

## Peroral cholangioscopy in the new millennium

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### Abstract

Peroral cholangioscopy was first described in 1970s and has recently gained popularity. Peroral cholangioscopy is appealing to therapeutic endoscopists because a direct intraluminal view of the biliary duct system offers possibilities for diagnosis and interventions beyond that which other imaging or endoscopic modalities can provide. As the image quality of cholangioscopies improves, so too does their diagnostic capability, and as their durability and maneuverability increases, so too does their potential use for therapeutic applications. This editorial is intended to provide a brief review of recent developments in peroral cholangioscopy and current indications for its use.

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**Key words:** Endoscopic retrograde cholangiopancreatography; Cholangioscopy; Peroral cholangioscopy; Cholangiocarcinoma; Biliary stricture; Pancreatic cancer; Biopsy; Brush cytology

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### INTRODUCTION

Diseases of the biliary system are frequently encountered in clinical practice<sup>[1]</sup>. An examination of the bile ducts is often required for the appropriate diagnosis and management of patients with biliary diseases. The dramatic technical advances of flexible endoscopy during the last four decades have resulted in endoscopic retrograde cholangiopancreatography (ERCP) being used as a primary method of diagnosing and treating many biliary diseases<sup>[1]</sup>. In the United States alone, approximately half a million ERCP procedures are performed annually. ERCP can demonstrate the anatomy of the biliary tract and reveal anatomical abnormalities, strictures and intraductal filling defects. However, this technique does not always differentiate the biological nature of bile duct lesions and can fail to determine their intraluminal extension. Furthermore, it is unable to provide information about biliary mucosal lesions that do not project into the biliary lumen. Peroral cholangioscopy as an adjunct to ERCP is a promising procedure that provides direct visualization of the biliary tree. It has been shown to have value in treating difficult-to-remove biliary stones<sup>[2]</sup>, assessing indeterminate biliary strictures<sup>[3]</sup>, and distinguishing between different intraductal lesions of the biliary tree<sup>[4]</sup>. In recent years, cholangioscopy has gained popularity in the United States and is being performed in increasing numbers not only in academic institutions and large tertiary care referral centers, but also in smaller hospitals and private practices. In this paper, clinical applications of peroral cholangioscopy and its role in diagnosis and management of biliary disorders are reviewed.

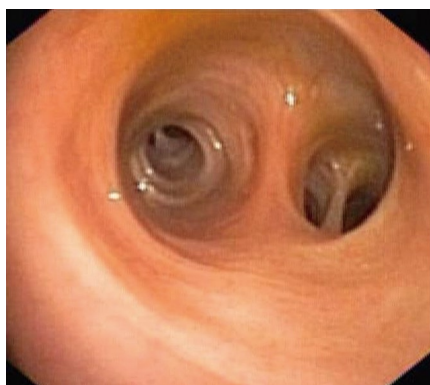
### HISTORICAL PERSPECTIVES

The first peroral cholangioscopy was performed in 1975

**Table 1** Comparison of currently available single and dual operator cholangioscopies

	Endoscopists needed	Image quality	Tip deflection	Simultaneous irrigation and instrumentation	Fragility
Single operator (SpyGlass) Dual operator	One	Moderate - good	4 way (up/down, left/right)	Yes	No <sup>1</sup>
Fiberoptic cholangioscopies	Two	Moderate - good	2 way (up/down)	No	Yes
Video cholangioscopies	Two	Excellent	2 way (up/down)	No	Yes

<sup>1</sup>All components of the spyglass system are single-use with the exception of the spyprobe (the light and image conveyor of the system) which is multi-use. The spyprobe is fragile and has to be handled with care.



**Figure 1** Cholangioscopic view of normal intrahepatic biliary mucosa (image by a prototype video cholangioscope, CHF type Y0002, Olympus Corporation, Tokyo, Japan).

using a prototype cholangioscope that was thin enough to pass through the accessory channel of a duodenoscope<sup>[5]</sup>. The concept of passing a thinner endoscope through a larger one later became known as the “mother-baby” or “mother-daughter” concept. Even today, almost all cholangioscopy systems are based on this concept. The initial prototype cholangioscope had poor image quality, no instrumentation or irrigation capability, and no tip deflection. Despite all its shortcomings, it proved that peroral cholangioscopy is feasible. In the mid-1980s second generation cholangioscopes were introduced<sup>[5]</sup>. These cholangioscopes had added tip deflection and an accessory channel that could be used either for irrigation or instrumentation. In the late 1990s and early in the new millennium, advances in imaging technology led to the introduction of video cholangioscopies with improved image quality that enabled satisfactory views of the biliary mucosa (Figure 1). Addition of narrow band imaging (NBI) capability led to further improvements in detection of abnormal vascularization of biliary mucosa, which is of importance for diagnosis of certain biliary malignancies<sup>[6]</sup>. The first semi-disposable single-operator cholangioscopy system was developed in 2005 and made it possible for a single endoscopist to operate both the baby and mother endoscopes.

## SINGLE AND DUAL OPERATOR CHOLANGIOSCOPY SYSTEMS

In cholangioscopy, the terms “single operator” and “dual

operator” refer to the number of endoscopists required to perform the procedure. As a general rule, dual operator cholangioscopy systems require two endoscopists, while single operator cholangioscopy systems require only one endoscopist for performance. There are, however, reports of use of dual operator cholangioscopy systems by a single operator with the help of appropriate accessory equipment<sup>[7]</sup>.

Currently, most cholangioscopy systems are dual operator. Dual operator cholangioscopies of varying length, diameter and image quality are available. Most dual operator cholangioscopies have fiberoptic image quality. There is limited commercial availability of video cholangioscopies with enhanced image quality. At present, all video cholangioscopies with NBI capability are prototypes and not commercially available.

The only single operator cholangioscopy system currently available is the SpyGlass direct visualization system (Boston Scientific, Natick, MA, USA). This system is fiberoptic-based and has single and multi-use components.

Some of the advantages and disadvantages of the currently available single and dual operator cholangioscopies are summarized in Table 1.

## CLINICAL APPLICATIONS

Several clinical applications for peroral cholangioscopy have been described. With expanded use, additional indications are expected to be reported. Clinical applications of cholangioscopy can be divided into common, uncommon and rare applications. Common applications include stone therapy and diagnosis of indeterminate biliary strictures. Uncommon applications include guidewire placement during ERCP, assessment of post-liver-transplantation biliary strictures, and evaluation of indeterminate intraductal filling defects or irregularities of the bile duct wall seen on imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS) or ERCP. Rare applications include staging and ablation of biliary neoplasms, investigation of recurrent pancreatitis, and evaluation of hemobilia.

### Common applications

Currently, most peroral cholangioscopy procedures are performed for two indications: biliary stones and indeterminate biliary strictures.

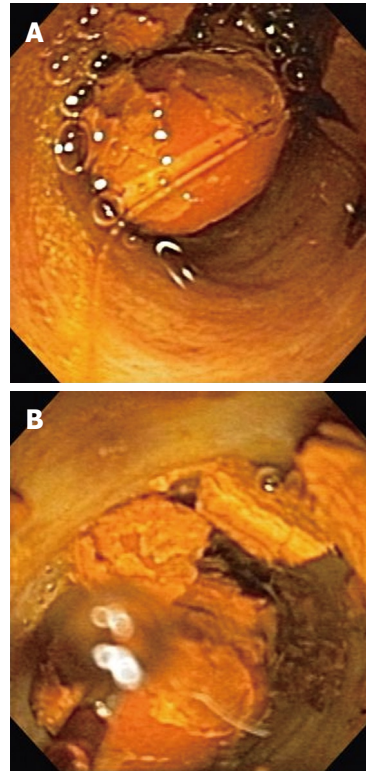
**Table 2** Common factors associated with failed biliary stone removal during endoscopic retrograde cholangiopancreatography

Patient factors
Abnormal anatomy
Prior surgery
Extremely J-shaped stomach
Large hernias
Malrotations
Unstable or difficult endoscope position
Short duodenal bulb
Abnormal anatomy
Long duodenoscope position
Bile duct abnormalities
Presence of ductal strictures
Severely dilated ducts
Stone factors
Size
Large size
Location
Intrahepatic
Cystic duct
Proximal to strictures
Impacted stones

### Biliary stones

**Difficult to remove stones:** Gallstone disease or cholelithiasis continues to be a major health problem throughout the world, and affects 10%-20% of the Caucasian population<sup>[8-13]</sup>. It has been estimated that 15%-20% of patients with gallstone disease also have stones in their bile ducts (choledocholithiasis)<sup>[13]</sup>. Stones in the bile ducts have to be removed because of their potential to cause jaundice, cholangitis, and pancreatitis<sup>[14-16]</sup>. This is accomplished in close to 95% of the cases during ERCP by conventional methods such as sphincterotomy with or without sphincter dilatation, use of extraction balloons or retrieval baskets, mechanical lithotripsy, or a combination of these methods<sup>[17]</sup>. At times, however, stone extraction by standard methods is not possible. There are a number of reasons as to why some stones cannot be removed by conventional means; some of the most common of which are presented in Table 2.

A variety of methods have been devised for endoscopic extraction of stones that are not removable by conventional means during ERCP. As a general rule, these methods involve using shock waves to crush or fragment the stones inside the bile duct, with subsequent removal of the fragments (Figure 2). The shock waves for fragmentation of biliary stones are usually generated using electric spark (electrohydraulic lithotripsy) or laser light (laser lithotripsy). Probes that pass through the accessory channels of cholangioscopies for laser or electrohydraulic lithotripsy are commercially available. Although use of these probes through an extraction balloon under fluoroscopic guidance has been reported<sup>[18,19]</sup>, in our institution, we use them under direct visualization by utilizing a cholangioscope. These probes have to be precisely positioned on the stone to increase effectiveness and reduce complications. Direct visualization ensures that the shock waves



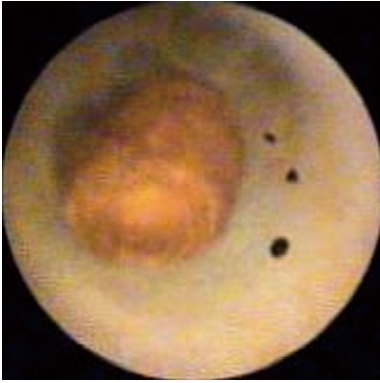
**Figure 2** Cholangioscopic views of a bile duct stone prior to (A) and after (B) electrohydraulic lithotripsy. The lithotripsy probe is visible in the left lower corner of (B).

are aimed at the stone and not the bile duct wall, because shock waves delivered to the bile duct wall can cause bleeding and perforation. Direct visualization by cholangioscopy also allows distinction between stone fragments, air bubbles or blood clots, which can be indistinguishable on contrast cholangiography<sup>[20]</sup>.

Laser or electrohydraulic lithotripsy has been used for fragmentation and subsequent extraction of difficult to remove stones for many years, and both techniques have been shown to be safe and effective<sup>[21,22]</sup>. In a recent multicenter study, cholangioscopy-guided laser or electrohydraulic lithotripsy were effective in > 90% of the cases<sup>[2]</sup>.

There are currently no randomized studies that have compared the effectiveness of laser and electrohydraulic lithotripsy for fragmentation and subsequent extraction of difficult-to-remove biliary stones.

**Missed stones:** Cholangioscopy allows detection of stones that might have been missed during cholangiography. Small stones can be “drowned” in contrast and be missed, and larger stones can block a duct, thus preventing passage of contrast, and evade detection during ERCP (Figure 3). In a study of patients with primary sclerosing cholangitis, stones were not detectable on cholangiography in seven of 23 patients (30%)<sup>[23]</sup>. In a more recent multicenter study, stones were missed in 29% of patients who presented for ERCP for different indications. In that study, ERCP was immediately followed by peroral cholangioscopy, which led to detection of the stones<sup>[24]</sup>.



**Figure 3** Cholangioscopic view of a small stone surrounded by contrast in an intrahepatic duct. The stone was missed during endoscopic retrograde cholangiopancreatography (image by Spyglass Direct Visualization System, Boston Scientific, Natick, USA).

### **Indeterminate biliary strictures**

Biliary strictures can be benign or malignant. Accurate diagnosis of biliary strictures is essential for treatment planning and the correct choice of treatment, such as surgical resection or endoscopic stenting. However, differentiation of malignant from benign ductal lesions remains a challenge<sup>[25]</sup>. Brush cytology during ERCP or fine needle aspiration by EUS has become the preferred initial method of pursuing a diagnosis in many patients with pancreatobiliary malignancies<sup>[25-27]</sup>. These techniques allow easy and convenient sampling and have a low complication rate<sup>[25,27,28]</sup>. The diagnostic specificity of biliary brush cytology or fine needle aspiration is very high and few false-positive diagnoses have been reported<sup>[25,29]</sup>. The major limitation of these techniques has been the relatively modest diagnostic sensitivity, ranging from 10% to 50% in most series<sup>[25,29]</sup>.

There have been attempts to improve the sensitivity of brush cytology obtained during ERCP. Physical changes to the brushing device itself, such as use of longer and stiffer brushes, have not been shown to improve sensitivity<sup>[30]</sup>. Balloon dilatation of strictures, to expose underlying tissue, prior to obtaining brush samples has been tried but not shown to be of any benefit<sup>[31]</sup>. Mutation analysis of the cells obtained by brushing does not seem to improve diagnostic accuracy<sup>[32]</sup>, and DNA methylation analysis of ERCP brush specimens has shown only small benefit<sup>[25]</sup>.

It has been suggested that peroral cholangioscopy can improve diagnosis of indeterminate biliary strictures by visualization of the mucosa at the site of the stricture, and by targeted biopsy.

**Visualization of the mucosa at the site of the stricture:** It is well known that the presence of irregularly dilated and tortuous blood vessels (so-called tumor vessels) due to neovascularization at the site of pancreatic or biliary strictures is indicative of malignancy<sup>[33]</sup>. Tumor vessels can be detected by direct visualization using a cholangioscope. Intraductal nodules or masses can also be indicative of malignancy and be easily detected by cholangioscopy. However, tumor vessels and intraductal masses can be ap-

preciated only in a fraction of malignant strictures; probably those with more advanced disease. Certain types of cholangiocarcinoma involve submucosal layers of the bile duct wall and cannot be detected by cholangioscopy, which visualizes the superficial layers. Biliary strictures caused by extraluminal compression, such as those associated with pancreatic cancer, cannot be detected by cholangioscopy, unless at later stages when the tumor has infiltrated and penetrated the bile duct wall.

Studies to assess the value of stricture visualization by cholangioscopy have reported high sensitivity for detection of malignant lesions<sup>[4,34]</sup>. The reported sensitivity in some of these studies has approached 100%<sup>[4]</sup>. In these studies, however, the criteria used for labeling a stricture as malignant have been somewhat lax. As an example, irregular biliary mucosa has been used to label a stricture as malignant. It is well known that irregular biliary mucosa on cholangioscopy can also be seen in benign lesions such as primary sclerosing cholangitis, or chronic inflammation associated with choledocholithiasis or recurrent cholangitis<sup>[35]</sup>. Therefore, the high sensitivity in such studies is often achieved at the cost of lower specificity. This is alarming, because false-positive results can have a devastating impact on the affected patients' lives.

Although, undoubtedly, direct visualization of indeterminate biliary strictures can aid in their diagnosis, the true value of peroral cholangioscopy for this purpose has not been vigorously studied.

**Targeted biopsy:** Targeted biopsy is defined as biopsy of the sites that are clearly affected by disease under direct visualization. Theoretically, targeted biopsy should improve cancer detection rate in malignant biliary strictures by allowing sampling of the sites that appear suspicious. In a recent multicenter study that assessed the role of cholangioscopy-guided targeted biopsy for diagnosis of indeterminate biliary strictures, initial observations suggested a large improvement in sensitivity<sup>[3]</sup>. However, later observations at conclusion of the study have indicated a somewhat more modest benefit<sup>[24]</sup>. Well-designed studies are needed to assess better the value of cholangioscopy-guided targeted biopsy for evaluation of indeterminate biliary strictures.

**Uncommon applications:** In our institution, 10%-20% of peroral cholangioscopy procedures are performed for indications other than stone disease and stricture diagnosis. Some of these indications are discussed below.

### **Characterization of indeterminate intraductal lesions or filling defects**

Increased use of imaging studies such as CT, MRI and EUS has led to an increase in incidental findings such as intraductal biliary lesions or filling defects. Although, most often these findings are real, they can also be due to artifacts.

Direct visualization of the intraluminal biliary tree is the most appropriate way to investigate further the nature of these findings. Cholangioscopy has been shown to be effective for this purpose<sup>[4,36]</sup>.

### Assessing post-liver-transplantation anastomotic strictures

Various refinements in surgical techniques and postoperative and immunosuppressive management have reduced the incidence of complications after liver transplantation. Biliary complications, however, continue to be a significant cause of morbidity after liver transplantation<sup>[37,38]</sup>.

In selected cases, cholangioscopy can prove beneficial in diagnosis and treatment of biliary complications after liver transplantation. In a study of 20 liver transplant patients, cholangioscopy helped diagnose ischemia, ulcerations, scar tissue, intraductal clots, and retained suture material, which otherwise might have been missed by ERCP alone<sup>[39]</sup>. The role of cholangioscopy in assessment of anastomotic strictures after liver transplantation is evolving.

### Assistance in guidewire placement

ERCP has attained a primary role in the treatment of biliary strictures and biliary stones. Success of ERCP in these cases, however, depends on the ability to traverse the stricture or the stone with a guidewire that is then used to direct instruments such as dilating balloons or lithotripsy baskets<sup>[40]</sup>. In the vast majority of cases, this is accomplished easily. With severe strictures or impacted stones, however, it can represent a time-consuming challenge, and in some studies, a failure rate of up to 20% has been reported<sup>[41]</sup>. In such cases, cholangioscopy can facilitate guidewire placement and prevent more invasive procedures such as transhepatic access or surgery. Several studies have highlighted the value of cholangioscopy in such instances<sup>[40,42]</sup>.

**Rare applications:** We define rare applications as those responsible for  $\leq 1\%$  of our peroral cholangioscopy volume. For obvious reasons, these indications have been reported only in one or two case reports and no studies have assessed the true value of peroral cholangioscopy in these settings.

### Evaluation of recurrent pancreatitis

Peroral cholangioscopy was used in a 62-year-old post-cholecystectomy patient with recurrent acute pancreatitis of undetermined etiology. It revealed a T-tube remnant in the cystic duct stump, which served as a nidus for biliary sludge and stone formation. The T-tube remnant had evaded detection by ERCP, CT and magnetic resonance cholangiopancreatography. Removal of the T-tube remnant prevented further episodes of pancreatitis<sup>[43]</sup>.

### Determination of source of bleeding in hemobilia

A 54-year-old man was reported to have bleeding from arteriovenous malformations of the bile duct, which was detected by peroral cholangioscopy, with subsequent successful treatment by endovascular intervention<sup>[44]</sup>. In another study, the cause of hemobilia in a 57-year-old man could not be identified by ERCP, CT or angiography. Peroral cholangioscopy revealed multiple biliary ulcers. Biopsies were consistent with cytomegalovirus cholangiopathy that responded to antiviral therapy, with subsequent cessation of bleeding<sup>[45]</sup>.

### Staging and ablation of biliary neoplasms

Peroral cholangioscopy was used in a 78-year-old man to determine the extent of a biliary neoplasm. Use of a video cholangioscope with NBI capability allowed precise determination of the margins of the lesion. Successful ablation of the neoplasm with brachytherapy was confirmed by repeat peroral cholangioscopy at 1 mo follow-up<sup>[46]</sup>.

## CONCLUSION

Recent advances such as introduction of a single operator cholangioscopy system or video cholangioscopies with high image quality have led to renewed interest in cholangioscopy, with subsequent expanded use. Currently, the most common indications for cholangioscopy are stone therapy and evaluation of indeterminate biliary strictures. Several other clinical applications have been described. As this technology is gaining more popularity and use, other indications are certain to be described.

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