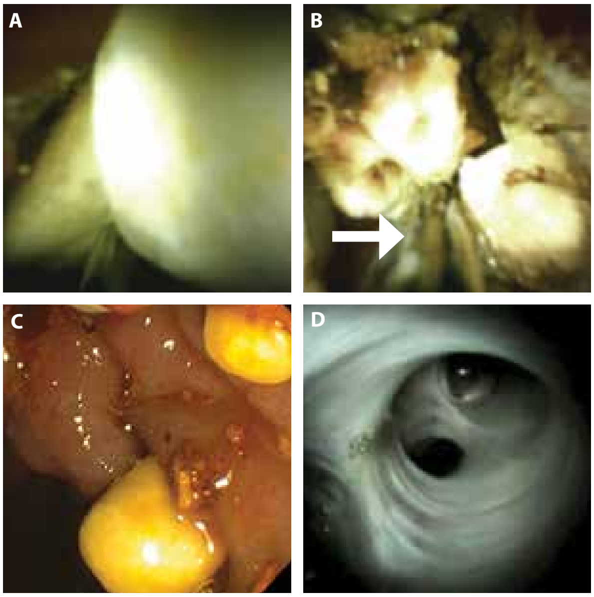

Figure 3. Examples of difficult bile duct stones successfully managed cholangioscopically. **A:** Cholangioscopic visualization of large, smooth common bile duct stones. **B:** Cholangioscopically guided electrohydraulic lithotripsy performed on an impacted common bile duct stone, with the arrow pointing to the lithotriptor. **C:** Endoscopic view of smooth stones (as well as stone fragments) in the duodenal lumen following lithotripsy and balloon extraction. **D:** Examination of the hepatic ductal confluence following stone removal to exclude an occult biliary neoplasm or residual stones proximally; normal-appearing biliary epithelium is seen.

Figure 3D is adapted with permission from Dr Isaac Raijman and Boston Scientific.

Table 2. Randomized, Controlled Trials Evaluating the Efficacy of Cholangioscopy-Guided Lithotripsy Vs Conventional Therapy

Study	Year	Sample Size, N	Randomized to Cholangioscopy-Guided Lithotripsy, n	Randomized to Conventional Therapy,[a] n	Cholangioscopy-Guided Stone Clearance, n (%)	Stone Clearance With Conventional Therapy, n (%)	*P* value
Franzini et al[16]	2018	100	50	50	37[b,c] (77)	36 (72)	>.05
Buxbaum et al[14]	2018	60	42	18	39 (93)	12 (67)	.009
Angsuwatcharakon et al[15]	2019	32	16	16	16[c] (100)	10 (63)	<.01

[a]Mechanical lithotripsy, endoscopic papillary balloon dilation, and balloon extraction.
[b]Two patients randomized to the cholangioscopy arm did not receive intervention due to a new diagnosis made during cholangioscopy.
[c]Crossover permitted.

removal did not statistically differ in the SOC-guided treatment arm vs the conventional therapy arm. Similarly, differences detected during crossover were not statistically significant (Table 2).[16]

A proposed treatment algorithm for incorporating D-SOC into the management of large bile duct stones is shown in Figure 4.[17]

Management of Indeterminate Biliary Strictures

Cholangioscopic Visual Evaluation Indeterminate biliary strictures refer to strictures that, despite cross-sectional imaging and ERCP with brush cytology or intraductal biopsies, remain nondiagnostic with regard to stricture etiology.[18] POC can aid in the evaluation of indeterminate

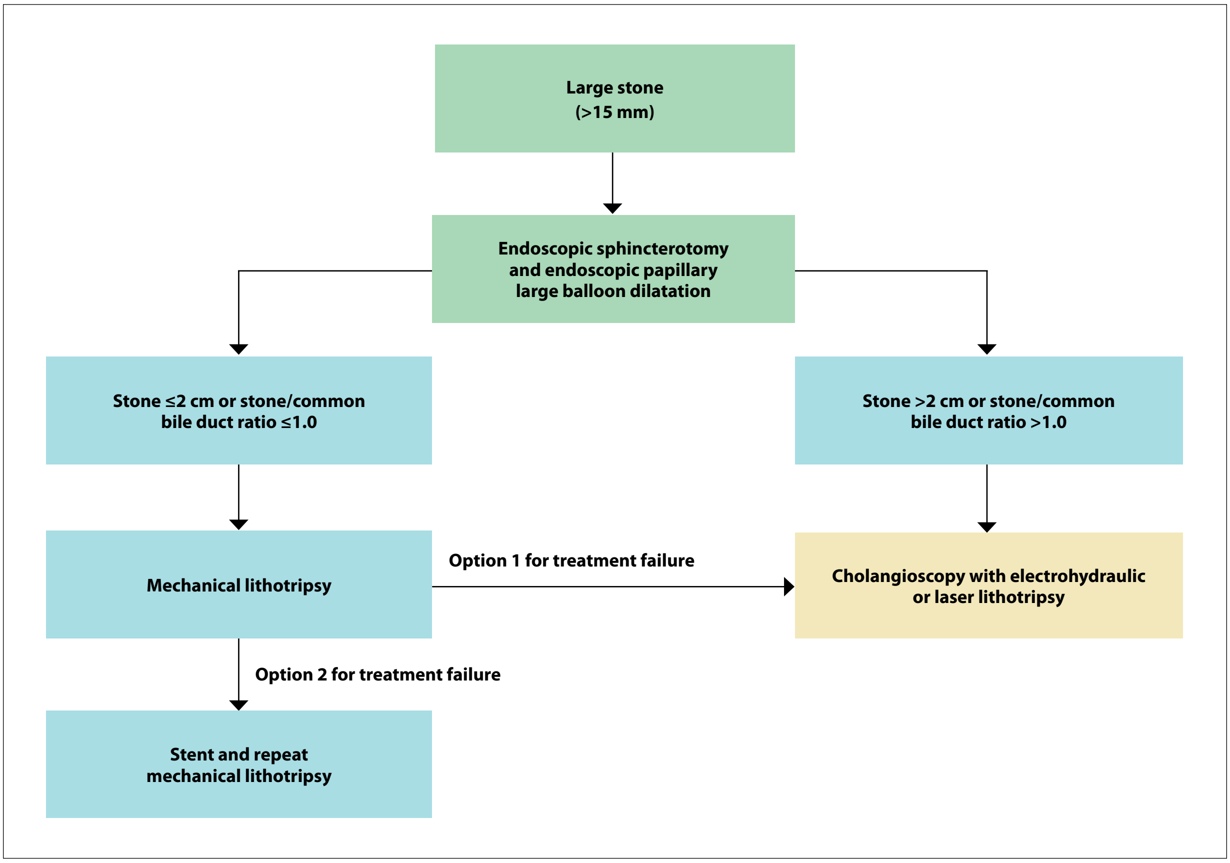

Figure 4. Proposed treatment algorithm for large bile duct stones. Adapted from Doshi et al.[17]

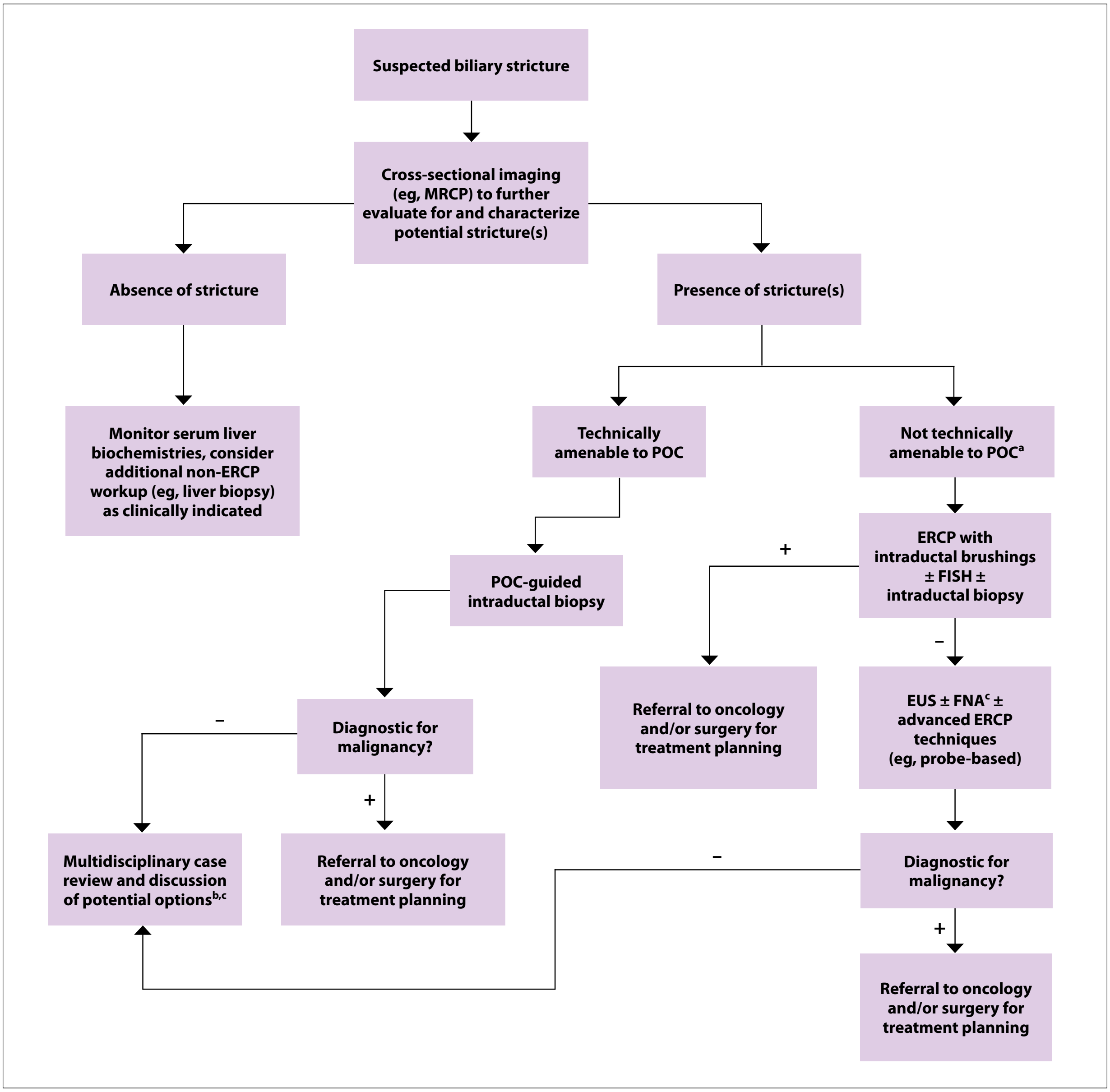

Figure 5. Simplified management algorithm for biliary strictures.

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FISH, fluorescence in situ hybridization; FNA, fine-needle aspiration; MRCP, magnetic resonance cholangiopancreatography; POC, peroral cholangioscopy.

[a]Strictures that are not amenable to POC include proximal strictures in ducts too small to be reached by the cholangioscope, distal strictures wherefore the cholangioscope cannot be stabilized intraductally, or in cases of surgically altered anatomy (eg, Roux-en-Y bypass).

[b]Potential options may include serial monitoring with serum laboratory tests and imaging, repeat ERCP with POC, EUS-FNA, balloon dilation and/or stenting, and/or referral for surgical management, depending on the clinical scenario.

[c]FNA of a primary tumor (as opposed to a regional lymph node), if performed, may render a tumor as unresectable and nontransplantable in most centers consequent to the risk of tumor seeding and, thus, should generally be avoided.

biliary strictures both visually and histopathologically (Figure 5). With regard to the former—although there is no widely accepted, standardized classification system for visual diagnosis—certain cholangioscopic findings have been demonstrated to be suggestive of malignancy (Figure 6). Of these, neovascularization is perhaps the best characterized. Neovascularization, also known as tumor vessels, refers to irregularly dilated and tortuous vessels seen within or adjacent to a lesion.[19,20] As a marker of malignancy, neovascularization has at least moderate diagnostic accuracy, which improves when combined with POC-directed biopsy.[21] This is exemplified by the

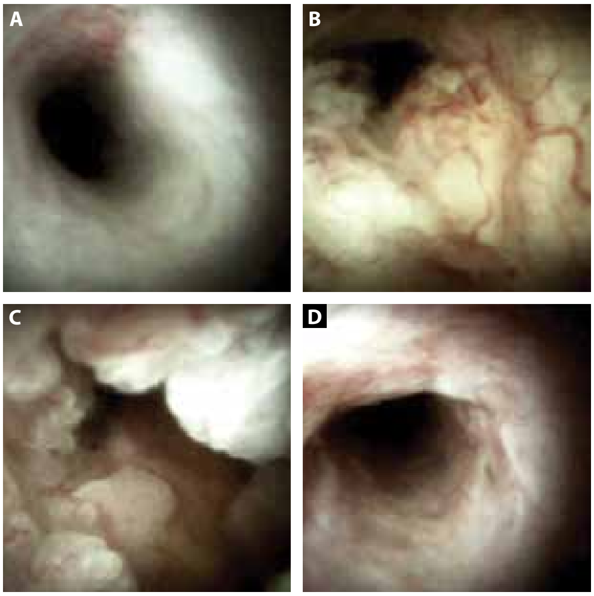

Figure 6. Examples of cholangioscopic images of benign, malignant, and indeterminate lesions. **A:** Benign biliary stricture exhibiting a bland, white appearance. **B:** Biliary stricture with tumor vessels confirmed as carcinoma following intraductal biopsies. **C:** Finger-like villiform projections suggestive of intraductal papillary neoplasm of the bile duct, among other potential intraductal biliary epithelial neoplasms. **D:** Common bile duct stricture with indeterminate cholangioscopic features equivocal for a reactive vs dysplastic process.

Figures 6A to 6D are adapted with permission from Dr Isaac Raijman and Boston Scientific.

results of a systematic review and meta-analysis of the performance of visual POC findings in the diagnosis of malignant biliary strictures. The pooled sensitivity and specificity were found to be 84.5% (95% CI, 79.2%-88.9%) and 82.6% (95% CI, 77.1%-87.3%), respectively.[22] Of note, these findings may not apply to primary sclerosing cholangitis (PSC), as will be discussed later.

Cholangioscopic Tissue Acquisition Cholangioscopically guided biopsies can offer critical additional data in the evaluation of indeterminate biliary strictures. In the aforementioned systematic review and meta-analysis, the pooled sensitivity and specificity of SOC-directed biopsy in the diagnosis of malignant biliary strictures were found to be 60.1% (95% CI, 54.9%-65.2%) and 98.0% (95% CI, 96.0%-99.0%), respectively.[22] Four studies in the review included patients who had previously undergone ERCP with indeterminate and/or negative brushing or biopsy results. In this subset of studies, the pooled sensitivity and specificity of SOC-directed biopsy for diagnosis of malignancy in biliary strictures were 74.7% (95% CI, 63.3%-84.0%) and 93.3% (95% CI, 85.1%-97.8%), respectively.[22] A multicenter, observational study performed by the same group reported even more promising findings with D-SOC. In this study, 44 patients underwent D-SOC–guided biopsies for the purpose of diagnosing malignancy. Sensitivity and specificity were 85% (95% CI, 64.0%-94.8%) and 100% (95% CI, 86.2%-100.0%), respectively.[23] Overall, POC-directed biopsy (and especially D-SOC–guided biopsy) appears to provide a moderate yet important increase in sensitivity in the evaluation of malignant biliary strictures even in cases with previously negative brushings and/or biopsies. Furthermore, POC-directed biopsies combined with biliary lavage cytology have been shown to improve diagnostic yield over POC-directed biopsy alone.[24]

Analogous to other tissue sampling techniques, the question of performance of off-site vs on-site methods of tissue processing as regards D-SOC has been recently answered. The SOCRATES study randomized 62 patients with indeterminate biliary strictures to an off-site cohort (n=30) and an on-site cohort (n=32).[25] Off-site tissue evaluation with a centralized system resulted in a diagnostic accuracy of 90% (95% CI, 73.5%-97.9%), compared with 84.4% (95% CI, 67.2%-94.7%) with on-site evaluation (*P*=.86). The overall costs of D-SOC were $14,423 for the off-site cohort and $13,015 for the on-site cohort (*P*=.61). Thus, this trial showed that POC was a cost-effective procedure for the evaluation of indeterminate biliary strictures for centers without on-site cytopathology. A secondary finding was that 3 biopsies are sufficient for diagnosing indeterminate lesions.[25]

Dominant Strictures in Primary Sclerosing Cholangitis

Patients with PSC are at risk for the development of focal, clinically significant strictures, referred to as dominant strictures, some of which may harbor underlying cholangiocarcinoma. Dominant strictures are defined as stenosis of 1.5 mm or less in diameter in the common bile duct or 1.0 mm or less in diameter in the right and left hepatic ducts, and are associated with worse long-term outcomes.[18,26,27] The data to date regarding the utility of POC in PSC are limited but suggest that POC may be superior to conventional ERCP techniques in detecting malignancy, with statistically significant improvements in specificity (93% vs 51%), positive predictive value (79% vs 29%), and negative predictive value (97% vs 84%), respectively,[26,28] and a trend toward improved sensitivity (92% vs 66%, although not statistically significant).

A systematic review and meta-analysis found that the pooled sensitivity and specificity of POC in the diagnosis of cholangiocarcinoma in patients with PSC were 65%

(95% CI, 35%-87%) and 97% (95% CI, 87%-99%), respectively.[29] Overall, the sensitivity of detecting biliary malignancy in PSC remains a challenge.[26,30,31] A retrospective cohort study of 92 patients (36 with and 56 without PSC) examined the performance characteristics of SOC-guided biopsies and/or fluoroscopically guided biopsies when combined with cytology and fluorescence in situ hybridization, compared with conventional cytology alone. In the cohort without PSC, the combination of all 4 diagnostic modalities compared with cytology alone trended toward statistical significance in improving sensitivity (75.0% vs 40.9%; *P*=.06). However, the PSC cohort did not show such a trend (60.0% vs 50.0%; *P*=1).[32]

Consensus on the exact role of POC as a diagnostic modality for cholangiocarcinoma in PSC remains an area of ongoing investigation. It is hoped that advances in POC and the advent of larger-capacity forceps will result in meaningful diagnostic improvements.

Preoperative Assessment of Neoplasms

Cross-sectional imaging can lead to overdiagnosis of suspected malignancy as regards biliary strictures. A review article found that 15% to 24% of patients referred for surgery for suspected biliary malignancy have benign pathology.[33] This is due to radiologic or clinical features that cannot reliably distinguish between benign and malignant disease. POC can play a role in presurgical mapping of presumed diagnoses of pancreatobiliary malignancies, including cholangiocarcinoma and pancreatic intraductal papillary mucinous neoplasm. In a multicenter prospective trial of 118 patients, cholangiopancreatoscopy altered the initially established surgical plan in 34% (8 of 13 patients in the pancreatic arm and 32 of 105 patients in the biliary arm). In particular, 5% of patients in the biliary arm and 31% of patients in the pancreatic arm required less extensive surgery, and one-quarter of the patients in the biliary arm avoided surgery altogether.[34] Of the patients who underwent surgery, the overall concordance between cholangiopancreatoscopy and surgical histology was 88%. Thus, cholangiopancreatoscopy offers useful data regarding the presence and extent of malignancy and can help guide surgical resection.

Analogous to the aforementioned utility of cholangiopancreatoscopy, an additional application is in the evaluation and differentiation of pancreatic duct abnormalities such as pancreatic duct dilation related to chronic pancreatitis vs main duct intraductal papillary mucinous neoplasm.[35] Cholangiopancreatoscopy is often complementary to the findings of noninvasive imaging and can provide essential diagnostic information, both through visual inspection and targeted biopsies as well as a platform for therapeutic intervention.

Ablation of Biliary Tumors

Radiofrequency ablation (RFA) of malignant biliary strictures is another potential application of POC. Investigators conducted a retrospective study of 12 consecutive patients who underwent D-SOC–RFA (as an alternative to ERCP-RFA) to assess its safety to directly maintain biliary tree and/or stent patency. In the study, only 1 patient had an AE in the form of cholangitis after RFA. Visual reduction of tumor was seen in all patients, and median stent patency was 154 days after D-SOC–RFA.[36]

Photodynamic therapy delivered by POC is an additional modality that has been shown to improve symptoms and prolong survival in patients with biliary tumors. Photodynamic therapy involves intravenous administration of photosensitizer that is preferentially retained by neoplastic tissue. Light energy is subsequently delivered to the appropriate location under POC guidance. In a randomized, multicenter trial of 39 patients with nonresectable cholangiocarcinoma, photodynamic therapy plus endoscopic stenting had a mean survival of 493 days vs 98 days with endoscopic stenting alone. Photodynamic therapy also led to improvements in cholestasis and overall quality of life.[37] The rate of AEs was 7% in both groups. Another study, which compared SOC-guided photodynamic therapy with photodynamic therapy without SOC, showed a similar increase in median survival (386 vs 200 days, respectively).[38,39]

Limitations of Cholangioscopy

Inadequate Evaluation of Extrinsic Biliary Strictures and Distal Biliary Lesions

POC has limited utility when considering certain anatomic factors. One anatomic challenge is posed by extrinsic strictures or compression such as that from metastatic disease, which can impact accuracy in determining the cause of a lesion. In a multicenter observational study, POC-based visual impression had a sensitivity of 84% for intrinsic strictures compared with 62% for extrinsic strictures. Not surprisingly, the sensitivity of forceps biopsy also was demonstrated to be significantly better for intrinsic malignant lesions (66%) compared with extrinsic lesions (8%).[40] Very distal ductal disease can also pose a considerable technical challenge. In such cases, maintaining intraductal stability with the cholangioscope can be difficult to achieve. Furthermore, saline irrigation in the distal ducts can be inadequate when attempting to distend them to evaluate the biliary lumen because of immediate drainage into the duodenum.

Lack of Standardized Cholangioscopic Classification

No standardized classification system to characterize and, thereby, distinguish benign and malignant lesions currently exists. In an international study that examined interobserver agreement, 9 interventional endoscopists assessed 27 deidentified video clips, which were all performed by a single endoscopist.[41] The observers showed slight to poor interobserver agreement in evaluating intraductal strictures and lesions to determine a final diagnosis (benign, malignant, indeterminate) based on previously published criteria.[42] In an attempt to address this limitation, a separate group of researchers has proposed a classification system that distinguishes neoplastic from nonneoplastic disease, with excellent interexpert agreement ($\kappa > 0.8$).[43] However, this proposed classification system has yet to be externally validated, and the original study population did not include patients with PSC.

Additionally, the use of narrow-band imaging in conjunction with POC has been investigated to detect dysplasia, but with unsatisfactory findings and only with a dual-operator videocholangioscope setup.[44] Further studies are needed to assess the utility of advanced imaging techniques in conjunction with POC followed by validation of those techniques.

Small Specimen Size of Cholangioscopically Guided Biopsies

One of the technical challenges of POC-guided biopsy has historically been the small capacity of SpyBite biopsy forceps.[7] To address this limitation of the first-generation SpyBite (legacy) forceps, the SpyBite Max biopsy forceps was developed with an identical outer sheath diameter but double the capacity due to several structural improvements.[45] Published clinical data regarding the diagnostic yield of SpyBite Max are awaited.

Adverse Events

A meta-analysis of 45 studies on the efficacy of POC found that the overall AE rate was 7% (95% CI, 6%-9%).[13] Rates of cholangitis, pancreatitis, perforation, and other AEs were 4% (95% CI, 3%-5%), 2% (95% CI, 2%-3%), 1% (95% CI, 1%-2%), and 3% (95% CI, 2%-4%), respectively.[13] Studies of POC may inadvertently underestimate AE risk relative to ERCP alone given that most POC cases are performed during a nonindex ERCP, such as after sphincterotomy has already been performed.[46] In addition, there may be positive publication bias. Another consideration is that POC typically requires general anesthesia due to the duration of the procedure and volume of irrigating agent (saline) instilled, whereas ERCP without cholangioscopy often can be performed with only deep sedation.

Financial Impact

High capital costs for the processor and disposable scopes limit the widespread use of POC. Estimates of the start-up costs range from $50,000 to $90,000.[47] In a study conducted in Spain that evaluated the standard direct costs of various advanced endoscopic techniques (determined by the time, equipment, materials/consumables, medications, and stent devices used in each procedure), the investigators found that ERCP with SpyGlass (with stent placement) carried the highest cost of all endoscopic procedures.[48] This is largely due to the single-use consumable materials used in POC (eg, SpyBite forceps, SpyGlass snare) and the single-use nature of the SpyScope. In comparing the costs of POC with the average procedural cost of the surgical alternative, cost-savings were not always realized with cholangioscopic management.[48] However, the applicability of the cost-effectiveness data is limited, as the study was performed at a university hospital in Spain. Therefore, the true cost comparison of POC vs the surgical alternative in the United States cannot be fully determined.

Investigators in Belgium have used a micro-costing approach calculated by multiplying the number of resources used by the unit costs in addition to hospitalization costs, thereby using an average length of stay for a procedure to examine cost efficacy. Their analysis showed that POC was cost-effective for both treatment of difficult bile duct stones and diagnosis of indeterminate strictures compared with the surgical alternative.[49] Cost reduction was 11% and 5%, respectively. However, the applicability of these data to the United States is limited. Further research regarding cost-effective applications of POC in the United States is needed.

Developing and Future Applications and Directions

Primary Sclerosing Cholangitis Classification

A number of additional uses of POC have recently been proposed. Researchers have produced a novel classification system, known as Edmonton Classification, for the phenotypic classification of extrahepatic dominant PSC strictures (n=30) based on a single center's review.[50] Following review, the strictures were classified into the following 3 phenotypes: inflammatory type, with mucosal erythema and active inflammatory exudate; fibrostenotic type, with concentric fibrotic scars; and nodular or mass-forming type, with a mass in the extrahepatic bile duct. Based on this classification, further management was proposed, including no intervention, targeted therapy with POC follow-up for treatment response, and close follow-up with repeat POC and surveillance biopsies. With the proposed classification system and management algorithm, the natural history of dominant strictures in PSC may be better understood and potentially modified.

Selective Biliary Duct Guidewire-Assisted Cannulation

Another area of increasing clinical utility for POC is in selective guidewire placement across biliary strictures. A retrospective study examined the use of D-SOC and selective guidewire placement across biliary strictures at a single university hospital in Germany.[51] Cases were included only if a conventional endoscopic guidewire approach had previously failed. Thirty of 167 cases met this inclusion criterion in 23 patients. Guidewire placement was ultimately successful in 21 (70%) of these 30 cases. AEs were reported in 16.7% of all cases.

Notably, the use of POC solely for selective guidewire cannulation purposes may pose cost concerns, albeit with incremental improvement in stricture transversal. As such, other means, such as varying guidewire diameters and tip conformations, may first need to be exhausted.

Postorthotopic Liver Transplant Complications

POC also has been described for the evaluation and targeted treatment of anastomotic strictures in patients post–orthotopic liver transplantation. In a case series of 3 patients who failed standard treatment of biliary anastomotic strictures following orthotopic liver transplantation, ERCP with balloon dilation followed by POC-guided corticosteroid injection was performed.[52] Two of the 3 patients remained stent-free at a mean follow-up of 26 months. The third patient required repeat balloon dilation of new strictures above the anastomotic site.

Radiation-Free Management of Choledocholithiasis

POC may have particular utility in pregnant women as a potential radiation-free technique to mitigate teratogenic risk, particularly during the first trimester.[53] Although ERCP is considered the standard technique for common bile duct stone removal, nonradiation ERCP combined with POC has been reported to be a safe, alternative technique.[54] Direct visualization with POC can be used to confirm biliary cannulation and/or to confirm ductal clearance without need of fluoroscopy.[55] Although the application of POC appears promising in pregnancy, its reported use has thus far been limited.[56-58]

Other Clinical Applications and Device Development

POC also has been shown to have utility in the retrieval of migrated stents. This is typically attempted following failed endoscopic retrieval or radiologic interventions. In these circumstances, the SpyGlass retrieval basket and/or retrieval snare have been shown to be effective for successful removal, avoiding further invasive procedures, such as surgery.[59,60] In highly selected cases of cholecystitis, POC also has been used to transverse the cystic duct with subsequent stent placement to achieve gallbladder drainage.[61-63] New cholangioscope options and cholangioscopic accessories are expected to be available for clinical use from other manufacturers within the next several years, thus expanding potential applications.

With regard to videocholangioscopy, a new generation of videocholangioscope was released (CHF-B290, Olympus Medical System) in certain Asian markets in May 2019 and in European markets in October 2019.[64] Although limitations remain with this platform, including the need for 2 endoscopist operators and 2 towers, this videocholangioscope retains excellent image quality while addressing concerns of device durability and waste associated with single-use devices and increasing the diameter of the working channel.[64] However, it remains unclear whether and to what extent videocholangioscopy may be brought to the United States.

Conclusion

POC has considerably improved the way physicians can visualize and treat biliopancreatic pathology. The D-SOC system, with its improved quality of digital images, has been shown to be superior in the evaluation of indeterminate biliary strictures and mapping of biliopancreatic neoplasia. POC also has been shown to have improved outcomes related to its interventional indications, specifically POC-assisted guidewire placement for biliary strictures and removal of difficult biliary stones by POC-guided lithotripsy.

However, this new technology does present limitations. There is currently no standardized terminology for visual description of findings during POC and, therefore, no criteria on how to reliably distinguish between benign and malignant lesions. Data are also limited regarding the histologic yield of biopsy specimens. Future research should evaluate the establishment of biopsy site and specimen number criteria to improve diagnostic value. The device itself is costly, and the training to use POC is time- and resource-intensive, leaving only a limited number of endoscopists able to efficiently use this technology.

The future is promising for POC. Technologic advancements in cholangioscope design, a wider array of accessories, and a growing number of applications are expected. Over time, the role of POC will likely further expand outside of tertiary referral centers.

Disclosures

The authors have no relevant conflicts of interest to disclose.

References

1. Urakami Y, Seifert E, Butke H. Peroral direct cholangioscopy (PDCS) using routine straight-view endoscope: first report. *Endoscopy*. 1977;9(1):27-30.

2. Choi JH, Lee SK. Percutaneous transhepatic cholangioscopy: does its role still exist? *Clin Endosc*. 2013;46(5):529-536.

3. Hoffman A, Rey JW, Kiesslich R. Single operator choledochoscopy and its role in daily endoscopy routine. *World J Gastrointest Endosc*. 2013;5(5):203-210.
4. Ghersi S, Fuccio L, Bassi M, Fabbri C, Cennamo V. Current status of peroral cholangioscopy in biliary tract diseases. *World J Gastrointest Endosc*. 2015;7(5):510-517.
5. Ayoub F, Yang D, Draganov PV. Cholangioscopy in the digital era. *Transl Gastroenterol Hepatol*. 2018;3:82.
6. Moon JH, Terheggen G, Choi HJ, Neuhaus H. Peroral cholangioscopy: diagnostic and therapeutic applications. *Gastroenterology*. 2013;144(2):276-282.
7. Boston Scientific. SpyGlass™ DS Direct Visualization System [brochure]. https://www.bostonscientific.com/content/dam/bostonscientific/endo/portfolio-group/spyglass/spyglass_detail_brochure.pdf. Accessed September 22, 2020.
8. Boston Scientific. SpyGlass™ DS Direct Visualization System. https://www.bostonscientific.com/en-EU/products/direct-visualization-systems/spyglass-ds-direct-visualization-system.html. Accessed September 29, 2020.
9. Boston Scientific. SpyGlass™ DS II Direct Visualization System: Accessories and Applications. https://www.bostonscientific.com/en-EU/products/direct-visualization-systems/spyglass-ds-direct-visualization-system/accessories-and-applications.html. Accessed October 1, 2020.
10. Dasari BVM, Tan CJ, Gurusamy KS, et al. Surgical versus endoscopic treatment of bile duct stones. *Cochrane Database Syst Rev*. 2013;(12):CD003327.
11. Carr-Locke DL. Difficult bile-duct stones: cut, dilate, or both? *Gastrointest Endosc*. 2008;67(7):1053-1055.
12. McHenry L, Lehman G. Difficult bile duct stones. *Curr Treat Options Gastroenterol*. 2006;9(2):123-132.
13. Korrapati P, Ciolino J, Wani S, et al. The efficacy of peroral cholangioscopy for difficult bile duct stones and indeterminate strictures: a systematic review and meta-analysis. *Endosc Int Open*. 2016;4(3):E263-E275.
14. Buxbaum J, Sahakian A, Ko C, et al. Randomized trial of cholangioscopy-guided laser lithotripsy versus conventional therapy for large bile duct stones (with videos). *Gastrointest Endosc*. 2018;87(4):1050-1060.
15. Angsuwatcharakon P, Kulpatcharapong S, Ridtitid W, et al. Digital cholangioscopy-guided laser versus mechanical lithotripsy for large bile duct stone removal after failed papillary large-balloon dilation: a randomized study. *Endoscopy*. 2019;51(11):1066-1073.
16. Franzini T, Moura RN, Bonifácio P, et al. Complex biliary stones management: cholangioscopy versus papillary large balloon dilation—a randomized controlled trial. *Endosc Int Open*. 2018;6(2):E131-E138.
17. Doshi B, Yasuda I, Ryozawa S, Lee GH. Current endoscopic strategies for managing large bile duct stones. *Dig Endosc*. 2018;30(suppl 1):59-66.
18. Hilscher MB, Tabibian JH, Carey EJ, Gostout CJ, Lindor KD. Dominant strictures in primary sclerosing cholangitis: a multicenter survey of clinical definitions and practices. *Hepatol Commun*. 2018;2(7):836-844.
19. Seo DW, Lee SK, Yoo KS, et al. Cholangioscopic findings in bile duct tumors. *Gastrointest Endosc*. 2000;52(5):630-634.
20. Shah RJ, Raijman I, Brauer B, Gumustop B, Pleskow DK. Performance of a fully disposable, digital, single-operator cholangiopancreatoscope. *Endoscopy*. 2017;49(7):651-658.
21. Kim HJ, Kim MH, Lee SK, Yoo KS, Seo DW, Min YI. Tumor vessel: a valuable cholangioscopic clue of malignant biliary stricture. *Gastrointest Endosc*. 2000;52(5):635-638.
22. Navaneethan U, Hasan MK, Lourdusamy V, Njei B, Varadarajulu S, Hawes RH. Single-operator cholangioscopy and targeted biopsies in the diagnosis of indeterminate biliary strictures: a systematic review. *Gastrointest Endosc*. 2015;82(4):608-614.e2.
23. Navaneethan U, Hasan MK, Kommaraju K, et al. Digital, single-operator cholangiopancreatoscopy in the diagnosis and management of pancreatobiliary disorders: a multicenter clinical experience (with video). *Gastrointest Endosc*. 2016;84(4):649-655.
24. Motomura Y, Akahoshi K, Kajiyama K, et al. Utility of lavage cytology plus targeted biopsy during cholangioscopy for the diagnosis of indeterminate biliary lesions. *Gastroenterol Hepatol Endosc*. 2017;2(3):1-4.
25. Bang JY, Navaneethan U, Hasan M, Sutton B, Hawes R, Varadarajulu S. Optimizing outcomes of single-operator cholangioscopy-guided biopsies based on a randomized trial. *Clin Gastroenterol Hepatol*. 2020;18(2):441-448.e1.
26. Fung BM, Fejleh MP, Tejaswi S, Tabibian JH. Cholangioscopy and its role in primary sclerosing cholangitis. *Eur Med J Hepatol*. 2020;8(1):42-53.
27. Fung BM, Tabibian JH. Biliary endoscopy in the management of primary sclerosing cholangitis and its complications. *Liver Res*. 2019;3(2):106-117.
28. Tischendorf JJW, Krüger M, Trautwein C, et al. Cholangioscopic characterization of dominant bile duct stenoses in patients with primary sclerosing cholangitis. *Endoscopy*. 2006;38(7):665-669.
29. Njei B, McCarty TR, Varadarajulu S, Navaneethan U. Systematic review with meta-analysis: endoscopic retrograde cholangiopancreatography-based modalities for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. *Aliment Pharmacol Ther*. 2016;44(11-12):1139-1151.
30. Schramm C. Concise commentary: why cholangioscopy for indeterminate biliary strictures in PSC is still not good enough. *Dig Dis Sci*. 2020;65(5):1479-1480.
31. Tabibian JH, Baron TH. Endoscopic management of primary sclerosing cholangitis. *Expert Rev Gastroenterol Hepatol*. 2018;12(7):693-703.
32. Kaura K, Sawas T, Bazerbachi F, et al. Cholangioscopy biopsies improve detection of cholangiocarcinoma when combined with cytology and FISH, but not in patients with PSC. *Dig Dis Sci*. 2020;65(5):1471-1478.
33. Singh A, Gelrud A, Agarwal B. Biliary strictures: diagnostic considerations and approach. *Gastroenterol Rep (Oxf)*. 2015;3(1):22-31.
34. Tyberg A, Raijman I, Siddiqui A, et al. Digital pancreaticocholangioscopy for mapping of pancreaticobiliary neoplasia: can we alter the surgical resection margin? *J Clin Gastroenterol*. 2019;53(1):71-75.
35. De Luca L, Repici A, Koçollari A, Auriemma F, Bianchetti M, Mangiavillano B. Pancreatoscopy: an update. *World J Gastrointest Endosc*. 2019;11(1):22-30.
36. Ogura T, Onda S, Sano T, et al. Evaluation of the safety of endoscopic radiofrequency ablation for malignant biliary stricture using a digital peroral cholangioscope (with videos). *Dig Endosc*. 2017;29(6):712-717.
37. Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology*. 2003;125(5):1355-1363.
38. Talreja JP, DeGaetani M, Sauer BG, Kahaleh M. Photodynamic therapy for unresectable cholangiocarcinoma: contribution of single operator cholangioscopy for targeted treatment. *Photochem Photobiol Sci*. 2011;10(7):1233-1238.
39. Talreja JP, Degaetani M, Rehan ME, Sauer BG, Kahaleh M. T1521: Single operator cholangioscopy for unresectable cholangiocarcinoma treated with photodynamic therapy: what are the benefits? *Gastrointest Endosc*. 2010;71(5):AB299.
40. Chen YK, Parsi MA, Binmoeller KF, et al. Single-operator cholangioscopy in patients requiring evaluation of bile duct disease or therapy of biliary stones (with videos). *Gastrointest Endosc*. 2011;74(4):805-814.
41. Sethi A, Doukides T, Sejpal DV, et al. Interobserver agreement for single operator choledochoscopy imaging: can we do better? *Diagn Ther Endosc*. 2014;2014:730731.
42. Itoi T, Neuhaus H, Chen YK. Diagnostic value of image-enhanced video cholangiopancreatoscopy. *Gastrointest Endosc Clin N Am*. 2009;19(4):557-566.
43. Robles-Medranda C, Valero M, Soria-Alcivar M, et al. Reliability and accuracy of a novel classification system using peroral cholangioscopy for the diagnosis of bile duct lesions. *Endoscopy*. 2018;50(11):1059-1070.
44. Azeem N, Gostout CJ, Knipschield M, Baron TH. Cholangioscopy with narrow-band imaging in patients with primary sclerosing cholangitis undergoing ERCP. *Gastrointest Endosc*. 2014;79(5):773-779.e2.
45. Boston Scientific. SpyBite™ Max Biopsy Forceps. https://www.bostonscientific.com/en-US/products/forceps/spysbte-max-biopsy-forceps.html. Accessed September 29, 2020.
46. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol*. 2007;102(8):1781-1788.
47. Komanduri S, Thosani N, Abu Dayyeh BK, et al; ASGE Technology Committee. Cholangiopancreatoscopy. *Gastrointest Endosc*. 2016;84(2):209-221.
48. Loras C, Mayor V, Fernández-Bañares F, Esteve M. Study of the standard direct costs of various techniques of advanced endoscopy. Comparison with surgical alternatives. *Dig Liver Dis*. 2018;50(7):689-697.
49. Deprez PH, Garces Duran R, Moreels T, et al. The economic impact of using single-operator cholangioscopy for the treatment of difficult bile duct stones and diagnosis of indeterminate bile duct strictures. *Endoscopy*. 2018;50(2):109-118.
50. Sandha G, D'Souza P, Halloran B, Montano-Loza AJ. A cholangioscopy-based novel classification system for the phenotypic stratification of dominant bile duct strictures in primary sclerosing cholangitis—the Edmonton Classification. *J Can Assoc Gastroenterol*. 2018;1(4):174-180.
51. Bokemeyer A, Gross D, Brückner M, et al. Digital single-operator cholangioscopy: a useful tool for selective guidewire placements across complex biliary strictures. *Surg Endosc*. 2019;33(3):731-737.
52. Franzini T, Sagae VMT, Guedes HG, et al. Cholangioscopy-guided steroid injection for refractory post liver transplant anastomotic strictures: a rescue case series. *Ther Adv Gastrointest Endosc*. 2019;12:2631774519867786.
53. Wu W, Faigel DO, Sun G, Yang Y. Non-radiation endoscopic retrograde cholangiopancreatography in the management of choledocholithiasis during

pregnancy. *Dig Endosc*. 2014;26(6):691-700.
54. Barakat MT, Girotra M, Choudhary A, Huang RJ, Sethi S, Banerjee S. A prospective evaluation of radiation-free direct solitary cholangioscopy for the management of choledocholithiasis. *Gastrointest Endosc*. 2018;87(2):584-589.e1.
55. Neuhaus H. Choledocholithiasis in pregnancy: when and how to perform ERCP? *Endosc Int Open*. 2020;8(10):E1508-E1510.
56. Shelton J, Linder JD, Rivera-Alsina ME, Tarnasky PR. Commitment, confirmation, and clearance: new techniques for nonradiation ERCP during pregnancy (with videos). *Gastrointest Endosc*. 2008;67(2):364-368.
57. Tarnasky PR, Lee DP, Kedia PS. Stone delivery during pregnancy: when no photos allowed. *VideoGIE*. 2020;5(12):697-698.
58. Uradomo L, Pandolfe F, Aragon G, Borum M. Spyglass cholangioscopy for management of choledocholithiasis during pregnancy: decreasing fetal risks with advancement in technology: 2010 ACG/AstraZeneca Clinical Vignette Award, 2010 Presidential Poster: 581. *Am J Gastroenterol*. 2010;105:S211.
59. Fejleh MP, Thaker AM, Kim S, Muthusamy VR, Sedarat A. Cholangioscopy-guided retrieval basket and snare for the removal of biliary stones and retained prostheses. *VideoGIE*. 2019;4(5):232-234.
60. Maselli R, Troncone E, Fugazza A, et al. Endoscopic retrieval of a proximally migrated biliary plastic stent using direct per-oral cholangioscopy. *J Gastrointestin Liver Dis*. 2019;28(1):8.
61. Gutkin E, Hussain SA, Kim SH. The successful treatment of chronic cholecystitis with SpyGlass cholangioscopy-assisted gallbladder drainage and irrigation through self-expandable metal stents. *Gut Liver*. 2012;6(1):136-138.
62. Tyberg A, Zerbo S, Kahaleh M, Sharaiha RZ. Digital cholangioscopy-assisted gallbladder drainage: seeing is accessing. *Endoscopy*. 2015;47(suppl 1 UCTN):E417.
63. Kedia P, Kuo V, Tarnasky P. Digital cholangioscopy-assisted endoscopic gallbladder drainage. *Gastrointest Endosc*. 2017;85(1):257-258.
64. Murabayashi T, Ogawa T, Koshita S, et al. Peroral cholangioscopy-guided electrohydraulic lithotripsy with a SpyGlass DS versus a conventional digital cholangioscope for difficult bile duct stones. *Intern Med*. 2020;59(16):1925-1930.