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Review Article

Recent advances of diagnostic approaches for indeterminate biliary tract obstruction

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A B S T R A C T

Patients with indeterminate biliary stricture frequently pose a challenge in the clinical management. Discrimination between benign and malignant biliary strictures is important to prevent the morbidity and mortality associated with incorrect diagnoses. Traditional tissue sampling using endoscopic retrograde cholangiography does not always produce a definitive diagnosis, with a considerable proportion of cases remaining as indeterminate biliary strictures. Recent advances in endoscopic and molecular techniques have the potential to improve the diagnostic and prognostic accuracy of biliary strictures. This article reviews various etiologies of biliary strictures and discusses the recent advances of diagnostic approaches for indeterminate biliary tract obstruction.

Keywords: Cholangioscopy; Confocal laser endomicroscopy; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasound; Indeterminate biliary stricture

Introduction

Biliary stricture is often a diagnostic dilemma in which the underlying cause cannot be determined even after extensive evaluation. Such biliary stricture is referred to as “indeterminate biliary strictures” and presents a therapeutic dilemma for clinicians involved in management. Various differential diagnoses exist for indeterminate biliary tract obstruction, including benign or malignant lesions. Diagnosis of indeterminate biliary tract obstruction includes physical examination, laboratory tests, imaging techniques, and endoscopic procedures. Despite advances in less invasive imaging techniques such as transabdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), endoscopy plays an essential role in accurate diagnosis, including histological diagnosis. Imaging findings and brush cytology and/or forceps biopsy fluoroscopic guidance with endoscopic retrograde cholangiopancreatography (ERCP) is widely used as a standard for diagnosing biliary strictures. However, ERCP cannot provide an intraluminal view of biliary tract lesions and the results are unsatisfactory. Recently, oral cholangioscopy, confocal laser endoscopy, endoscopic ultrasound (EUS), and EUS-guided fine-needle aspiration (FNA) and/or biopsy were reported to be useful for indeterminate biliary strictures. The appropriate endoscopic method should be selected according to the patient’s condition, lesion, and endoscopist. The discovery of recent advanced endoscopic modalities, and multimodal evaluations could improve diagnostic yields. Although the majority of indeterminate biliary strictures have a malignant origin, 20% of indeterminate biliary strictures are benign.[1,2] In addition, up to 25% of initially classified malignant strictures were found to be benign after surgical resection.[3,4] High diagnostic accuracy is the goal in order not to delay correct treatment or to avoid unnecessary surgery.

Etiology of Biliary Strictures

A broad differential diagnosis exists between benign and malignant conditions (Table 1). The etiology of benign biliary strictures is diverse. Benign biliary strictures are caused by primary sclerosing cholangitis (PSC), immunoglobulin G4-related cholangitis, bile duct stones, infection, ischemia related to surgical interventions, or iatrogenic injury. The most frequent benign causes are iatrogenic and secondary to biliary injury after chole-

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cystectomy or liver transplantation.[1] In contrast to the variety of benign causes that can lead to biliary strictures, the two primary causes of malignant biliary strictures are cholangiocarcinoma and pancreatic adenocarcinoma. Pancreatic adenocarcinoma should be suspected in patients with distal common bile duct strictures regardless of whether a mass is identifiable on cross-sectional imaging. By contrast, cholangiocarcinoma is more likely in patients with mid and proximal bile duct strictures than those with distal strictures. Rare causes include metastatic cancer, hepatocellular carcinoma and extrinsic compression by large periportal lymph nodes or extension of gallbladder and ampullary tumors into the biliary tree.

Endoscopic Modalities

Various endoscopic methods are available for the diagnosis and evaluation of indeterminate biliary tract strictures are described below.

Endoscopic retrograde cholangiopancreatography/intraductal ultrasound/brush cytology and forceps biopsy

ERCP is still the most widely used diagnostic method for the evaluation of biliary strictures. When performing ERCP, interpretation of cholangiographic results is the first step. It allows precise differentiation of benign and malignant biliary strictures by accurately defining the location, extent, and morphology of biliary strictures.[5] Malignant strictures are suggested when the cholangiography shows strictures that are longer than 10 mm, asymmetric, and irregular. Benign strictures are suggested when cholangiography shows short, regular, and symmetric strictures. Using these criteria, the diagnostic sensitivity and specificity for cholangiography findings were reported to be 74% and 70%, respectively.[6] After cholangiography, intraductal ultrasound (IDUS) is performed to evaluate the main lesion. This technique makes use of a wire-guided thin ultrasound probe that can be inserted into the biliary tract without sphincterotomy. Mechanical rotation of the probe permits a cross-sectional view of the bile duct. When inserting the IDUS probe into the bile duct, some cases are difficult due to the tension in the sphincter of Oddi. In such cases, endoscopic sphincterotomy may be performed. When inserting the IDUS catheter over the stricture, balloon dilation may be performed to pass the stricture. However, it should be limited for mandatory cases where investigation of proximal superficial extension is required because it might damage the main lesion. IDUS can be used to identify superficial expansions from major lesions or vascular invasion.[7,8] In a large retrospective study, a sensitivity of 93.2%, a specificity of 89.5%, and an accuracy of 91.4% for the assessment of malignant strictures were reported.[9] Malignant suggestive features include the presence of a sessile tumor, an interrupted wall structure, and a tumor size > 10 mm.[7] IDUS was diagnostically superior to endoscopic transpapillary biopsies, EUS, and CT in detecting malignant biliary strictures. The sensitivity and specificity of IDUS in this study were determined to be 93% and 89%, respectively.[10] A major limitation of earlier IDUS was the inability to obtain biopsies for pathologic diagnosis. More recently, transpapillary biopsies have been performed under IDUS guidance. Kim et al[11] performed a prospective comparative study that showed that IDUS-guided transpapillary biopsy has a higher diagnostic accuracy than fluoroscopic-guided transpapillary biopsy for the diagnosis of malignant biliary strictures (90.8% vs 76.9%; $P = 0.027$). IDUS may play a role in evaluating indeterminate biliary strictures; however, previously placed stents can produce acoustic interference, reducing the diagnostic yield of IDUS. Although cholangiography or IDUS findings provide information on whether biliary strictures are benign or malignant, these methods alone are difficult to make a definitive diagnosis. To make a definitive diagnosis, brush cytology/intraductal forceps biopsy under fluoroscopic guidance using ERCP is still gold standard. Obtaining a specimen of adequate cellularity is essential for the evaluation of any potential malignancy. Brush cytology is more commonly performed because it is easier and associated with fewer complications.[12] Conversely, intraductal forceps biopsies provide greater microarchitecture detail, but require sphincterotomy and can be challenging in narrow bile ducts.[13] Brushing to obtain cytologic material involves advancing a brush with its catheter sheath through the endoscope into the biliary tree, generally over the guidewire. The device is advanced to the proximal part of the stricture, then the brush is advanced from the catheter, withdrawn slightly, and moved back and forth across the stricture approximately 15 times. The brush is then withdrawn into the catheter, and the device is withdrawn from the endoscope. The brush can be smeared onto glass slides, cut off from the device and placed into a fixative solution, or both. Forceps biopsy is more time consuming and more technically challenging than brush cytology because it is sometimes difficult to insert thick forceps into the bile duct and grasp a targeted specimen. However, it could provide a sample of bile duct tissue from deep in the epithelium, which is expected to improve diagnostic yield compared with brush cytology. The biopsy forceps are thicker than an ERCP catheter so it could be difficult to insert them into the bile duct. Difficult cannulation has been identified as a risk factor of post-ERCP pancreatitis. Therefore, it may be better to perform sphincterotomy in advance to facilitate biliary cannulation using biopsy forceps to prevent post-

Table 1 Etiology of Biliary Strictures

Variable	Cause
Benign cause	Iatrogenic
	Cholecystectomy
	Liver transplantation
	Autoinflammatory
	Primary sclerosing cholangitis (PSC)
	Immunoglobulin G4-related cholangitis
	Sarcoidosis, Eosinophilic cholangitis, Mast cell cholangitis, Histiocytosis X
	Choledocholithiasis (Mirizzi syndrome)
	Chronic pancreatitis
	Infectious (tuberculosis, viral, parasitic, HIV cholangiopathy)
	Vascular (vasculitis, ischemic cholangiopathy)
	Others (trauma, chemotherapy, post radiation therapy)
Malignant cause	Pancreatic adenocarcinoma
	Cholangiocarcinoma
	Gallbladder cancer
	Ampullary adenocarcinoma
	Hepatocellular carcinoma
	Metastatic disease/cancer
	Lymphoma

ERCP pancreatitis. Under fluoroscopic guidance, the forceps are advanced to the part of the stricture, opened, and then closed to grasp a specimen from the distal aspect of the stricture. The diagnostic advantage of intraductal biopsies over cytology brushings has also not been demonstrated. A meta-analysis reported that the pooled sensitivity and specificity of the brush cytology for the diagnosis of biliary strictures was 45% and 99%, respectively,[14] whereas forceps biopsy had a pooled sensitivity and specificity of 48.1% and 99.2%, respectively. Although forceps biopsy may have better sensitivity than brush cytology, these results have an insurmountable limit under fluoroscopic guidance. Combining the two modalities increased the sensitivity marginally to 59.4% with a specificity of 100%.

Endoscopic ultrasound and endoscopic ultrasound-guided fine-needle aspiration/biopsy

EUS can differentiate between benign and malignant strictures by allowing sonographic visualization of the biliary tract along with the surrounding viscera including the pancreas. EUS is an ultrasound technique in which a high-frequency transducer is mounted at the end of an endoscope. Regarding detection of malignant biliary stricture, EUS without FNA was found to provide a sensitivity of 78% and specificity of 84%.[15] Another study proved that EUS was superior for the detection of malignancies compared to CT and MRI (94%, 30%, and 42%, respectively).[16]

Regarding adverse events, EUS, especially for observation purposes, can avoid pancreatitis, which is mainly problematic for ERCP. EUS-FNA is the established diagnostic modality to obtain specimens, particularly of pancreatic tumors.[17] EUS-FNA enables the acquisition of histological evidence of cancer when chemotherapy is being considered to distinguish benign or malignant tumors when deciding whether surgery or follow-up is needed, and assessment of the degree of progression of malignant tumors when unexplained lymph node swelling is detected. A recent meta-analysis established the pooled sensitivity and specificity of EUS-guided FNA in the diagnosis of malignant biliary strictures to be 80% and 97%, respectively. When the location of the biliary stricture was taken into consideration, EUS-guided FNA of distal strictures had a higher sensitivity (83%) than that of proximal strictures (76%); however, there was no difference in specificity.[18] At present, the most frequently used needle sizes are 22 gauge and 25 gauge. In a recent meta-analysis, it was reported that the mean sensitivities of ERCP and EUS-FNA for the diagnosis of malignant biliary strictures were 49% and 75% while specificities were 96% and 100%, respectively.[19] EUS-FNA might offer a safer alternative to ERCP. With the recent progress of needles, the fine-needle biopsy (FNB) device, which was designed primarily to obtain core tissue samples, was introduced to overcome the FNA sampling material limitation.[20] A recent randomized cross-over trial demonstrated that EUS-guided FNB had considerably higher diagnostic yield and specimen adequacy than FNA.[21] In a recent meta-analysis comparing FNA with FNB needles, FNB provided a higher pooled diagnostic accuracy, tissue core rate, and allowed diagnosis with fewer passes in both pancreatic and nonpancreatic lesions.[22] Although there were no reports using FNB needles regarding the biliary tract, FNB needles have the potential to increase the diagnostic accuracy. Hence, studies regarding EUS-FNB use for the biliary tract are warranted. Recently, increasing case reports of needle tract seeding following EUS-FNA/FNB are emerging. In a recent review regarding needle tract seeding following EUS-FNA/FNB, 33 patients (27, pancreatic cancer; 6, others) with needle tract seeding following EUS-FNA/FNB have been reported up to January 2020.[23] Although there were no reports regarding the biliary tract, needle tract seeding could be caused. Thus, EUS-FNA should not be performed when it does not guide treatment selection.

Cholangioscopy

As described above, ERCP is the gold standard for diagnosing biliary strictures. However, ERCP does not provide an intraluminal view of biliary strictures. Direct visualization of the bile duct can be achieved using peroral cholangioscopy (POCS). Moreover, it can perform targeted biopsies of the site of interest. The traditional "mother–baby" POCS requires two endoscopists, with one operating the cholangioscope, while the second endoscopist controls the duodenoscope. The limitations of this system are the need for two operators, baby scope fragility, and time consumption. The development of single-operator cholangioscopy (SOC) has recently led to a resurgence of interest in the use of this technique. Over the past decade, SOC (SpyGlass™ Direct Visualization System; Boston Scientific, Marlborough, MA, USA) has been widely utilized with disposable fiberoptic technology.[24] The setup of SOC is easy; only one operator is needed, four-way tip deflection is allowed, and targeted biopsies and therapeutic procedures such as lithotripsy can be performed. Nowadays, the new digital SOC with high-resolution digital technology (SpyGlass DS™ Direct Visualization System) provides improved image quality and maneuverability of the catheter tip.[25] The system consists of a 10.8-Fr catheter. The POCS is generally advanced over a guidewire into the bile duct through the working channel of a duodenoscope. Before insertion, sphincterotomy is generally performed. The working channel (1.2-mm diameter in SOC) allows the passage of accessory devices and aspiration. POCS findings are defined as either malignant or benign according to the previous reports.[26–29] Malignant findings include: (i) irregular thick tortuous vessels, (ii) oozing, (iii) irregular papillogranular surface, and (iv) a nodular elevated surface such as a submucosal tumor. Benign findings include: (i) a fine network of thin vessels and a flat surface with or without shallow pseudodiverticula; (ii) a lower homogeneous papillogranular surface without primary masses, suggesting hyperplasia; (iii) a bumpy surface with or without pseudodiverticula, suggesting inflammation; and (iv) a white surface with a convergence of folds, suggesting scarring. Cholangioscopic inspection of the epithelium may provide macroscopic clues pertaining to malignancy. Any intraductal masses, nodules, or ulcerations should prompt direct biopsies from the region. The presence of a "tumor vessel," an irregular, dilated, and tortuous vessel, is considered a reliable feature of biliary malignancy.[29] A meta-analysis performed by Sun et al[30] demonstrated that visual inspection alone using cholangioscopy is useful for detecting biliary malignancy, with pooled sensitivity and specificity of 90% and 87%, respectively. However, confirmation using cholangioscopic-directed biopsies is still needed, which has an overall sensitivity and specificity of 69% and 98%, respectively. Despite good outcomes, the visual criteria for malignancy are not yet fully established, and there is significant inter observer variation in interpretation of POCS visualization. These variations can be misleading and may result in false-positive malignant diagnoses. Therefore, definite pathological confirmation is important for a definitive diagnosis of indeterminate biliary strictures.

In a meta-analysis regarding POCS procedures, overall and serious adverse event rates of 7% and 1%, respectively, were reported.[31] When performing POCS, we must be mindful that cholangitis could be caused by an increase in intraductal pressure due to water irrigation during the procedure. Therefore, it is necessary to

use antibiotic prophylaxis and perform biliary drainage to prevent cholangitis. Cholangioscopy has been assessed by many studies to be a safe procedure even in elderly and comorbid patients.[32,33] Despite its diagnostic utility, the uptake of cholangioscopy has been relatively limited in many endoscopy centers. Many endoscopists perceive the procedure to be technically difficult, as it requires mastery in ERCP while concurrently operating the cholangioscope through the working channel. Nonetheless, studies have demonstrated a relatively quick learning curve with reportedly only 10 procedures needed to gain proficiency.[34,35] Further research and development in cholangioscopy may increase the uptake of this technique in the future.

Confocal laser endomicroscopy

In addition to the direct or indirect methods to evaluate the bile duct changes already mentioned above, confocal laser endomicroscopy (CLE) is a real-time microscopy providing histopathological diagnoses of biliary diseases. CLE is an endoscopic imaging technique that can provide *in vivo* histological assessment in real-time, known as "virtual biopsy." This technique is performed using a catheter probe that is inserted through the working channel of an endoscope (probe-based CLE, pCLE) or FNA equipment (needle-based CLE). The probe is advanced into the biliary system and the patient is injected with a contrast agent such as fluorescein, which extravasates into the biliary vasculature, highlighting the epithelial and subepithelial structures.[36] pCLE (CholangioFlex, Cellvizio; Mauna Kea Technologies, Paris, France) has been cited in the recent American Society for Gastrointestinal Endoscopy guidelines for the management of biliary neoplasia as a useful alternative to the existing diagnostic work up.[37] pCLE is performed under fluoroscopy guidance or direct view with POCS during ERCP. The CholangioFlex pCLE probe is designed to obtain *in vivo*, real-time, microscopic images of the bile duct during ERCP procedures. The probe has a diameter of 0.94 mm, a field of view of 325 μm, and a lateral resolution of 3.5 μm. Each probe provides images from 40 to 70 μm below the tissue surface. The confocal probe is advance the working channel of the POCS and gently applied to the part of interest to carry out confocal imaging at 12 frames per second. Intraductal images are recorded and saved to a computer unit connected to the probe. Although pCLE can be performed both under fluoroscopy guidance or direct view with POCS, the pCLE findings under direct view with POCS can be accurately matched with biopsy tissue. Therefore, these results could be diagnostically more reliable.[38,39] The Miami classification was initially created to differentiate malignant and benign tumors.[40] The criteria for the diagnosis of malignancy are listed as follows: (1) thick white bands (> 20 μm), (2) thick dark bands (> 40 μm), (3) dark clumps, and (4) epithelium. The criteria for the diagnosis of benign lesions are as follows: (1) a reticular network of thin dark branching bands (20 μm), (2) a light-gray background, and (3) blood vessels (< 20 μm). CLE and the Miami classification have demonstrated better sensitivity but poorer specificity than traditional histology in the evaluation of biliary strictures. The low specificity has been attributed to changes induced by chronic inflammation or procedures performed during ERCP, such as cytology brushing.[38] To address this issue, the Paris classification[41] was created to differentiate between benign inflammatory strictures and malignant strictures. The presence of vascular congestion, increased inter glandular space, thickened reticular structures, and a granular pattern with scales are all features indicative of inflammatory biliary strictures. Results from early studies exploring the use of CLE in the diagnosis of biliary strictures suggested an optimistic future. In a recent meta-analysis determined that the pooled sensitivity and specificity of CLE in discriminating between benign and malignant biliary strictures were 87% and 76%, respectively.[42] When used in combination with tissue sampling, the sensitivity and specificity increased to 93% and 82%, respectively.[42] However, the uptake of CLE has been slow. This may be because the procedure is technically difficult, as it requires probe stability to ensure high-quality images. Furthermore, a high interobserver variability to the classification system and expensive acquisition and running costs are limitations of the CLE for the implementation in the routine. Further studies are needed to confirm these findings. Currently, CLE is practiced at only a few specialized centers and requires further validation to consolidate its place in clinical practice.

Molecular Diagnostics

Fluorescence in situ hybridization

Fluorescence *in situ* hybridization (FISH) is a cytological technique that correlates chromosomal aneusomy with malignancy. FISH enables the radioactive labeling of nucleic acid sequences using single-stranded DNA probes. Chromosomal aneuploidies such as numerical or structural aberrations can indicate cancer karyotypes, so that the technique can also be used in the diagnosis of unclear bile duct strictures. It has been estimated that approximately 80% of pancreaticobiliary cancers have some sort of chromosomal aneuploidy or polysomy.[43] This technique makes use of fluorescently labeled DNA probes to detect aneuploidy associated with malignant biliary strictures. Usually kits with probes for chromosomes 3, 7, 9, and 17 are utilized and the samples can be obtained with an ordinary brush cytology. Multiple studies have demonstrated that FISH can increase the sensitivity of cytology brushing while preserving specificity. The recent study that performed a retrospective analysis of 30 consecutive patients who underwent both routine cytology and FISH performed at a tertiary care center. When used independently, routine brush cytology had a higher sensitivity (53.8% vs 30.8%) but a lower specificity (82.4% vs 100%) than FISH. However, when the FISH results were interpreted in cases of negative or atypical cytology findings, the sensitivity of brush cytology improved from 53.8% to 69.2% without compromising specificity.[44] A well-studied aspect of FISH is the detection of cholangiocarcinoma in PSC. PSC can be difficult to distinguish from cholangiocarcinoma because these two conditions can have similar imaging features. In such cases, FISH can be used to determine whether cholangiocarcinoma progression has occurred. A meta-analysis of eight studies involving 828 patients demonstrated that the pooled sensitivity and specificity for the diagnosis of cholangiocarcinoma in PSC were 68% and 70%, respectively.[45] These results showed that FISH increases the sensitivity of tissue sampling only slightly in PSC. However, the high cost of FISH has prompted some endoscopists to be selective in using this tool for detecting malignancies.[46] FISH is not recommended as a screening tool for all patients with PSC but should be considered if the suspicion of malignancy remains high after an inconclusive brush cytology.

Next-generation DNA sequencing

A promising technology is the next-generation sequencing (NGS) with the detection of cholangiocarcinoma-associated mutations from bile duct biopsies and brush cytology. It allows for the rapid and simultaneous sequencing of genetic material on a

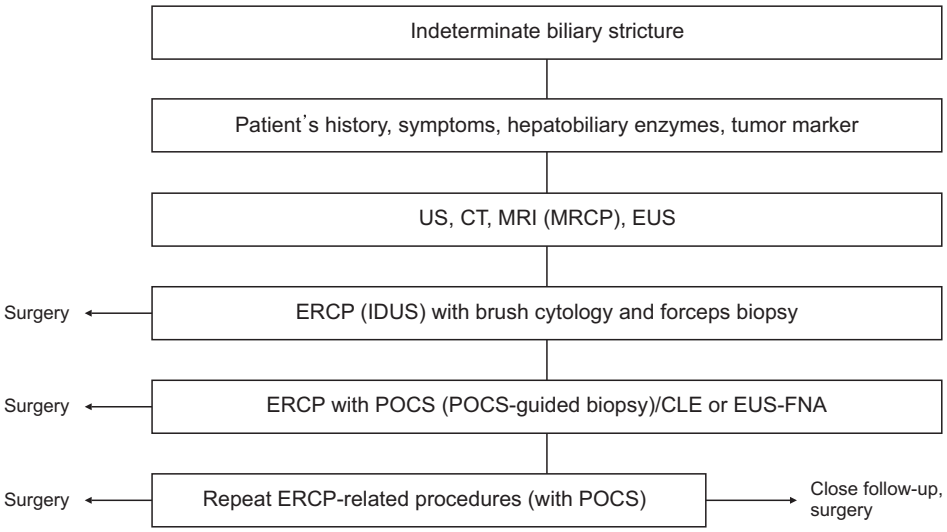

Fig. 1. Diagnostic algorithm for indeterminate biliary strictures. US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasound; POCS, peroral cholangioscopy; CLE, confocal laser endomicroscopy; FNA, fine-needle aspiration.

single medium or surface.[47,48] This method can potentially increase the sensitivity of the histology or cytology and thus represents a good and technically simple addition. In a recently published study with 252 patients, the combination of NGS and histology achieved a sensitivity of 83% with a specificity of 99%.[48] Due to the increasingly broader and more cost-effective application of panel sequencing, implementation in routine diagnostics appears possible in the future. Although further studies are required, it has the potential to diagnose biliary strictures and identify targetable genomic alterations.

Diagnostic Process for Biliary Strictures

We discussed the diagnostic process using endoscopy for indeterminate biliary strictures. Various modalities using endoscopy for the diagnosis of biliary strictures have been reported, and their capabilities have improved. We propose the diagnostic algorithm (Fig. 1). First of all, noninvasive evaluation such as taking the patient's history, examining the patient's symptoms, hepatobiliary enzymes, and tumor markers should be performed. Second, cross-sectional imaging such as US, CT, and MRI (magnetic resonance cholangiopancreatography, MRCP) should be performed. EUS imaging is also useful at the same time. Third, an ERCP-related procedure should be performed. As we showed, POCS findings and POCS guided biopsy/CLE provide better outcomes than ERCP under fluoroscopic guidance. However, as POCS and CLE are too expensive to use in the first instance, ERCP (IDUS) with brush cytology and forceps biopsy should be performed first. If the ERCP with brush cytology and forceps biopsy is positive, surgery should be performed. If the stricture remains indeterminate, ERCP with POCS (POCS-guided biopsy)/CLE should be performed. Although EUS-FNA may be performed at this time, we must take into consideration that seeding could be caused. If the stricture remains indeterminate, repeat consideration should be made for repeat ERCP with brushings, POCS with biopsies, and pCLE. If the stricture remains indeterminate even though repeat procedures were performed and suspicion for malignancy remains high, close follow-up or surgery might be considered. Although progress has been made regarding endoscopic procedures, further improvement is needed.

Conclusions

Despite recent advances in endoscopic techniques, the assessment of biliary strictures is still difficult. The diagnosis of biliary strictures may be aided by advances in cytopathological staining and imaging practices. Therefore, a multidisciplinary approach involving endoscopists, surgeons, pathologists and radiologists is necessary to provide a holistic direction for diagnosis. To accurately distinguish indeterminate biliary strictures, clinicians must adjust their decisions based on the clinical condition of the individual patient. In addition, an appropriate endoscopic method is selected according to the patient's condition, lesion, and endoscopist.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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