Douglas G. Adler MD, FACG, AGAF, FASGE, Series Editor

Cholangioscopy

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Key Points

- **Cholangioscopy has evolved substantively over the last few decades to enable a single operator to directly examine the biliary tree using digital platforms.**
- **Cholangioscopy-guided intraductal therapy with electrohydraulic or laser lithotripsy is a safe and effective treatment for difficult bile duct stones.**
- **Cholangioscopy with guided biopsies represents a powerful diagnostic tool for indeterminate biliary strictures and new diagnostic criteria and technology promises that its role will increase.**
- **The adverse event rates of cholangioscopy are acceptable when it is performed by trained endoscopists using appropriate precautions including judicious biliary stent use.**

INTRODUCTION

Technology to enable direct visualization of the bile duct has gone through several stages of revision.[1] While widespread clinical use has emerged only over the past 5-10 years, the first percutaneous cholangioscopy was reported in 1951[2] and peroral exam in 1976.[3] It was first utilized for laser and electrohydraulic lithotripsy in the late 1980's.[4,5]

The first commercially available cholangioscopes used a mother-baby system that required a high degree of coordination between two endoscopists: one controlling the mother duodenoscope and the other controlling a slim through-the-channel baby scope. The major limitations of this system were the fragility of the cholangioscopes, suboptimal image quality and limited maneuverability related to the need for two operators.[6]

Direct peroral cholangioscopy with ultraslim cholangioscopes, which did not pass through a "mother" scope, provided higher resolution images, and mitigated challenges associated with fragility. However, the technical success was low and inconsistent, due to the need to anchor a flexible scope through the mouth deeply into the biliary tree. Specific problems included unstable position, requirement for a large sphincterotomy, and the

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lack of the ability to examine the bile ducts beyond the bifurcation of the main hepatic duct given the scope size and need to inflate an anchoring balloon in the biliary tree itself.[7,8]

These issues limited widespread use. In 2007, a cholangioscope which could be passed via the accessory channel and controlled by a single operator was introduced. These devices used a reusable fiberoptic cable in a disposable scope.[9] A channel in the scope enables passage of a biopsy forceps and introduction of laser and electrohydraulic lithotripsy probes.[10] The most recent major innovation in cholangioscopy has been the introduction of a single-use, digital imaging version of the single-operator cholangioscopes (DSOC) which provided a higher image quality, simplified assembly and a flexible introduction system (Figure 1).[1,11]

Over the past decade, cholangioscopy has become a widely used tool in academic and community medical centers. In this article, we will address its role in biliary disease. It represents a primary tool for difficult choledocholithiasis, and the assessment of indeterminate biliary strictures. In addition to its major therapeutic and diagnostic roles, we will discuss technique, emerging applications, cost and safety of this technology.

BASIC CHOLANGIOSCOPY TECHNIQUE

Most contemporary cholangioscopic procedures are performed with a disposable DSOC via peroral approach during endoscopic retrograde cholangiopancreatography (ERCP). After testing the light and the dials of the cholangioscope, and flushing the channel with water for lubrication, the handle of the scope is strapped just below the duodenoscope working channel. An adequate sphincterotomy or balloon sphincteroplasty is indicated to allow passage of the cholangioscope. Then, the cholangioscope is advanced through the duodenoscope channel preferably over a previously inserted guidewire into the bile duct under fluoroscopic guidance. Once the cholangioscope is in a stable position in the distal or middle common bile duct, irrigation with sterile water allows visualization of the bile duct aided by four-way tip deflection. The cholangioscope is advanced over the guidewire to a targeted biliary site before the wire is removed to allow optimal visualization and to allow advancing any instruments through its channel if needed. It may be necessary to gently advance the duodenoscope forward to favor parallel alignment of the cholangioscope and the bile duct to allow deeper insertion. The locks on the duodenoscope and cholangioscope may need to be released to advance the cholangioscope.

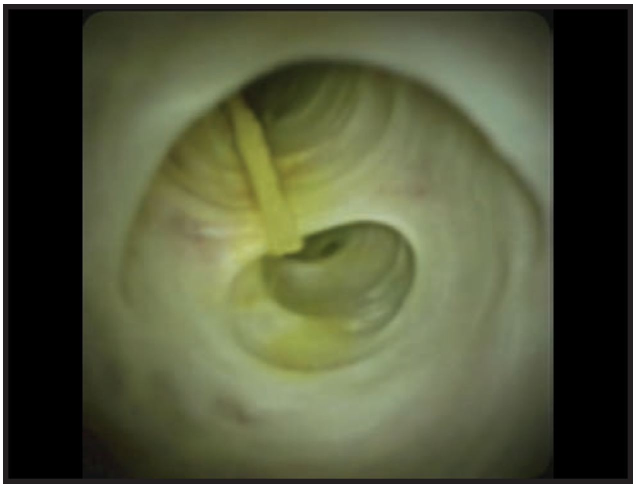

Figure 1. Normal cholangioscopic appearance of the bifurcation of the biliary tree.

These maneuvers may also be needed to advance instruments (i.e., electrohydraulic lithotripsy (EHL)/laser probe or biopsy forceps) through the cholangioscope channel. Another technique is to advance the cholangioscope gently forward at the same time as the instrument is passed through the working channel. Sometimes, it is necessary to advance the cholangioscope to the hilum to pass tools through its channel and then slowly back it distally toward the ampulla. Advancement of instruments (e.g., laser fiber and forceps) may be particularly difficult at the level of the cholangioscope traversing the duodenoscope elevator or deflected tip of cholangioscope. No force must be used to push instruments within the cholangioscope channel to avoid damage. Gentle advancement or withdrawal of the duodenoscope or cholangioscope and release of all locks is important to negotiate this challenge. Repetitive opening and closing of the forceps while advancing it through the cholangioscope channel may also facilitate successful advancement.

Attention must be paid to the duodenoscope position throughout the procedure and fluoroscopy should be obtained intermittently to determine the location of the cholangioscope and avoid

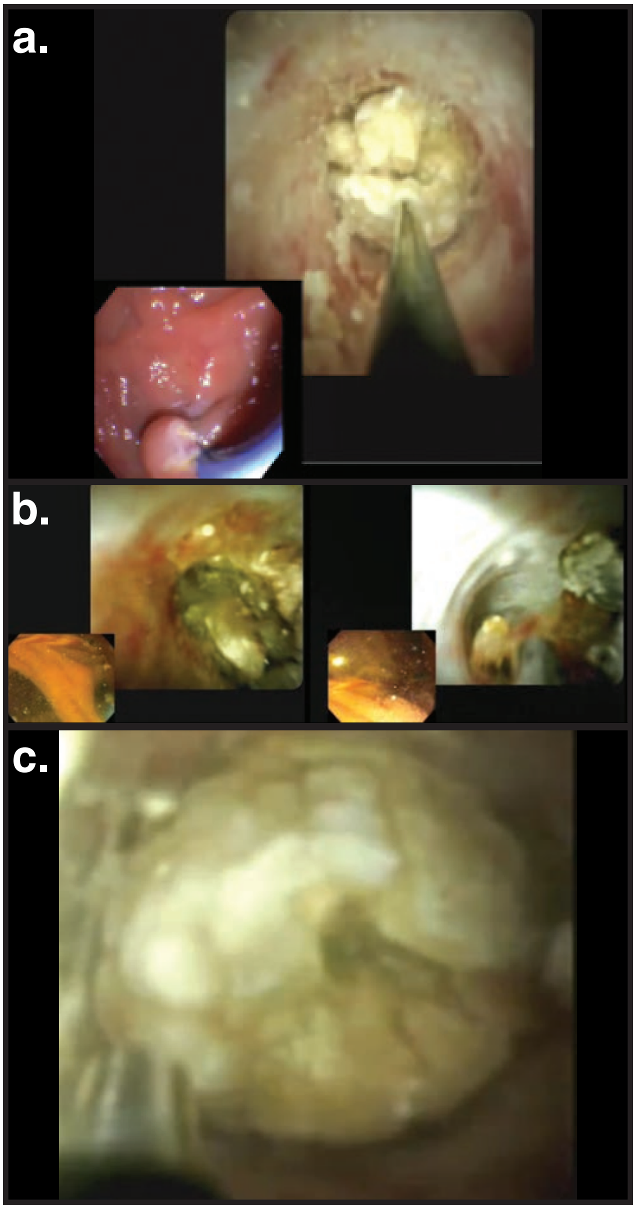

Figure 2. Targeting of the electrohydraulic lithotripsy (EHL) probe at the center of an impacted stone (a) will typically achieve fracture (b). If a cavity forms centrally without fracture, the EHL probe may be aimed at the sides to achieve disruption (c).

accidentally falling out of the bile duct. To optimize visibility, contrast use before cholangioscopy should be minimized. Additionally, irrigation with water or saline should be kept to a level necessary to facilitate evaluation to reduce the risk of bacterial translocation and the development of cholangitis, although it is not clear from available evidence whether irrigation is a definite risk factor for biliary infection.[12] The four-way dials may need to be locked when a certain intervention is considered, such as sampling of a lesion or performing lithotripsy in an oblique position. However, the use of dial locking should be used with caution to avoid ductal injury and must not be used whenever the cholangioscope is advanced up within the bile duct.

Table 1. Indications of Cholangioscopy-Guided Lithotripsy

Failure of conventional ERCP methods due to stone factors: Size[31, 32] Shape Consistency Faceted (stacked) configuration
Failure of conventional ERCP methods due to anatomical factors: Narrowed or short common bile duct[31] Angulation of the distal bile duct[31] Periampullary diverticula[32]
Failure of conventional ERCP methods due to patient-related factors Age > 65 [31]
Impacted lithotripsy basket

INDICATIONS FOR CHOLANGIOSCOPY

Management of Choledocholithiasis

ERCP is the primary treatment modality for bile ducts.[13] A broad armamentarium of tools can be used through the duodenoscope channel to allow lithotripsy, stone removal and ductal clearance. These tools include extraction balloons, sweeping baskets, mechanical lithotripsy baskets, papillary dilation balloons, and biliary stents.[14,15] Nevertheless, in approximately 10-15% of cases, fundamental techniques fail either due to very large stone size, extremely hard consistency, barrel or piston shape, faceted configuration or ductal features such as a diminutive orifice, distal narrowing or sigmoid shape.[14, 16-19]

Cholangioscopy-guided lithotripsy represents a core therapeutic approach for the most difficult bile duct stones (Table 1). There are two commonly used modalities used to perform direct intraductal lithotripsy: electrohydraulic lithotripsy (EHL) and pulsed laser lithotripsy (LL). These modalities are most frequently guided by peroral cholangioscopes. While they may also be guided by fluoroscopy or percutaneously-introduced cholangioscopes, the former is limited by relatively blind targeting and the latter by hemobilia and bile leaks. [20,21]

EHL delivers high-energy shockwaves generated by high voltage electric sparks delivered via fiber advanced through the accessory channel of the cholangioscope. The bile ducts are irrigated with saline to allow transfer of energy to the stone and minimize buildup of thermal energy.[22] The probe should be positioned about 2 mm from the stone and directed towards the center (Figure 2a) and typically application of energy will result in a shattering of the stone (Figure 2b). If a cavity forms in the center without fracture the EHL probe may be aimed at the resulting joints to disrupt the stone into small fragments (Figure 2c). In LL, the shockwave is generated by the creation of a plasma cloud by high energy pulsed light delivered through flexible fiber (via the cholangioscope) into an aqueous media (saline or water).[23] An aiming light allows precise targeting and helps prevent bile duct injury (Figure 3a). Intermittent irrigation and suctioning of the bile duct to wash away the minute fragments allow optimal visibility during the lithotripsy and dissipate heat energy. When LL is performed, safety measures must be observed and the manufacturer's instructions must be followed including proper eye protection.[24] Several technical maneuvers to weaken stones are to drill centrally through its core (Figure 3b) versus cutting it horizontally by using a saw motion generated by rocking the laser probe back and forth using the cholangioscope controls (Figure 3c).

A randomized trial demonstrated that peroral-cholangioscopy-guided lithotripsy reduced the need for surgical removal of difficult bile duct stones by four-fold.[25] A meta-analysis of 2,204 patients with difficult bile duct stones revealed that the overall clearance was 92% (95% CI 90-94%).[13] While overall adverse events for intraductal therapy was 8% (95% 6-11%), this was comparable to the rate for difficult stone treatment by conventional (non-intraductal) methods, 9% (95% 8-11%). The comparative safety and efficacy of cholangioscopy-guided EHL and LL has been investigated in a multicenter, international, observational study.[26] Complete ductal clearance was high and comparable in both methods (97% and 99%, respectively). However, the mean procedure time was longer in the EHL group as compared to LL group (74

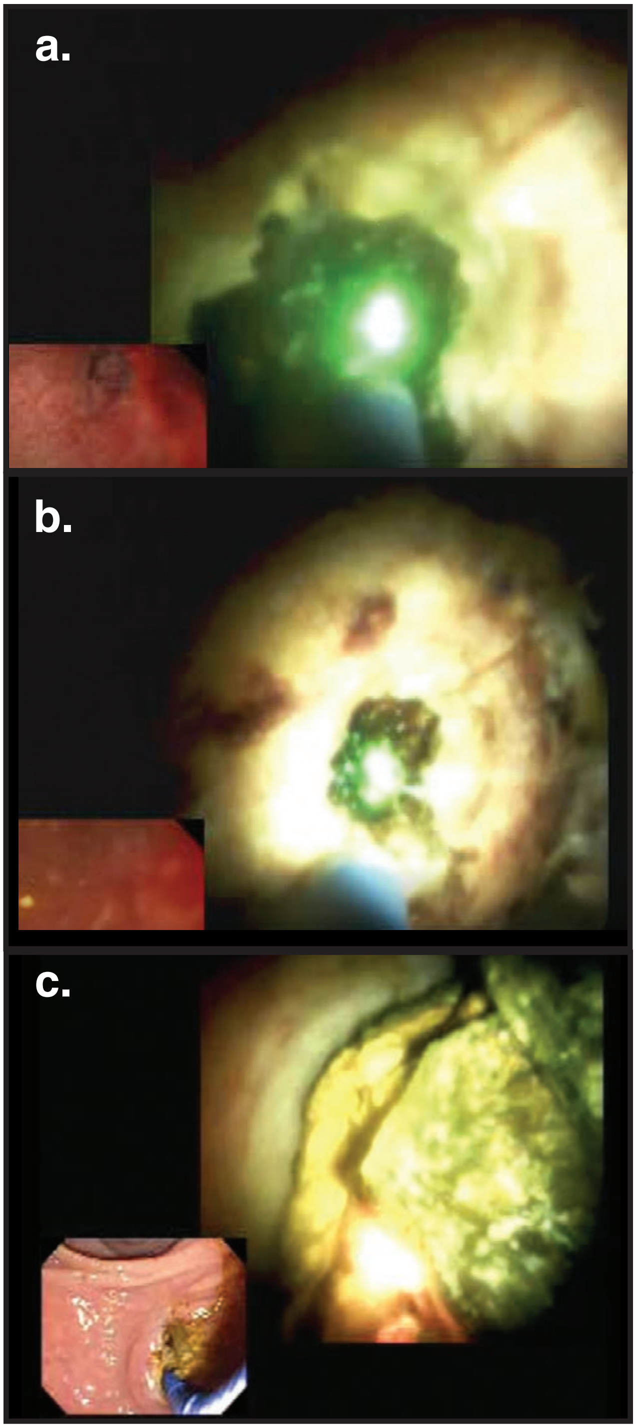

Figure 3. A guide light enables targeting of the of laser lithotripsy (LL) into the center (a) of very hard bile duct stone. The stone may be weakened by centrally drilling through its core (b) versus cutting it in a saw-like fashion by gently moving the laser back and forth horizontally using the cholangioscope dials (c).

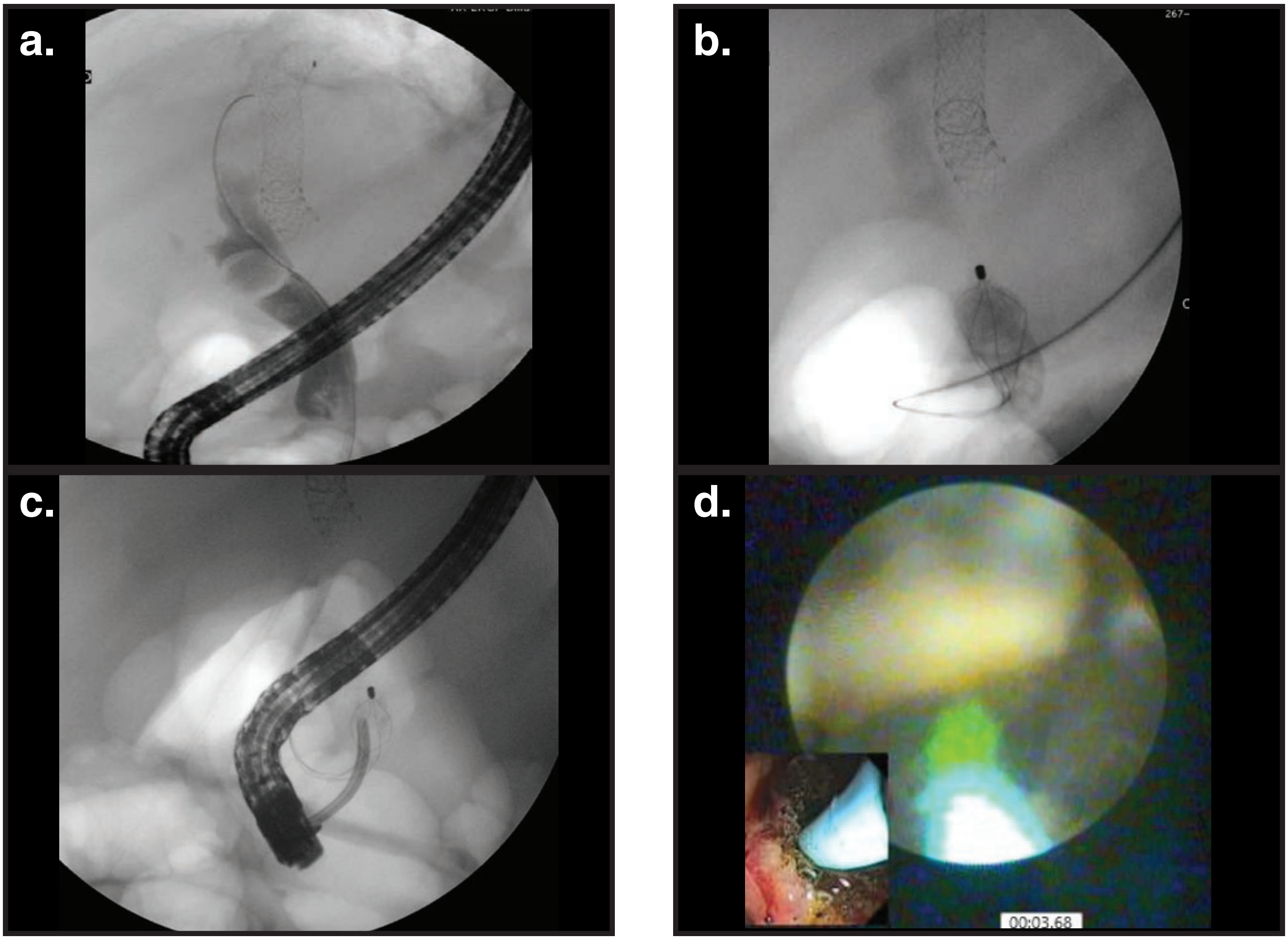

Figure 4. A giant stone (a) results in basket impaction (b). A cholangioscope is introduced into the duct (c) and within the basket laser lithotripsy is performed to free the basket (d).

min and 50 min; P < 0.001). Adverse events were reported in 3.7% and they included cholangitis, bleeding and abdominal pain. Another prospective, multicenter study on peroral cholangioscopy-guided lithotripsy with EHL or LL in patients with difficult bile duct stones showed that ductal clearance was achieved within a single session in 80% (95% CI 73 – 86%) of patients.[27]

Cholangioscopy may also enable stone removal without fluoroscopy and can be used to identify missed bile duct stones in the context of patients with marked ductal dilatation and other features which reduce sensitivity of cholangiography.[28] Cholangioscopy guided intraductal therapy has also emerged as a safe and effective endoscopic approach for the dreaded scenario in which stones become impacted in lithotripsy baskets within the bile duct.[29] While this problem used to frequently require surgery, in most cases effective intraductal lithotripsy of the impacted stone will result in a prompt release of the impacted apparatus (stone + basket) from the duct (Figure 4). Finally, baskets introduced directly through the cholangioscope may be used to target and remove stones, particularly if located in an obliquely oriented duct (Figure 5).[30]

Therefore, cholangioscopy with intraductal therapy has a well-defined role in the management of difficult stones to obviate the need for surgery (Figure 6). Additionally, in cases in which there is suspicion of retained stones or other diagnostic uncertainty it has a burgeoning role.

EVALUATION OF INDETERMINATE BILIARY STRICTURES

Indeterminate biliary strictures represent a major and frequently encountered challenge for advanced endoscopists. While the ERCP brush cytology and trans-papillary intraductal forceps biopsy have high (95-99%) specificity for malignancy, the sensitivity is suboptimal (<50%) for both techniques (Figure 7a-b).[33,34]

Fine needle aspiration of biliary strictures via endoscopic ultrasound (EUS-FNA) has a comparably high specificity, 97% (95% CI 94-99%) and 80% (95% CI 74-86%), sensitivity.[35] Furthermore, EUS-FNA specifically following negative ERCP-guided cytologic brushing and biopsy has a 77% sensitivity and 100% specificity (Figure 7c).[36] Nevertheless, there is concern about malignant seeding for EUS-FNA of proximal or hilar biliary lesions, though trials suggest that this may be overstated.[37] EUS-FNA is a contraindication for patients with cholangiocarcinoma who are potentially candidates for a liver transplant treatment protocol.[38]

Given that cholangioscopes are introduced via the "natural" papillary orifice and do not cross a tissue plane there is less concern for seeding. It provides an opportunity both for visual assessment and diagnostic sampling. The identification of cholangioscopic visual features associated with benign, inflammatory and malignant diseases of the bile ducts has been the subject of multiple studies.[39-44] Intraductal mass lesions and irregular nodules are strongly suggestive of malignancy (Figure 8).[43] Dilated and tortuous vessels have also been proposed as concerning features.[39,42] Papillary and villous projections are suggestive of neoplasia,[44] while a smooth glandular surface is consistent with benign etiology (Figure 9). Diffuse but symmetric and homogenous narrowing may suggest a non-neoplastic inflammatory process such as primary sclerosing cholangitis (Figure 10) or IgG4 mediated cholangiopathy. Systematic review and meta-analysis of the visual features suggest a pooled diagnostic sensitivity of 60.1% (95% CI 54.9%-65.2%) and specificity of 98.0% (95% 96.0-99.0%).[45] Nevertheless, studies of interobserver agreement suggest only slight to fair agreement for most individual visual features.[46]

Several classification systems have been

Table 2. Cholangioscopic Features in Indeterminate Strictures

Favoring malignant stricture:	Favoring benign stricture:
Papillary Projections[39, 40] Ulceration[40] Identifiable lesion[39, 40] or nodule[39] "Tumor vessel"[39, 42]	Scarring[40] Pronounced pit appearance[40]

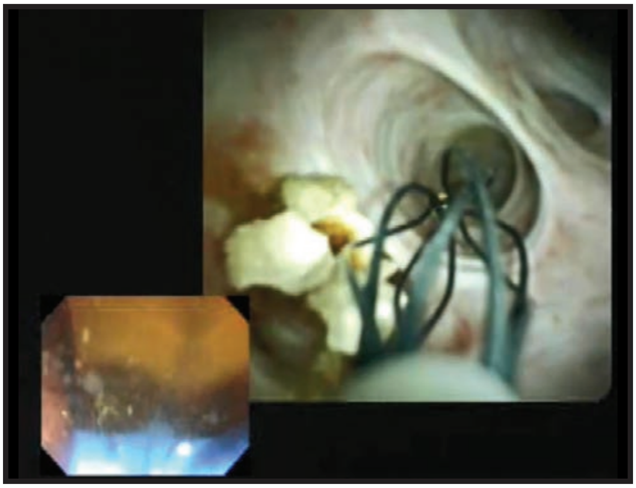

Figure 5. Extraction baskets passed directly through, and guided by, cholangioscopy may be used to directly remove stone fragments from oblique shaped ducts.

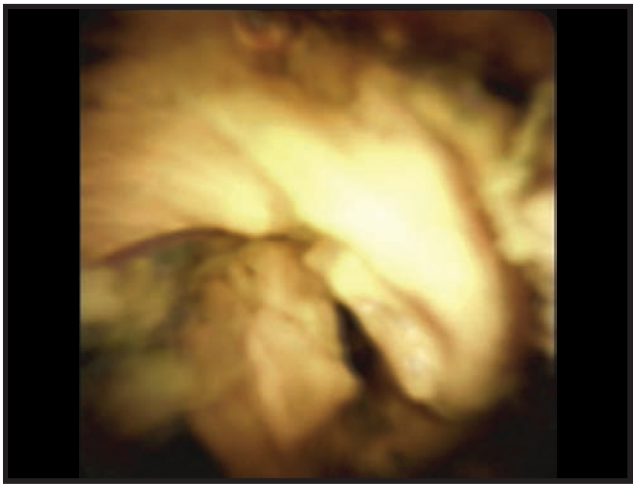

Figure 6. Cholangioscopy guided intraductal therapy plays a major role for stones whose size and shape makes them very difficult to remove by mechanical lithotripsy and papillary dilation approaches. Stone fragmentation allows subsequent balloon or basket sweeping.

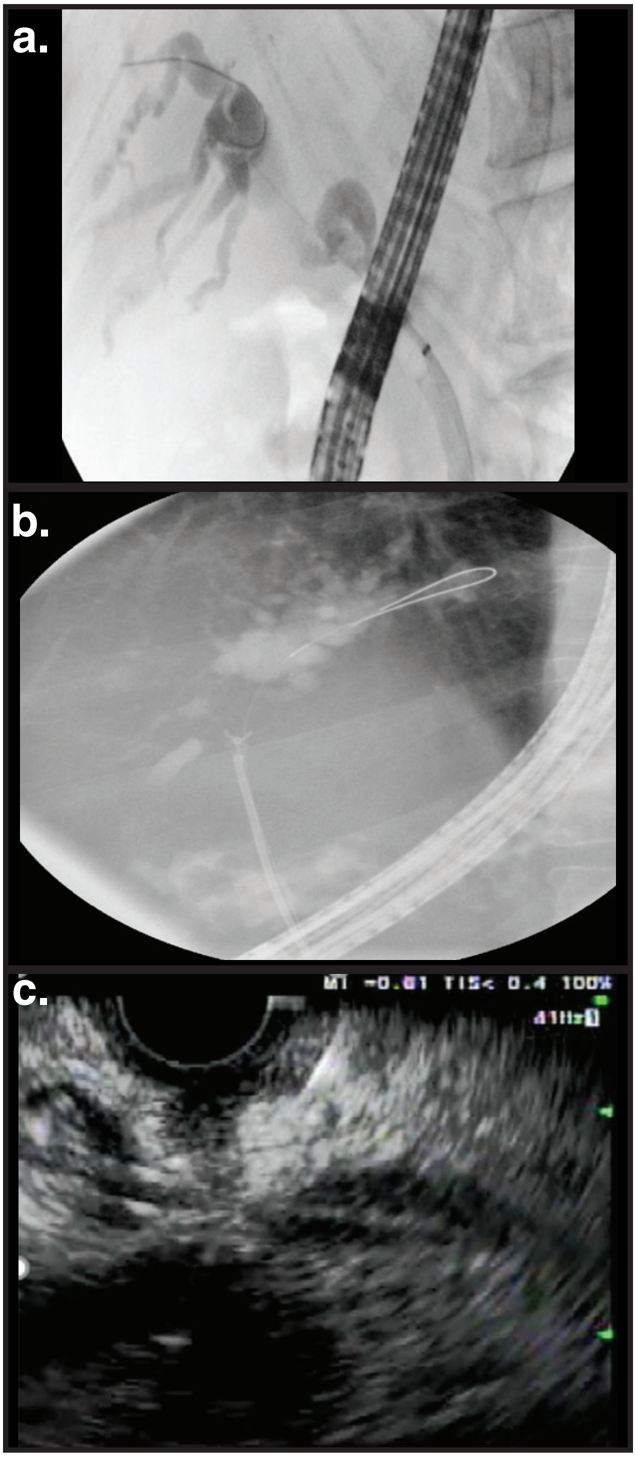

Figure 7. ERCP guided cytologic brushing (a) and biopsy (b) have very high specificity but poor sensitivity. While performance of EUS-FNA of biliary strictures has a favorable yield, it is associated with malignant seeding and is contraindicated in transplant candidates (c).

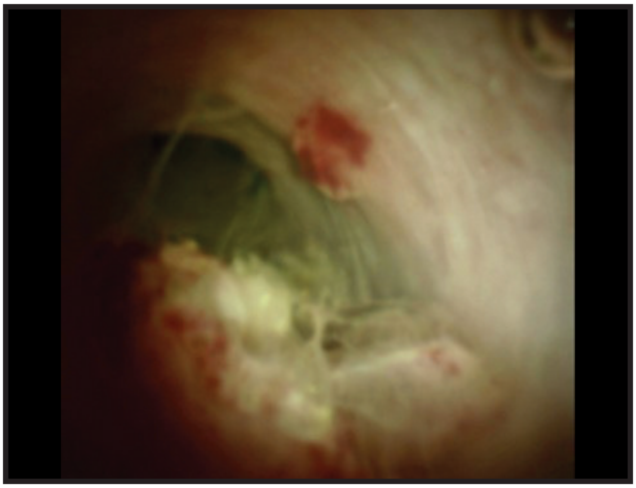

Figure 8. Intraductal mass, irregular narrowing and friable intraductal nodules seen by cholangioscopy are worrisome for malignancy.

developed to better categorize the cholangioscopic impressions of the bile duct. The *Monaco Classification* was developed by a recent multicenter group of expert biliary endoscopists using direct peroral cholangioscopy and digital single-operator cholangioscopy.[40] The interobserver agreement (IOA) was slight in scoring for ulceration, white linear bands, and pronounced pits. The IOA was fair in scoring for the presence of stricture, a lesion, mucosal changes, and abnormal vessels. The IOA was moderate in scoring for papillary projections. The presumptive diagnosis IOA was fair ($\kappa = 0.31$, SE = 0.02) (Table 2). The overall accuracy of Monaco Classification based on visual impression alone was 70%. An alternative classification system is the *Carlos Robles Medrana (CRM) criteria.*[41] Recently, the authors of the Monaco and CRM criteria convened to develop the newest visual criteria for cholangioscopy*, the Mendoza criteria*.[47] These include the presence of tortuous and dilated vessels, irregular nodularity, raised intra-ductal lesions, irregular or ulcerated surface, and friability. The authors report a diagnostic accuracy of 77% for the criteria, nevertheless these criteria require external validation. As the use of cholangioscopy expands and more studies on endoscopic features of bile duct diseases are performed, the accuracy of visual inspection will likely continue to improve over time.

In addition to direct visualization of the bile duct lumen, cholangioscopy allows targeted biopsies using small diameter forceps which pass through the working channel of the cholangioscope (Figure 11). Systematic review and meta-analysis of observational studies indicated that the pooled sensitivity and specificity of cholangioscopy guided biopsies is 60.1% (95% CI 54.9%-65.2%) and 98.0% (95% CI 96.0%-99.0%), respectively.[45] In a recent multicenter randomized trial, DSOC-guided biopsy sampling significantly improved the sensitivity of a tissue diagnosis, 68.2%, versus ERCP guided brushing, 21.4%. Specificity was 100% for both modalities.[48] Given small size of biopsies specimen it is recommended to take multiple biopsies from each biliary lesion. While meta-analysis indicates reduced yield for 2 or fewer biopsies, the precise number is undefined.[49]

Recently, a larger forceps passed via the cholangioscopes which obtains more tissue per pass has been introduced (Figure 11b). While the aim is to improve yield, improved performance has not yet been demonstrated in studies.[50]

Given favorable performance characteristics and minimal risk of seeding it is frequently utilized in the central diagnostic algorithm of biliary strictures in patients who are potentially resectable, candidates for transplantation, and those who have failed other diagnostic maneuvers (Figure 12).

FACILITATING THERAPY FOR CHALLENGING BILE DUCT STRICTURES

Successful guidewire placement is essential to allow therapeutic interventions during ERCP such as dilation and decompression using stents. Using different kinds of guidewires with different

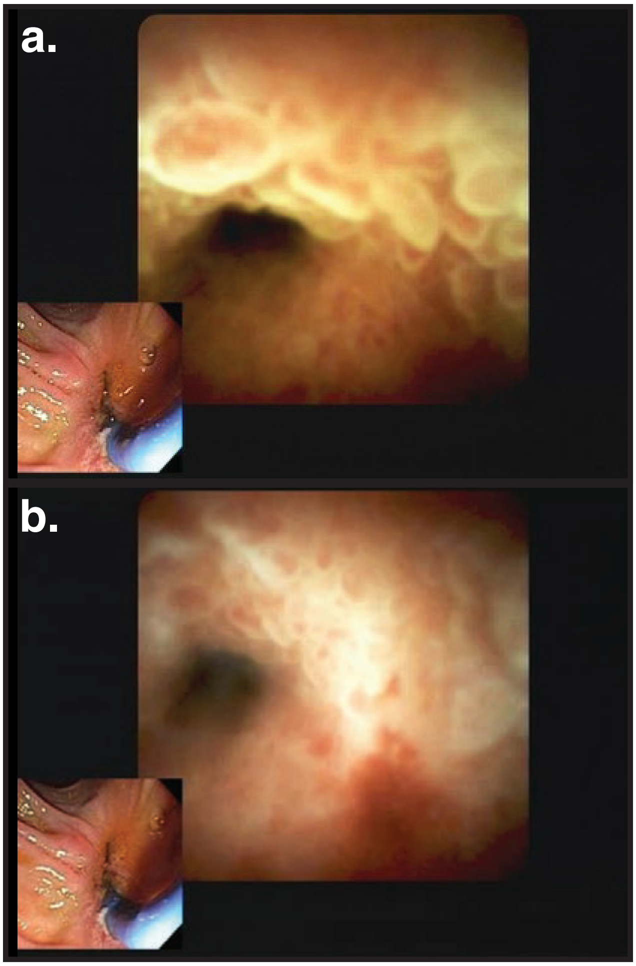

Figure 9. Benign cholangioscopic features of biliary strictures include benign homogenous glandular mucosa (a) and smooth surface without irregular vasculature (b).

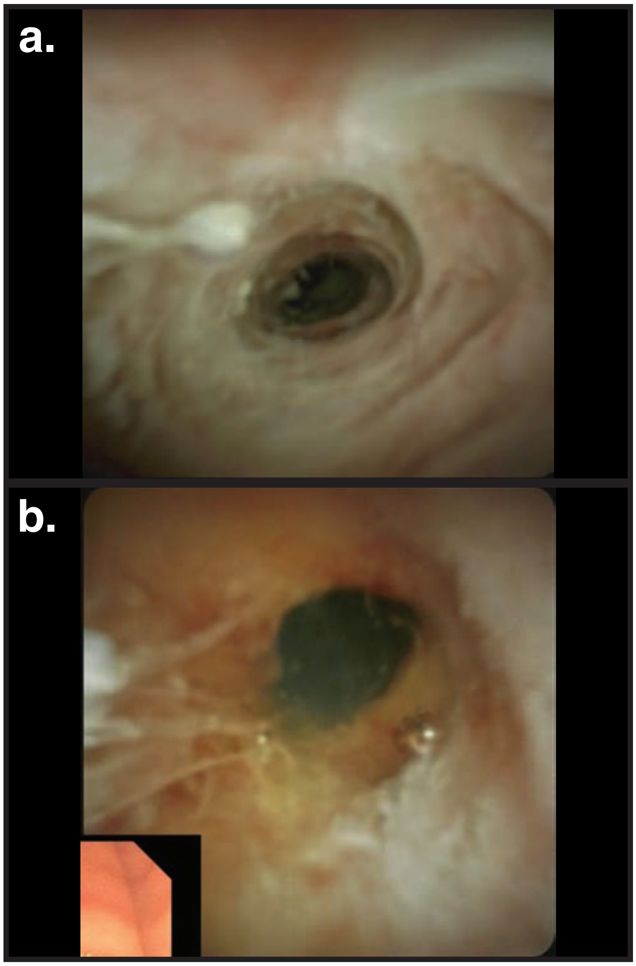

Figure 10. Cholangioscopic appearance of primary sclerosing cholangitis showing (a) homogenous narrowing of the bile duct, and (b) narrowed duct with irregular surface.

characteristics (e.g., angled vs. straight tip, wire size, stiffness) along with trying different scope positions often allows successful guidewire placement. However, in some cases these conventional techniques and instruments fail to reach the duct of interest. By enabling direct visualization of bule ducts, cholangioscopy allows selective passage of wires and subsequent therapy into very specific biliary targets (Figure 13).[51-55] In addition, selective bile duct cannulation by direct cholangioscopic visualization mitigates the likelihood of extensive fluoroscopy use and may reduce procedure time.

OTHER INDICATIONS

An important and specialized scenario where direct visualization by POC has been successfully used is the evaluation of biliary complications after liver transplantation. Post-transplant strictures may have extremely oblique angulation or high-grade nature, particularly following living donor procedures, which may benefit from cholangioscopy.[56,57] In addition to facilitating guidewire placement across difficult angulation or strictures, cholangioscopy may have a diagnostic role in post-transplant patients to identify surreptitious mural ulceration retained sutures, and stones or casts which are not apparent on cholangiography.[57,58] It is unclear whether the utilization of POC for evaluation of biliary complications during first ERCP is warranted. Nevertheless, it is worth considering in cases that are not responsive to initial ERCP with interventions and when there is diagnostic uncertainty.

POC has been successfully used for a number of other indications. Prior to complex resection, it may be used to perform mapping which can guide surgery.[59] It may also play an important diagnostic role to evaluate malignancy in choledochal cysts,[60,61] guide tumor ablation with radiofrequency or photodynamic therapy[62], and evaluate source of hemobilia.[63-65] POC was also found beneficial in retrieval of migrated biliary stents.[66] As technology, training and access to cholangioscopy grow, additional novel applications will emerge.

COST AND ADVERSE EVENTS

Cost and safety are additional vital considerations for the use of cholangioscopy in clinical practice. The cost of single operator cholangioscopes increased with conversion from fiberoptic to digital platforms. The cost of the latter many exceed $3000 per case which requires careful assessment of resource utilization. Definitive cost-effectiveness studies are needed. A model of the economic consequences of single-operator cholangioscopy in a Belgian hospital system found that early use of cholangioscopy-guided therapy for difficult stones could potentially result in cost savings by decreasing the overall number of procedures.[67]

Prospective studies of cholangioscopy indicate that bacteremia and cholangitis occur in 8.8% and 6.6%, respectively.[68] While meta-analysis does not suggest a higher rate of overall adverse

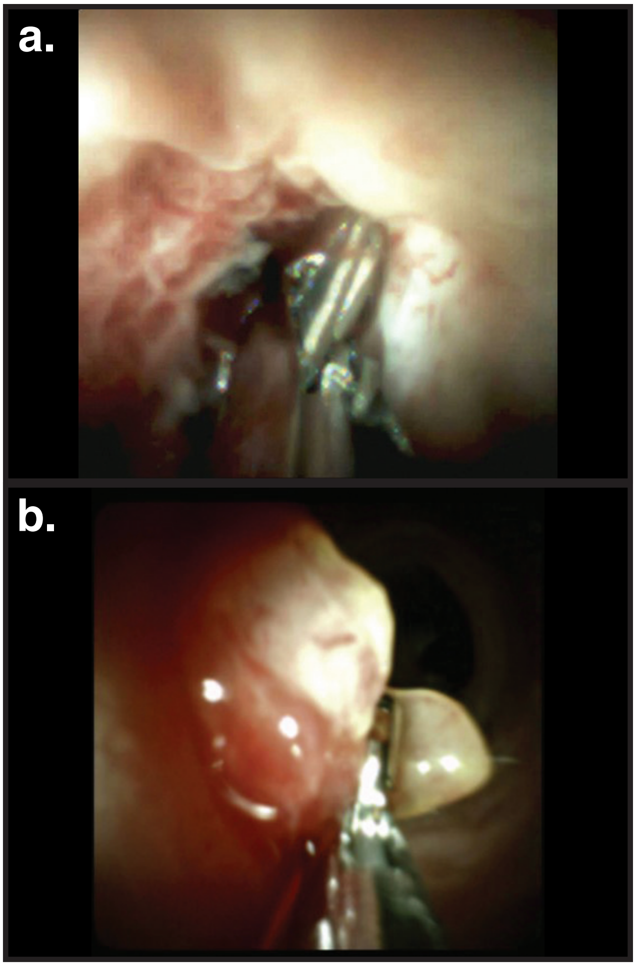

Figure 11. Cholangioscopy-guided biopsy of indeterminate stricture of the bile duct revealed cholangiocarcinoma (a). A nodule is sampled using a recently introduced large diameter cholangioscopic forceps (b) which theoretically captures larger amounts of tissue.

events than conventional ERCP for indications such as difficult bile duct stones,[13] likelihood of cholangitis is greater. This increases with hilar and multifocal strictures.[69] In high-risk settings, i.e., primary sclerosing cholangitis, complex stones, and proximal strictures, administration of peri-procedural antibiotics such as fluoroquinolones and 3rd or 4th generation cephalosporins in addition to bile duct stent should be considered. Cholangioscopy should be avoided in cases of purulent.

When laser lithotripsy is performed, sufficient irrigation and aspiration to optimize visibility along with strictly avoiding use of laser blindly are important precautions to avoid ductal injury. Other adverse events include post-ERCP pancreatitis, perforation, and bleeding, though the rates of these complications for cases with cholangioscopy do not appear to be significantly higher than adverse events from ERCP alone.[9,12, 70-74]

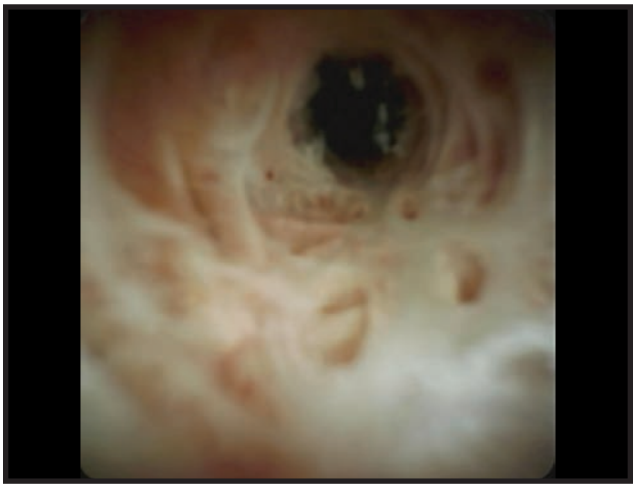

Figure 12. Cholangioscopy is a core component for the evaluation of indeterminate strictures in patients with resectable tumors, who are transplant candidates, and those who have failed other extensive diagnostic maneuvers.

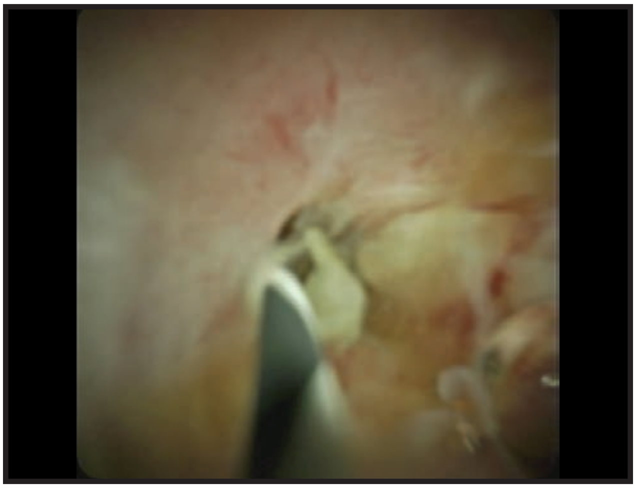

Figure 13. Selective cannulation of tight common hepatic duct stricture is guided by cholangioscopy.

Another important consideration is the use of general anesthesia to protect airways when irrigation may increase the fluid content of the upper GI tract.

FUTURE DIRECTIONS

Rapid advancements in medical technology have already expanded the use of and role of cholangioscopy. Deep learning algorithms promise to increase the diagnostic power of cholangioscopy as do integration of image enhancement techniques from other types of endoscopy including narrow band imaging.[75] Technical advances will also make scopes easier to use and intensify their therapeutic potential. Direct POC using a novel multi-bending ultra-slim scope shortens procedure time and may improve success rates.[76] Slimmer, more flexible scopes may facilitate cholangioscopy's role in patients with primary sclerosing cholangitis and high-grade strictures where success is lower. Additionally, it will likely emerge as a high precision ablative therapy with radiofrequency and photodynamic therapy and future modalities.[77-79] Simpler less expensive devices to exclude residual stones will likely emerge which will have a complementary role with cholangioscopes with broader therapeutic capability.

CONCLUSION

Cholangioscopy has emerged as a core tool in diagnosis and management of neoplastic and non-neoplastic biliary diseases. It is especially important in the treatment of complex bile duct stones and evaluation of indeterminate strictures. An expanding role in biliary practice including treatment of early neoplasia, pre-operative staging, and exclusion of residual stones is emerging. While cost might still be a limiting factor in some practices, the proper utilization of this tool in the appropriate clinical context is likely cost-effective as it improves non-operative management of biliary disease. ■

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