The role and utility of cholangioscopy for diagnosing indeterminate biliary strictures

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ABSTRACT

Biliary strictures are considered indeterminate when evaluation with imaging and standard tissue sampling during endoscopic retrograde cholangiopancreatography (ERCP) are non-diagnostic. Standard tissue sampling techniques include cytologic brushings, with or without fluorescence in situ hybridization (FISH), and endoscopic intraductal biopsies. These strictures are often clinically suspicious for malignancy. The management of these patients can vary substantially and relies on an accurate diagnosis of the lesion. Unfortunately, despite numerous modalities, the sensitivity of existing tissue sampling techniques remains low and can lead to delays in diagnosis and the need for additional procedures. Cholangioscopy has emerged as a means to visually inspect and obtain image-guided biopsies of the lesion in question, with improved sensitivity as well as a high specificity and accuracy for diagnosing the etiology of indeterminate biliary strictures. The types of cholangioscopy systems and a summary of the pertinent literature are discussed in this review.

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Introduction

Cholangiocarcinoma (CCA) and pancreatic adenocarcinoma are the most common causes of biliary strictures, but up to 30% of biliary strictures are benign.1,2 The diagnosis of CCA relies on a multimodal approach including some combination of clinical and laboratory features, cross sectional imaging, endoscopic ultrasound (EUS), and as well as endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology, forceps biopsy, and/or genetic analysis. Accurate differentiation of benign from malignant disease is important, and histologic confirmation is often required to guide surgical and/or oncologic planning.3,4 Unfortunately, the reported success of ERCP with brushing or intraductal biopsies to diagnose malignancy in biliary lesions has been variable and limited, despite multiple efforts to improve its performance. This often necessitates repeat procedures when tissue diagnosis is mandatory or when the clinical suspicion for CCA remains high. The definition of an indeterminate biliary stricture varied among the studies reviewed here, but was most often defined as a stricture in which prior ERCP with brushings and/or intraductal biopsy did not provide definitive diagnosis or if the results were benign or inconclusive despite a strong clinical suspicion for malignancy.5,6 In other studies, a stricture was defined as indeterminate if there was a clinical suspicion of malignancy based on patient history and imaging characteristics alone, prior to tissue sampling. Diagnostic challenges associated with indeterminate biliary strictures have driven improvements in cholangioscopy, which allows both a direct visual inspection of the ductal epithelium as well as the ability to obtain endoscopically, rather than fluoroscopically, guided biopsies.

Sampling of Biliary Pathology

In contrast to its high specificity, the reported sensitivity of ERCP tissue sampling of bile duct lesions is disappointing. A 2015 meta-analysis of nine studies including 730 patients reported a pooled sensitivity of 45% and specificity of 99% for endoscopic brush cytology, and 48% and 99%, respectively, for intraductal biopsies.7 When these two modalities were combined, the pooled sensitivity only increased to 59% (ranging up to 70%) with a specificity of 100%.8 These values are also affected by patient characteristics. For example, the sensitivity of bile duct brushings...
for the detection of CCA in primary sclerosing cholangitis, specifically, appears to be only 43% in a 2014 meta-analysis. Efforts to improve the diagnostic sensitivity have included the use of ERCP with fine-needle aspiration (FNA), probe-based confocal laser endomicroscopy (CLE), EUS with FNA, intraductal ultrasound, optical coherence tomography (OCT), and new tissue sampling accessories (including updated biopsy forceps and an endoscopic tissue scraper). Studies have also evaluated fluorescence in situ hybridization (FISH) using probes for genetic alterations associated with CCA, with reported sensitivities ranging from 38% to 58% and specificities between 91% and 100%. Newer FISH probes may increase the sensitivity to 65% and next generation genetic sequencing techniques are also promising, but the data is still limited. The sensitivity may increase up to 59% when combining FISH with cytology and up to 82% when combined with both brushing and biopsy. Therefore, despite a high specificity, these methods have not reliably been shown to provide the sensitivity needed to be stand-alone tools, and a multimodal sampling approach is often required. Alternative sampling techniques such as percutaneous biopsy or EUS with FNA can be useful, but are usually avoided for hilar lesions in pre-liver transplant patients due to the risk for disease dissemination and its impact on the patient’s subsequent transplant candidacy. Despite these efforts, the diagnosis remains uncertain in up to 20% of biliary strictures after full preoperative evaluation with standard techniques. This represents a commonly applied definition of an “indeterminate stricture,” especially in the setting of a high clinical suspicion for malignancy, and may require surgical intervention to confirm a diagnosis.

The difficulties in obtaining adequate tissue may be due to the superficial nature of brushings and intraductal biopsies, which may not reach subsurface CCA cells. The stricture itself may also obstruct passage and full opening of the biopsy forceps. Cholangioscopy overcomes some of these limitations by allowing visually directed biopsies, enabling better real time assessment of the adequacy and location of the bites. Cholangioscopy also enables direct visual inspection of the concerning lesion. Irregular margins, dilated/tortuous vessels (also known as “tumor vessels”), fibrosis, surface pitting, papillary projections, and ulceration are considered features of malignant lesions in the cholangioscopy literature (Fig. 1). Visual inspection has consistently been shown to have a higher sensitivity for detecting malignancy than visually-guided biopsies in indeterminate strictures, but at the expense of specificity and accuracy. However, since validated consensus criteria regarding the characteristics of benign and malignant strictures have not yet been developed, these features cannot reliably be used alone, necessitating additional tissue sampling to achieve an accurate diagnosis.

**Indications and Techniques**

Cholangioscopy with directed biopsy is currently recommended as an adjunctive technique for the characterization of biliary strictures. It is usually performed on patients with increased risk for CCA (i.e., patients with primary sclerosing cholangitis, who are post-liver transplant with prior history of CCA, or with a cholecystic cyst) who could not be diagnosed on prior attempts at tissue sampling. These are often patients in whom the sensitivity of ERCP with brushings or biopsy alone is reported to be lower. Cholangioscopy also enables electrohydraulic or laser lithotripsy...
of bile duct or cystic duct stones (Mirizzi syndrome) which can produce a narrowing of the extrahepatic duct.\textsuperscript{22,23}

Cholangioscopy is most commonly performed via the per-oral route, usually through a duodenoscope, although percutaneous and surgical cholangioscopy are also possible. Several different systems exist for the per-oral approach, including mother-daughter (or “mother-baby”) cholangioscopy (MDC), single-operator cholangioscopy (SOC), and direct per-oral cholangioscopy (DPOC) (Table 1). The MDC and the initial SOC devices rely on fiberoptic imaging, but the latest SOC and DPOC technologies employ higher quality digital imaging.\textsuperscript{21}

Mother-Daughter Cholangioscopy

MDC (Fig. 2A) is performed through a dedicated reusable cholangioscope which is typically advanced to the bile duct through the working channel of a therapeutic duodenoscope over a guidewire.\textsuperscript{23} This system requires two operators, including one to manage the duodenoscope and the other to control the cholangioscope. The cholangioscope control knob provides a two-way range of motion (up/down) as well as air and/or water insufflation and suction channels.\textsuperscript{23} MDC cholangioscopes provide a fiberoptic image and have a 1.2 mm working channel for accessories.\textsuperscript{23}

The first large study comparing tissue sampling with ERCP vs ERCP with MDC guided biopsies was a 2010 multicenter retrospective investigating 144 patients in Japan.\textsuperscript{17} One hundred twenty of these patients underwent biopsies. ERCP with biopsy without cholangioscopy resulted in an 87% sensitivity, which was higher than previously reported rates for this technique. However, the addition of MDC-guided biopsies increased the sensitivity to 99% and the accuracy from 85% to 98%.\textsuperscript{17} It should be noted that this study was not limited to indeterminate biliary strictures as in the above definition since patients did not have prior nondiagnostic biopsy or cytology.\textsuperscript{4}

One of the largest prospective investigations was a 2013 multicenter study including 87 patients with bile duct lesions and of whom 38 did not yet have a definitive diagnosis. In this study, indeterminate strictures were defined in this study as patients with suspicious imaging findings with or without prior ERCP and biopsy or cytology.\textsuperscript{16} MDC correctly identified 27 of 28 malignant lesions and 8 of 10 benign lesions by visual inspection (sensitivity 96.4%, specificity 80%, accuracy 92.1%).\textsuperscript{16} The authors noted that narrow-band imaging (NBI; Olympus Medical Systems, Tokyo, Japan) was useful in differentiating benign from malignant lesions by enhancing the surface features or margins of lesions. Endobiliary biopsies under cholangioscopic guidance of 27 malignant lesions resulted in a sensitivity of 81.5%, specificity of 100%, and accuracy of 85.7%. Five patients had inadequate bi-

![Fig. 2. A fiberoptic “daughter” cholangioscope (A) and a digital single-operator cholangioscope (B). Images courtesy of Pentax Medical (A) and Boston Scientific (B).](image-url)
opsy specimens for accurate histologic assessment. This study also reported a 35.5% sensitivity for mucosal extension of extrahepatic bile duct cancers (total n = 49) for ERCP, compared to 88.2% for ERCP with MDC visualization and 93.8% for ERCP with MDC and biopsy.14 Mucosal extension for bile duct cancer was defined in this study as tumor extension of at least 20 mm from the margin of the main tumor on at least one side, proximal or distal.16

Other small observational studies have reported similar findings. For visual inspection alone, the reported sensitivities range from 92%–100%, specificity 80%–93%, and accuracy 92%–97%.5 For cholangioscopy with biopsy, the values range from 38%–82%, 96%–100%, and 61%–86%, respectively.5

The main advantage of MDC is that it has been associated with a significantly higher visual sensitivity (P = 0.01) and visual accuracy (P < 0.01) compared to SOC and DPOC on meta-regression performed in a recent meta-analysis. However, as mentioned above, the investigations had a broad definition for indeterminate strictures, without the requirement for prior attempts at ERCP with tissue sampling, perhaps affecting these values. Additionally, two experienced operators are required to complete the procedure, which is a major limitation of these devices.23 The reusability of the scopes is also appealing from a resource standpoint, but they have been noted to be prone to damage and costly to maintain and noted to have limited suction and irrigation capabilities.23 These limitations have restricted the utility of MDC.

### Single-Operator Cholangioscopy

The two operator requirement was overcome with the development of SOC (Fig. 2B) using a disposable cholangioscope which is similarly advanced through the channel of the duodenoscope. The first generation model (SpyGlass; Boston Scientific, Marlborough, MA, USA) used fiberoptic imaging with a separate imaging probe that was inserted through the optical channel of a reusable catheter. The latest generation (SpyGlass DS) provides higher resolution digital imaging built directly into a disposable scope. The SpyGlass system has dedicated irrigation and aspiration connections as well as 1.2 mm working channel for accessories.23

Many studies have reported the characteristics of SOC, although they are mostly observational in nature and performed using the first generation SpyGlass device (Table 2).24-32 The largest study was a 2011 prospective cohort study including 15 referral centers in the United States and Europe. This study included 297 patients, with 226 who underwent SOC for diagnosis of suspected bile duct disease and 95 who received biopsies for sensitivity and specificity analysis.2 The mean procedure duration was 25 minutes. The overall sensitivity and specificity of SOC visual impression of malignancy was 78% and 82%, respectively. However, the sensitivity of biopsy histology was only 49%. Biopsies yielded adequate tissue for histological evaluation in 88% of cases.3

A subsequent prospective cohort study evaluating 52 patients with indeterminate strictures or filling defects with inconclusive/unsuitable brush cytology on prior ERCP reported a higher sensitivity of 88% from the 42 patients who underwent SOC guided biopsies with 94% specificity.24 Biopsy was not performed in 7 cases due to an alternate diagnosis (stones or varices), was unsuccessful in two cases because the biopsy forceps could not exit the operative channel of the cholangioscope, and in one case yielded material unsuitable for pathologic analysis.25 Another large study published in 2012 involved a multicenter cohort including > 95% of all SOC performed in the United Kingdom over a ~2 year period.26 It included 109 patients with indeterminate strictures and 21 with indeterminate filling defects.26 The overall sensitivity, specificity, and accuracy for SOC was 66%, 98%, and 87%, respectively, for a diagnosis of malignancy using either biopsy or visual inspection. For SOC-guided biopsy specifically, the respective values were 62%, 100%, and 84%. This study also noted that sample adequacy was significantly higher in those with at least four biopsy specimens compared to those with less than four (90% vs 64%, P = 0.037).26

Two recent meta-analyses focusing on SOC with the first generation SpyGlass including a combined total of 10 distinct studies reported a pooled sensitivity of 60.1% and 69.0%, respectively and specificity of 98% (in both studies) for biopsy-based diagnosis of malignant strictures.5,9 For visual diagnosis of malignancy, the sensitivity and specificity ranged from 85%–90% and 83%–87%, respectively.6,9 When brushings and/or biopsies were inconclusive on prior procedures but there was a persistent suspicion for malignancy, the sensitivity was 75% and the specificity was 93%.7 Another recent meta-analysis assessing diagnostic modalities for CCA specifically in primary sclerosing cholangitis (PSC) patients found that SOC with targeted biopsies was the most accurate diagnostic modality at 96% compared to ERCP with brush cytology (accuracy 87%), FISH polysomy (50%), FISH trisomy (47%), and probe-based CLE (75%).33

The advantages of SOC, especially the newest generation SpyGlass DS, include improved visualization, the need for only one operator, and greater flexibility with four-way control knobs.23

### Table 2: Studies Evaluating Biopsies in Single Operator Cholangioscopy (SOC)

| First author | Year | Study design         | Patients biopsied (n) | Biopsies per patient (n) | Sensitivity | Specificity |
|--------------|------|----------------------|----------------------|--------------------------|-------------|------------|
| Alameel24    | 2013 | Single center, retrospective | 16 | NR | 0.4 | 1 |
| Chen1        | 2011 | Multicenter, prospective | 95 | 3 | 0.49 | 0.98 |
| Chen25       | 2007 | Multicenter, prospective | 20 | 4.5 (median) | 0.71 | 1 |
| Draganov26   | 2012 | Single center, prospective | 26 | NR | 0.77 | 1 |
| Hartman27    | 2012 | Single center, retrospective | 29 | 3 | 0.57 | 1 |
| Kalaitzakis28 | 2012 | Multicenter, retrospective | 49 | 3 | 0.62 | 1 |
| Mantha29     | 2013 | Single center, prospective | 42 | NR | 0.88 | 0.94 |
| Ramchandani30 | 2011 | Single center, prospective | 33 | NR | 0.82 | 0.82 |
| Siddiqui31   | 2012 | Single center, retrospective | 30 | 5 (median) | 0.77 | NR |
| Woo32        | 2014 | Single center, retrospective | 19 | 2.8 (mean) | 0.64 | 1 |

NR, not reported.
Additionally, a recent cost-utility study discovered that SOC was a more cost-effective diagnostic modality for CCA in PSC compared to ERCP with brush cytology, ERCP with brush cytology plus FISH, and ERCP with intraductal biopsies in the overall management of these patients.\(^3\)

One limitation in applying SOC is that the majority of existing literature evaluated the first generation, fiberoptic SpyGlass rather than the digital SpyGlass DS system, which provides a substantial improvement in image quality.\(^2\) The 1st generation SpyGlass system also consisted of a disposable delivery catheter, but its reusable fiberoptic probe had limited durability with repeat reprocessing.\(^2\) These limitations are overcome with the entirely single-use SpyGlass DS probe, eliminating the need for reprocessing and resulting image degradation.

The lack of control or comparison groups in SOC studies limits the conclusions that can be drawn compared to non-cholangioscopic biopsy techniques (such as percutaneous, ERCP alone, etc.). Additionally, there are no rigorous studies comparing the outcomes of SOC to MDS (for which reported sensitivity and accuracy values tend to be higher) and DPOC.\(^3\) However, SOC represents an evolution from a complicated, two-person procedure to a simpler system with superior images and no need for reprocessing/maintenance. To date, the data regarding SOC demonstrates a modest sensitivity and high accuracy for the diagnosis of malignancy in indeterminate biliary strictures. Further studies using the latest generation device, compared to and combined with other diagnostic modalities, are required.

### Direct Per-Oral Cholangioscopy

While MDC and SOC are performed through the working channel of a duodenoscope, DPOC refers to the per-oral insertion of a thin gastroscope or dedicated ultrasound cholangioscope directly into the bile duct, usually after having performed a biliary sphincterotomy.\(^4\) Direct cholangioscopy with a trans-nasal approach and balloon-assisted direct cholangioscopy in patients with altered anatomy have also been described.\(^5\)

The larger studies on direct cholangioscopy have reported technical success rates between 78% and 89%.\(^6\) Outcomes data specifically for indeterminate biliary strictures are limited and mostly from smaller cohorts, but a 2014 multicenter retrospective study on 84 patients, 26 of whom underwent DPOC guided biopsies, reported 90% sensitivity for neoplasia via stricture biopsy.\(^5\)

The advantages of DPOC are the superior digital images without the need for a separate cholangioscopy platform, precise control of the endoscope, a larger working channel, and the availability of electronic chromoendoscopy (i.e., NBI).\(^7\) Like SOC, DPOC is a single-operator technique. However, advancement of these scopes into the bile duct is technically challenging, especially due to gastric looping and instability within the bile duct. Techniques to achieve successful biliary cannulation and scope stability include advancement over a guidewire, use of an overtube, free-hand retroflexed biliary intubation, anchoring/straightening of the bile duct using a balloon, and use of a prototype double-bending direct cholangioscope.\(^4\)

### Safety and Adverse Events

The estimated overall adverse event rate for cholangioscopy is reported at 7%, with a 1% rate of serious events on a meta-analysis including MDC, SOC, and DPOC.\(^1\) The most common complications were cholangitis (4%) and pancreatitis (2%).\(^1\) This analysis included cholangioscopy for multiple indications, including indeterminate strictures but also for the removal of difficult bile duct stones. The risk of complications, especially cholangitis, bile leak, and hemobilia may be related to the use of fluid irrigation of obstructed ducts, lithotripsy, and the route of access.\(^2\) A recent prospective study found an 8.8% rate of post-procedure bacteremia and a 7% rate of cholangitis.\(^6\) Antibiotic prophylaxis for cholangioscopy is therefore generally recommended, especially if biopsy sampling is expected.\(^6\)

A very rare but severe complication is air embolization, which appears to be more common with DPOC but has also been reported with MDC and SOC.\(^1\) An intraductal anchoring balloon was withdrawn from the market as a result of this complication, and bile duct insufflation with CO\(_2\) water, and/or saline is recommended during direct cholangioscopy to mitigate this risk.\(^2\) Air should not be used for insufflation.

It is important to note that patients undergoing cholangioscopy have often undergone a failed prior ERCP, either due to indeterminate tissue sampling, unusual appearing fluoroscopic findings, difficult anatomy (such as post-liver transplant, tight stricture, very proximal biliary lesions), or large stones. Therefore, selection bias must be considered when assessing safety data.\(^1\) A 2011 single-center retrospective study found that the complication rate of cholangioscopy (mostly via MDC) was significantly higher compared to ERCP alone (7% vs 2.9% respectively, odds ratio 2.5, 95% confidence interval 1.56–3.89); however, the complication rate for ERCP alone in this study was lower than in other published reports for ERCP alone.\(^8\) A more recent study found a similar complication rate for ERCP with cholangioscopy compared to ERCP alone, without an increased risk for cholangitis or pancreatitis after adjusting for confounders.\(^5\)

### Future Needs

Before cholangioscopy is accepted into wider routine practice, there are several outstanding needs. Now that higher quality digital imaging using SOC and DPOC (often with NBI) are available, more precise evaluation and validation of the visual characteristics of malignant versus benign strictures is required.\(^1\) Much of the existing data relies on older generation fiberoptic-based technology.\(^4\) Also from a procedural standpoint, there are limited and varied data regarding the number of biopsy specimens required for an adequate sample.\(^6\) The development and study of larger forceps, such as the latest generation “Spybite” (Boston Scientific) is also required for effectiveness. Finally, the recent meta-analyses have demonstrated that there is a paucity of high-quality prospective data on cholangioscopy, especially in comparison to other techniques used to evaluate indeterminate biliary strictures such as EUS with FNA, FISH, next generation sequencing, and advanced imaging techniques such as CLE and OCT. Much of the data is observational in nature.\(^4\)

The applicability of the data is limited due to small sample sizes and heterogeneity in the methods and definitions used in published studies. More prospective trials are required, either comparing cholangioscopy head-to-head with other the modalities mentioned above or, perhaps more usefully, implemented as part of a multimodal algorithm with ERCP and a combination of brushing, biopsy, FISH, and/or endomicroscopy.

### Conclusion

The need for improved diagnostic and therapeutic capabilities
in the biliary tract and the limitations of prior techniques have driven the advancement of cholangioscopy. Per-oral cholangioscopy has evolved to become a cost-effective, single-operator procedure with higher quality images than earlier generations. The available data demonstrate that it can improve the diagnostic yield in the evaluation of indeterminate biliary strictures, which continue to pose a challenge based on current practices. The accuracy for visual diagnosis appears to be ~10% greater than for histological sampling techniques. While the optimal approach to these lesions continues to be refined, the strategy will likely combine multiple diagnostic modalities. Cholangioscopy is expected to play an important role in this algorithm and will likely improve with the latest versions of the devices and accessories, facilitating wider clinical use.

Conflicts of Interest

Dr. Thaker has nothing to disclose. Dr. Muthusamy is a consultant for Boston Scientific.

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