Editorial Commentary

Enhancing diagnostic strategies for biliary strictures: an evolving landscape

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The diagnosis of patients with biliary strictures of undetermined etiology remains a significant challenge. Biliary strictures, whether benign or malignant, often present with similar clinical features and imaging findings. For patients, this uncertainty can lead to repeated laboratory and radiological tests, invasive procedures, as well as delayed treatment and considerable anxiety. The complexity of these cases necessitates the integration of multiple diagnostic modalities to enhance accuracy while balancing patient safety and resource utilization.

The recent ASGE guideline on the role of endoscopy in the diagnosis of malignancy in biliary strictures of undetermined etiology presents three key recommendations and emphasizes the importance of a multimodal approach to enhance diagnostic accuracy (1). It advocates for the integration of fluoroscopic-guided biopsy sampling with brush cytology during endoscopic retrograde cholangiopancreatography (ERCP), particularly for hilar strictures. Cholangioscopy is recommended for patients with non-distal biliary strictures or those who have undergone nondiagnostic ERCP without cholangioscopy. This technique requires specialized equipment and expertise, which limits its widespread availability. The guideline recommends endoscopic ultrasound (EUS) in combination with ERCP for patients with nondiagnostic ERCP results, particularly those with distal biliary strictures or exhibiting lymphadenopathy or metastasis. Despite the comprehensive nature of these recommendations, several limitations persist. The three recommendations are grounded in evidence of very low quality, and as such, they are recommended with certain conditions. Secondly, the guideline's application is constrained by the availability of endoscopic expertise and resources, particularly in non-tertiary settings. Additionally, the guideline underscores the importance of a multidisciplinary approach, involving collaborations with surgical and medical oncologists and interventional radiologists, to optimize patient care. Such collaboration is crucial, given the complexity of diagnosing and treating biliary malignancies.

The future of diagnosing indeterminate biliary strictures rests in the integration of advanced molecular diagnostic techniques and cutting-edge imaging technologies, aiming to enhance diagnostic accuracy while minimizing patient burden and healthcare costs. Molecular diagnostics, such as next-generation sequencing and liquid biopsy, hold promise for identifying malignancy at an early stage by detecting genetic alterations in brush or biopsy samples, or circulating tumor DNA in bile or blood samples (2). These techniques, though still in the early stages of clinical application, could potentially offer a non-invasive or minimally invasive alternative to traditional biopsy methods, providing rapid and precise diagnosis. Emerging endoscopic technologies, such as confocal laser endomicroscopy (CLE) (3) and optical coherence tomography (OCT) (4), also show potential in

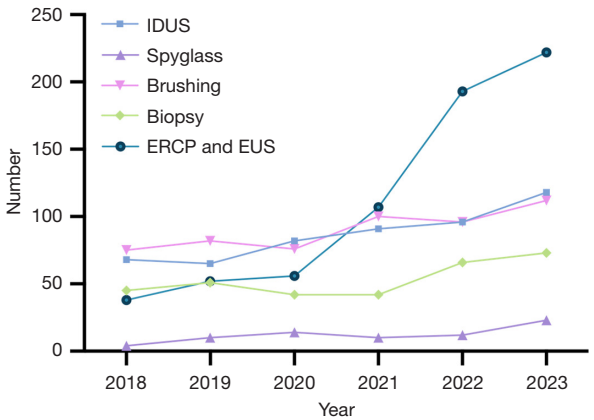

Figure 1 Endoscopic procedures to diagnose biliary stricture in Peking Union Medical Collage Hospital: from 2018 to 2023. IDUS, intraductal ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound.

enhancing the real-time evaluation of biliary strictures. CLE provides *in vivo* histological examination of the bile duct mucosa, offering a "virtual biopsy" that could reduce the need for multiple tissue samples. OCT, on the other hand, provides high-resolution cross-sectional imaging of the bile duct, which can help differentiate between benign and malignant strictures based on tissue architecture. These technologies, while promising, require further validation in larger clinical studies and are associated with high costs and technical demands, which may limit their immediate clinical adoption.

While advanced technologies hold great promise, optimizing traditional diagnostic methods remains crucial, especially in resource-limited settings. Enhancing the diagnostic yield of ERCP can be achieved through relatively simple modifications. For example, increasing the number of brushings during ERCP or employing novel brushes designed to obtain more cellular material can improve diagnostic sensitivity. A multicenter randomized controlled trial involving 443 patients demonstrated that brushing 30 times during ERCP significantly increased sensitivity compared to the standard 10 brushings (0.57 *vs.* 0.38, P=0.001), without increasing the risk of complications (5). A Chinese research team developed a novel rotating brush and conducted a multicenter prospective study, which found that the rotation *in situ* brush demonstrated higher sensitivity compared to conventional brushes (0.73 *vs.* 0.56, P=0.003) (6). Moreover, utilizing rapid on-site evaluation (ROSE) and liquid-based cytology (LBC) instead of conventional smear techniques can further enhance diagnostic accuracy. Studies have shown that LBC exhibits better sensitivity compared to traditional smears (0.78 *vs.* 0.56, P=0.009) while maintaining similar specificity (7). These improvements in cytological techniques are particularly important in cases where the clinical suspicion of malignancy is high, but initial sampling results are inconclusive. Intraductal ultrasound (IDUS) is also a valuable adjunct to ERCP, increasing its accuracy to 90% (8). Furthermore, selecting patients with specific clinical characteristics that make them more suitable for certain diagnostic modalities can also enhance diagnostic accuracy. Older age, larger mass size, longer stricture length, and higher serum total bilirubin have been recognized as predictors of positive yield in ERCP sampling (9-11). Biliary tract cancers are classified into three types: mass-forming, diffuse infiltrating, and intraductal growing. More real-world evidence is needed to guide the appropriate sampling methods for different types of cholangiocarcinoma. In patients with pancreatic cancer, strictures may be caused by extrinsic compression without bile duct invasion, making EUS with fine-needle sampling more appropriate than ERCP.

While the guideline represents significant progress, the diagnosis of biliary strictures remains a complex and evolving field. Traditional methods such as ERCP and brush cytology continue to play a central role, but the integration of advanced molecular diagnostics and novel imaging technologies offers the potential to significantly enhance diagnostic accuracy. It is essential to optimize existing techniques and adopt a multidisciplinary approach in order to improve patient outcomes. In recent years, the digestive endoscopy team at Peking Union Medical College Hospital has been promoting the application of IDUS, Spyglass, ERCP and EUS combined diagnosis, and other endoscopic techniques (*Figure 1*). As research and technology continue to advance, it is hoped that these innovations will lead to earlier and more accurate diagnoses, ultimately improving the prognosis for patients with biliary strictures.

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