Editorial Commentary

Guidelines on cholangioscopy for indeterminate biliary strictures: one step closer to consensus

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Described as early as the 1950s (1), cholangioscopy has evolved from a burdensome intra-operative maneuver performed during open surgery, to a minimally-invasive, widely-available tool that can be utilized on demand during endoscopic retrograde cholangiopancreatography (ERCP). The advent of the latest generation digital cholangioscopes with improved image quality, maneuverability, and the ability to pass tools through a dedicated instrument channel has revolutionized the modern approach to a wide variety of biliary disorders (2). Given its efficacy and safety, cholangioscopy-directed electrohydraulic and laser lithotripsy has become standard of care for difficult to remove bile duct stones (3). However, given the associated costs and slightly higher risk of complications during ERCP (4,5), its position in the algorithmic management of indeterminate biliary strictures is less clear. Frequently, cholangioscopy is used as second line modality when brush cytology or ERCP-directed fluoroscopic biopsies are inconclusive (6).

In the January 2022 issue of *HPB* (*Oxford*), Angsuwatcharakon *et al.* (7) published consensus guidelines on the role of cholangioscopy to diagnose indeterminate biliary strictures. At the time of publication, these guidelines represented the first recent guidance on the use of cholangioscopy for indeterminate biliary strictures, only recently followed by guidelines from the American College of Gastroenterology (ACG) on the overall management of all biliary strictures, including indeterminate strictures (8). Using a modified Delphi method, the authors formulated a total of nine total statements, starting with the definition of an indeterminate stricture, through guidance on the appropriate use of cholangioscopy directed sampling as well as when cholangioscopy may not be indicated. The recommendations are overall robust and backed by the best available evidence, but given the limitations of the literature on the topic, several of the recommendations were based on non-randomized trials and evidence from retrospective studies.

In the first key statement, an indeterminate biliary stricture is defined as that of an uncertain etiology despite adequate imaging and/or an attempt at tissue diagnosis. This definition differs somewhat from that adopted by the recent ACG guidelines (8) which define an indeterminate stricture as 'one for which a diagnosis has not been established despite initial ERCP with intraductal sampling'. The authors acknowledge that no unified definition exists in the literature and as such allowed for a broad definition in their definition statement. However, future versions of

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the guideline may benefit from mandating both adequate cross-sectional imaging and an attempt at tissue biopsy before a stricture is labeled indeterminate. This more focused definition may help decrease the heterogeneity of future studies and allow improved delineation of the true prevalence and etiologies of indeterminate strictures. For strictures without progression for at least 6 months, no mass on imaging [including endoscopic ultrasound (EUS)] and adequate tissue sampling with benign results, the authors suggest that a stricture be classified as benign. They do advise caution in patients with suspected primary sclerosing cholangitis (PSC), based on a prospective study (9) of 53 PSC patients undergoing cholangioscopy, demonstrating that cholangiocarcinoma was diagnosed as late as 35 months in some patients.

In their second and third statements, the authors advocate the use of both visualization and cholangioscopy-directed sampling on the first round of ERCP as a means to reduce the number of required procedures for diagnosis. These recommendations were supported by the majority of the author panel and are both based on IB level evidence (evidence from at least 1 randomized control trial (RCT) or meta-analysis using RCTs and non-RCTs). Visual evaluation of biliary strictures has been shown to be highly sensitive (10) yet lacks the specificity of biopsies. The addition of biopsies helps increase the specificity while maintaining the high sensitivity. Tumor vessel in particular appears to be the most agreed-upon characteristic visual finding that suggests malignancy. Kim *et al.* reported that visualization of a tumor vessel had a sensitivity of 61% for the detection of malignancy and combination with cholangioscopy-guided biopsy increased sensitivity to 96% (11). Acknowledging the high sensitivity and specificity of cholangioscopy, the authors recommend cholangioscopy at the time of initial ERCP. In making that recommendation, the authors refer to a study by Deprez *et al.* showing that cholangioscopy decreased the number of procedures and costs compared to ERCP alone (12). However, it is worth noting that over half of the included 111 patients in the study had difficult biliary stones rather than indeterminate strictures and the cost benefits were smaller in the indeterminate stricture population. The authors appropriately recognize that costs associated with both hospital stay and the cholangioscopy system in each country or health system will strongly influence the timing of cholangioscopy as first or second line. In addition to whether cholangioscopy is used first or second line, consideration should be given to the cholangioscopy platform used in different markets. Current digital single operator per-oral cholangioscopes are single use devices that come at a high cost. On the other hand, slim gastroscopes used for direct cholangioscopy are more attractive in settings with limited financial resources.

As mentioned previously, several platforms exist for cholangioscopy, including percutaneous cholangioscopy, legacy 'mother-baby' dual operator systems, digital single operator per-oral cholangioscopy (POC) and direct per-oral cholangioscopy using slim gastroscopes. The newest generation single operator POC systems such as the SpyGlass DS (Boston Scientific Marlborough, MA, USA) and the eyeMAX (Micro-Tech Endoscopy, Nanjing, China) have made significant improvements in image quality compared to earlier versions. However, direct POC still offers unique advantages including improved image quality, the ability to use electronic chromoendoscopy (e.g., narrow band imaging) and a larger 2.2 mm therapeutic channel. As such, the authors support direct POC as the highest quality cholangioscopy platform in their fifth statement. Direct POC however is particularly challenging (13), with gastric looping limiting the ability of the endoscope to enter the biliary tree, and the larger diameter of the slim endoscope preventing advancement through narrow caliber ducts and/or strictures. Regardless of the platform used, distal indeterminate biliary strictures (i.e., those in the lower third of the main duct) continue to be challenging to diagnose via cholangioscopy. This is due to technical difficulties in maintaining the cholangioscope position in the distal bile duct as well as limitations in tip deflection related to angulation of the endoscope as it enters the distal duct. The authors recognize this in their 9th statement and suggest consideration of alternative modalities such as EUS-guided fine needle biopsies or percutaneous cholangioscopy in cases of distal bile duct strictures. It is important to note that in such cases, the addition of cytological analysis of biliary fluid obtained during cholangioscopy may increase diagnostic accuracy. Our group has previously demonstrated this in 35 patients where cytological analysis was added to standard visualization and biopsies, leading to an increase in sensitivity from 81% to 94% (14).

Finally, cholangioscopy related adverse events are discussed and the recommendation for prophylactic antibiotics is made by the authors given the increased risk of cholangitis. The instillation of large amounts of fluid during cholangioscopy may cause bilio-venous reflux of bacteria. In addition, the presence of the cholangioscope within the bile duct may prevent adequate drainage. In a prospective study of 60 cholangioscopy procedures up to

9% of patients developed post-procedural bacteremia and 7% had clinical cholangitis (5). Peri-procedural antibiotics are thus recommended and have been shown to reduce the risk of cholangitis to as low as 1% (15). Other risks such as pancreatitis have been shown to be comparable to ERCP without cholangioscopy (4).

All in all, these comprehensive guidelines, being the first on the topic, represent an important milestone in delineating the role of cholangioscopy in the diagnosis and management of indeterminate biliary strictures. While the statements made by the authors are supported by the best available evidence, they highlight the limited number of high quality, prospective studies on the topic. Future iterations may benefit from a stronger definition of indeterminate stricture, a guidance on the yield of repeat biopsies, comparative data on the diagnostic yield of different cholangioscopy platforms, and an increased focus on the cost-benefits of cholangioscopy as a first line modality. In the interim, the algorithmic approach proposed by the authors, combined with the clinical acumen of the endoscopist performing cholangioscopy will serve to simplify and streamline the approach to indeterminate biliary strictures.

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Footnote

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