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Advanced endoscopic imaging of indeterminate biliary strictures

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Abstract

Endoscopic evaluation of indeterminate biliary strictures (IDBSs) has evolved considerably since the development of flexible fiberoptic endoscopes over 50 years ago. Endoscopic retrograde cholangiography pancreatography (ERCP) was introduced nearly a decade later and has since become the mainstay of therapy for relieving obstruction of the biliary tract. However, longstanding methods of ERCP-guided tissue acquisition (*i.e.*, biliary brushings for cytology and intraductal forceps biopsy for histology) have demonstrated disappointing performance characteristics in distinguishing malignant from benign etiologies of IDBSs. The limitations of these methods have thus helped drive the search for novel techniques to enhance the evaluation of IDBSs and thereby improve diagnosis and clinical care. These modalities include, but are not limited to, endoscopic ultrasound, intraductal ultrasound, cholangioscopy, confocal endomicroscopy, and optical coherence tomography. In this review, we discuss established and emerging options in the evaluation of IDBSs.

Key words: Cholangiocarcinoma; Bile duct diseases; Cholangiopathies; Gastrointestinal endoscopy; Pancreatic adenocarcinoma

Core tip: Indeterminate biliary strictures (IDBSs) remain a considerable challenge for endoscopists, clinicians, surgeons, and other medical professionals as well as patients. The limitations of current technologies have helped drive the search for novel techniques aimed to enhance the evaluation of IDBSs and thus improve diagnosis and clinical care. Here we review existing and emerging techniques and provide a synopsis of current understanding of their strengths, limitations, and role in the evaluation of IDBSs.

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INTRODUCTION

A substantial proportion of biliary strictures cannot be classified as benign or malignant on the basis of non-invasive imaging, endoscopic retrograde cholangiopancreatography (ERCP), and/or routine tissue sampling methods (*i.e.,* biliary brushing, intraductal forceps biopsy)[1]. Although the addition of fluorescence *in situ* hybridization (FISH) to conventional biliary cytology has been useful in assessing strictures with a higher suspicion for malignancy which may benefit from closer follow-up, sensitivity remains low. As a result, these "indeterminate biliary strictures" (IDBSs) remain a clinical challenge, especially when considering the resulting delayed diagnosis, deferred implementation of care, economic impact from repeated evaluations, and resulting angst among patients, clinicians, and endoscopists.

IDBSs may arise *de novo* or in patients with known chronic biliary disease. They typically manifest with (abrupt onset or slowly progressive) jaundice, pruritus, right upper quadrant pain, and/or cholangitis. IDBSs may also be incidentally discovered, often following abdominal computed tomography or magnetic resonance imaging performed for other indications. The differential diagnosis of IDBSs is broad (Table 1), and determination of the underlying etiology and pathobiology is often challenging. Endoscopic evaluation of IDBSs has traditionally consisted of ERCP, but several other ancillary techniques have been developed to help address this common diagnostic challenge.

In this article, we review these ancillary techniques, providing our current understanding of their strengths, limitations, and role in the evaluation of IDBSs.

ERCP

ERCP provides fluoroscopic images of the biliary tree and provides the primary portal for diagnosis and intervention. Cholangiographic features suggestive of a malignant stricture include length (> 14 mm), irregularity, abrupt shelf-like borders, presence of intraductal polypoid or nodular areas, and the presence of simultaneous common bile duct (CBD) and pancreatic duct dilation (*i.e.,* double duct sign)[2,3]. Efforts to improve the sensitivity of cholangiography have led to methods for tissue acquisition; however, conventional methods such as biliary brush cytology, intraductal biopsy, and fine needle aspiration (FNA) have yielded disappointingly low sensitivity for detecting malignancy. For example, a recent review of the literature that identified 16 studies reported an overall biliary brush cytology sensitivity of 42% with a negative predictive value (NPV) of 58%[4]. The poor sensitivity was attributed to sampling error, inadequate specimen (*e.g.,* due to desmoplastic reaction or biliary fibrosis), and/or difficult cytopathologic distinction of subtle differences between malignant and nonmalignant cells[5,6]. Biliary cytopathology interpretation is often challenging, even within high-volume centers. A recent meta-analysis by Navaneethan *et al*[7] compared the effectiveness of brush cytology and intraductal biopsy for evaluating biliary strictures; nine studies were included, and the pooled sensitivity and specificity for brushings was 45% and 99%, respectively, compared to 48% and 99% for intraductal biopsies, respectively. When the two modalities were combined, there was some incremental yield, with sensitivity improving to 59%[7]. Methods tested to potentially further increase the diagnostic sensitivity have included use of longer brush length, initial stricture dilation, and repeated brushing, with repeat brushing appearing to be most effective, albeit still with suboptimal results[8,9]. Intraductal FNA has also been associated with disappointing results, as data from five series (220 patients) demonstrated a sensitivity of 34%, in part perhaps due to technical challenges with performing intraductal FNA[10]. The suboptimal diagnostic performance of conventional tissue sampling techniques has provided the impetus for developing advanced cytologic methods such as FISH, digital image analysis (DIA), and flow cytometry, which are described further in a subsequent section.

A "dominant stricture" is a subtype of IDBS that arises in the setting of underlying primary sclerosing cholangitis (PSC) or other fibrosing cholangiopathies and may be loosely defined as a CBD stenosis of $\leqslant$ 1.5 mm or hepatic duct stenosis $\leqslant$ 1 mm in diameter[11]. Accurately detecting malignancy in the setting of PSC is especially critical given the 1560-fold increased risk of developing cholangiocarcinoma (CCA) in this cohort compared to the general population[12]. However, this imposes an even greater diagnostic challenge, as ERCP-guided approaches to tissue acquisition have performed poorly in this disease, with sensitivity ranging from 18%-40%[11,13,14]. Reasons for low sensitivity include but are not limited to periductal (or submucosal) as opposed to radial growth of some CCAs, desmoplastic reaction, and inadequate access of endoscopic devices and sampling under indirect visualization (chiefly due to the stenotic nature of the disease)[15]. Adjunctive modalities for endoscopic evaluation of IDBSs in this high-risk subset of patients may provide improved diagnostic value and are discussed below in their respective sections.

ADVANCED CYTOLOGIC TECHNIQUES FOR ERCP-ACQUIRED BILIARY BRUSHING SPECIMENS

Fluorescence in situ hybridization

FISH is a cytogenic technique that employs fluorescently labeled DNA probes to chromosomal loci of interest

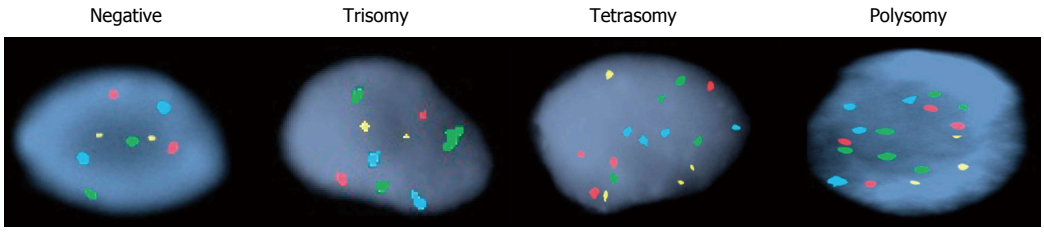

Figure 1 Representative fluorescence *in situ* hybridization microscopic image. Shown above are individual cells from biliary brushings showing distinct fluorescence *in situ* hybridization (FISH) results (arranged from lowest to highest risk of malignancy) using centromere enumeration probes (CEPs) to chromosomes 3 (red), 7 (green), 17 (aqua) and the 9p21 locus (gold). Potential FISH results include negative (two copies of each probe), trisomy 7 (≥ 10 cells with ≥ 3 CEP 7 signals and ≤ 2 signals for the other probes), tetrasomy (≥ 10 cells with four signals for all four probes), and polysomy (≥ 5 cells with ≥ 3 signals for ≥ 2 of the four probes).

Table 1 Potential etiologies of indeterminate biliary stricture

Benign
Primary sclerosing cholangitis
IgG4-associated cholangiopathy
Postoperative stricture (anastomotic, ischemic, cholecystectomy-related)
Ischemia (*e.g.*, hepatic artery thrombosis)
Infections (HIV cholangiopathy, parasites)
Pancreatitis (acute, chronic, autoimmune)
Choledocholithiasis
Mirizzi syndrome
Eosinophilic cholangitis
Vasculitis
Radiation
Portal biliopathy
Malignant
Pancreatic adenocarcinoma
Cholangiocarcinoma
Hepatocellular carcinoma
Lymphoma
Metastatic adenocarcinoma (*e.g.*, compressive lymphadenopathy)

HIV: Human immunodeficiency virus.

and thereby reveals losses or gains in these specific loci (*i.e.,* aneuploidy). Fluorescence microscopy is then used to quantify cells containing nuclei with abnormal probe signal numbers (Figure 1). The presence of ≥ 5 such cells showing gains of ≥ 2 of the (currently four) probes on FISH analysis, *i.e.,* polysomy, has been found to provide improved sensitivity compared to cytology while maintaining comparable specificity[16-20]. Recent studies have reported that incorporating 9p21 (*i.e.,* CDKN2A locus, critical in cell cycle progression and senescence[21,22]) deletion into the diagnostic criteria further improves the sensitivity to 76%-89%[23,24]. In individuals with PSC, detection of polysomy during subsequent ERCPs (*i.e.,* serial polysomy) or detection of polysomy in multiple segments of the biliary tree (*i.e.,* multifocal polysomy) appears to denote even greater risk of CCA[25,26].

DIA

DIA incorporates digital conversion and computer analysis to quantify nuclear DNA content and evaluate nuclear features; when compared to conventional cytology, it has been shown to have a higher sensitivity (39% *vs* 18%) but at the expense of lower specificity (77% *vs* 98%)[27]. In two studies comparing DIA with FISH, DIA appeared to have slightly lower sensitivity (38%-43% *vs* 44%-45%) and specificity (92%-95% *vs* 98%-100%). In one of the studies, routine cytology had a sensitivity of 15% and specificity of 100%, whereas in the other, DIA and FISH were performed only after negative cytology and histology[16,18]. Moreover, multivariable analysis of advanced cytologic methods in the evaluation of IDBSs showed FISH polysomy to be an independent predictor of malignancy, whereas DIA was not[19]. Despite the somewhat enhanced diagnostic sensitivity, the associated decrement in specificity has eliminated the use of DIA in many centers.

Flow cytometry

Flow cytometry relies on the detection of hyperploidy to identify malignant cells; it has similar sensitivity to routine cytology (42%) but has inferior specificity (77% *vs* 92%)[28]. It is not routinely used in the clinical evaluation of IDBSs.

ENDOSCOPIC ULTRASOUND

Endoscopic ultrasound (EUS) is increasingly being utilized in the evaluation of biliary strictures since reports of its first application in the mid-1980s[29,30]. Most of the hepatobiliary system can be examined with curvilinear echoendoscopy (EUS) from the gastric antrum (for visualization of the gallbladder), duodenal bulb (for visualization of the mid-CBD up to the confluence of the left and right hepatic ducts), or second portion of the duodenum (for visualization of the periampullary region)[31,32]. In addition, EUS provides other key information, including lymph node (Figure 2A), portal vein, and hepatic artery status for staging and through the detection of malignant ascites, omental deposits, and hepatic metastasis. Furthermore, EUS-guided FNA (Figure 2B) offers a minimally-invasive means for diagnostic tissue sampling (Table 2).

EUS with or without FNA may be useful in distinguishing malignant from benign biliary strictures. EUS findings of a pancreatic head mass (causing a biliary stricture secondary to extrinsic compression), an irregular outer edge of the bile duct wall, or bile duct wall thickness > 3 mm have been associated with malignancy when

Table 2 Comparison of advanced endoscopic imaging modalities

	Advantages	Disadvantages
ERCP	Widely available	Procedural risks
	Workhorse technique with numerous accessories	Fluoroscopic (and endoscopic) images only
	Facilitates other diagnostic modalities (*e.g.*, biliary brushing, biopsy, endomicroscopy) as well as therapy	Low sensitivity of conventional cytology and intraductal biopsies
EUS	Provides staging information	Limited views of the intrahepatic biliary tree (and non-visualization of the right intrahepatic ductal system)
	Permits FNA	Generally nondiagnostic in and of itself without FNA
	Can facilitate difficult biliary cannulation	Risk of tumor seeding if FNA primary tumor
IDUS	Can help direct ERCP-guided tissue acquisition	Limited depth of imaging
		Infrequently used in routine practice
Cholangioscopy	Excellent visualization of the biliary mucosa (with digital cholangioscopes)	High cost (disposable system $2000 per case)
	May improve sensitivity, specificity, and overall accuracy compared to ERCP alone	Likely higher rates of pancreatitis, cholangitis, and perforation compared to ERCP alone
		Time-consuming
		Not widely available
CLE	Excellent sensitivity and negative predictive value	Marginal interobserver agreement
	Provides imaging at a cellular and sub-cellular level (lateral resolution of 3.5 μm)	Contact imaging of a very limited regional surface
		Time-consuming
		Not widely available
OCT	High resolution	Suboptimal sensitivity
	Improved sensitivity compared to ERCP-guided tissue acquisition	Resolution not as high as CLE
	Highly specific	Not widely available
	Permits larger surfaces areas to be examined compared to CLE	Not well-validated

ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; IDUS: Intraductal ultrasound; CLE: Confocal laser endomicroscopy; OCT: Optical coherence tomography; FNA: Fine needle aspiration.

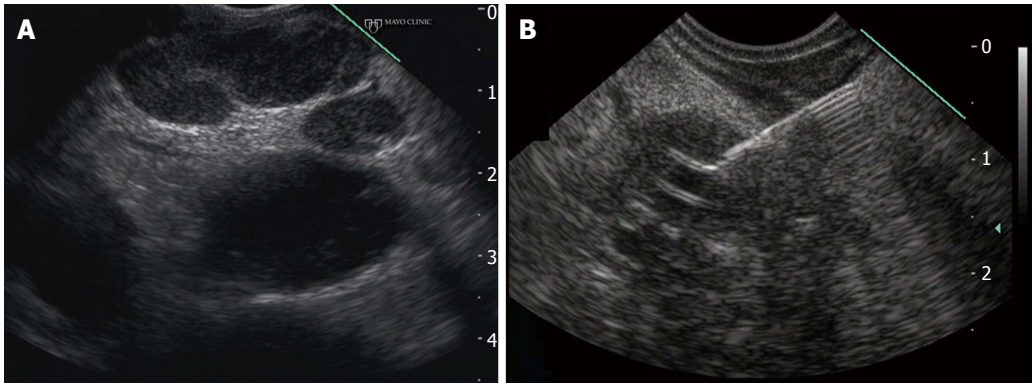

Figure 2 Endoscopic ultrasonographic findings in a patient found to have locally-advanced cholangiocarcinoma. A: Malignant lymphadenopathy; B: Endoscopic ultrasound-guided fine needle aspiration of primary cholangiocarcinoma.

evaluating IDBSs[33]. In a meta-analysis of nine studies including 555 patients, EUS without FNA was found to diagnose a malignant biliary stricture with a sensitivity and specificity of 78% and 84%, respectively[34]. The addition of FNA provides even more encouraging results, as a separate meta-analysis of 9 studies including 284 patients undergoing EUS-FNA demonstrated a sensitivity and specificity of 84% and 100%, respectively[35]. Many of these studies were performed following unsuccessful ERCP diagnosis, thus suggesting the value of EUS-FNA even among this more difficult-to-diagnose cohort.

A factor that appears to influence the sensitivity of EUS-FNA is the location of the stricture: Proximal (intrahepatic or hilar) *vs* distal (extrahepatic). In one study, the sensitivity for distal CCA was significantly higher than that for proximal CCA (81% *vs* 59%)[36]. This is perhaps explained by the greater ease of imaging and sampling of distal lesions as compared to proximal, which may be an important consideration when comparing EUS-FNA to ERCP data. Rösch *et al*[37] found EUS-FNA to be inferior to ERCP in patients with hilar biliary tumors (25% *vs* 75%) but superior for distal malignant strictures (60% *vs* 38%). Another variable that may impact performance of EUS-FNA is the presence of a bile duct stent, which results in acoustic shadowing and may occasionally interfere with sonographic imaging and FNA[38]. However, published data have not found the presence of plastic bile duct stents to lower the yield of EUS-FNA in the evaluation of IDBSs or suspected CCA[39].

A major limitation of EUS-FNA remains the concern for potential seeding of malignant cells along the needle track. This is less problematic for pancreatic head

lesions, as the path of trans-duodenal sampling would be resected during potential subsequent pancreatoduodenectomy. The concern is predominantly for proximal bile duct lesions, which require traversal of the hepatoduodenal ligament portion of the lesser omentum, which may not be resected during potential subsequent surgical intervention. In a series of 191 patients with hilar CCA receiving neoadjuvant chemoradiation followed by liver transplantation, 16 underwent transperitoneal FNA, and of the 6 (38%) that were positive for malignancy, 5 (86%) were later found to have peritoneal metastasis at operative staging *vs* 14/175 (8%) who did not undergo transperitoneal biopsy ($P < 0.01$)[40]. While nearly all patients in this study underwent FNA *via* a percutaneous route, the same concerns exists for EUS-guided FNA. Due to the potential for needle tract seeding, EUS-FNA of a primary bile duct tumor is considered a contraindication to liver transplantation; however, a recent retrospective study showed that preoperative EUS-FNA in patients with CCA did not affect overall or progression-free survival[41]. Until additional studies have further explored this area of uncertainty, biliary specimens to rule out CCA should be acquired intraductally rather than transmurally (*e.g.,* percutaneous or trans-duodenal) if liver transplantation is a consideration.

INTRADUCTAL ULTRASOUND

Intraductal ultrasound (IDUS) employs a thin (2.0-3.1 mm), high frequency (12-30 MHz) wire-guided radial ultrasound probe that is passed through the working channel of a duodenoscope and into the pancreatobiliary system during ERCP. With a radial penetration of 2 cm, IDUS allows for high-resolution characterization of IDBSs. Two to three mural layers are visualized during IDUS: (1) an inner hypoechoic layer representing mucosa, muscularis propria, and the fibrous layer of serosa; (2) an outer hyperechoic layer representing subserosal adipose tissue and serosa; and (3) sometimes an interface layer between bile and the inner hypoechoic layer[42].

IDUS features that have been associated with malignant rather than benign biliary strictures include sonographic disruption of the choledochal wall layers, wall thickening or irregularity, a hypoechoic mass with irregular margins, sessile tumor, infiltration of adjacent tissue or vasculature, or the presence of enlarged lymph nodes[43-45].

The published literature suggests that IDUS, although not often used in routine clinical practice, can be a useful ancillary technique in the evaluation of IDBSs. A retrospective review by Meister *et al*[46] of patients undergoing ERCP with IDUS demonstrated sensitivity as well as specificity of 98%, and a meta-analysis of 5 other studies found that IDUS accuracy for malignancy ranged from 84%-95%. Studies have also demonstrated that adding IDUS to ERCP-guided tissue acquisition improved sensitivity from 41%-68% to 90%-93%[47-49]. Domagk *et al*[50] found a combination of ERCP and IDUS to correctly diagnose malignancy in 88% of patients *vs* 76% and 58% of patients by ERCP alone and MRCP, respectively. Compared to EUS, IDUS has been shown to have greater sensitivity (91% *vs* 76%) and accuracy (89% *vs* 76%) in differentiating a malignant from a benign stricture[51]. IDUS was also found to have superior sensitivity (88% *vs* 63%) and specificity (91% *vs* 53%) in patients with PSC compared to ERCP alone[52].

IDUS, in a single experience reported cancer staging of T1, T2, T3/T4, N0 and N1 to be 84%, 73%, 71%, 69% and 69% accurate, respectively[46]. These results are intriguing; the low accuracy with N staging may be attributable to the limited depth of ultrasonic penetration, which limits IDUS largely to characterizing the mural features of the IDBS[51].

CHOLANGIOSCOPY

Cholangioscopy involves the use of a small-caliber, flexible endoscope to directly inspect the biliary epithelium and facilitate targeted sampling. The cholangioscope (daughter scope) is typically passed either through the working channel of a therapeutic (mother) scope during ERCP (Figure 3) or *via* direct peroral cholangioscopy following endoscopic papillotomy and percutaneous transhepatic cholangioscopy. Early cholangioscopy typically required two skilled endoscopists; this has since evolved to a single endoscopist effort with as-needed nurse assistance. In the last decade, a single-operator cholangioscopy system (SpyGlass Direct Visualization System, Boston Scientific Endoscopy, Marlboro, MA) with capability for 4-way tip deflection, a channel for insertion of a reusable fiberoptic probe, and irrigation and working channels, has been introduced. This system was severely hampered by poor image quality, but recent modifications, including the use of a video chip, has markedly improved image quality. Other cholangioscope options also exist, as alluded to above, but are currently not utilized clinically in the United States[53,54].

Cholangioscopy can help distinguish malignant from benign strictures, particularly *via* examination of epithelial vascular pattern (*e.g.,* irregularly dilated tortuous vessels, *i.e.,* "tumor vessels"), which is 100% specific and 96% sensitive when combined with targeted biopsies[55,56]. The presence of nodules, ulceration, or papillary or villous mucosal projections also suggest malignancy and warrant targeted biopsies[57].

Studies examining direct peroral or percutaneous cholangioscopy with or without biliary mucosal biopsies have demonstrated a sensitivity of 77%-100% and specificity of 79%-100%, with tissue adequacy achieved in 82%-97% of patients[58-63]. Addition of cholangioscopy to ERCP-guided tissue sampling enhances sensitivity for the diagnosis of biliary malignancy. For example, Fukuda *et al*[58] reported the sensitivity and accuracy of ERCP guided cytology and/or forceps biopsy improved from 58% and 78% to 100% and 93%, respectively. In a study by Draganov *et al*[63], sensitivity and accuracy of cytology, forceps biopsy, and cholangioscopy-guided mini-

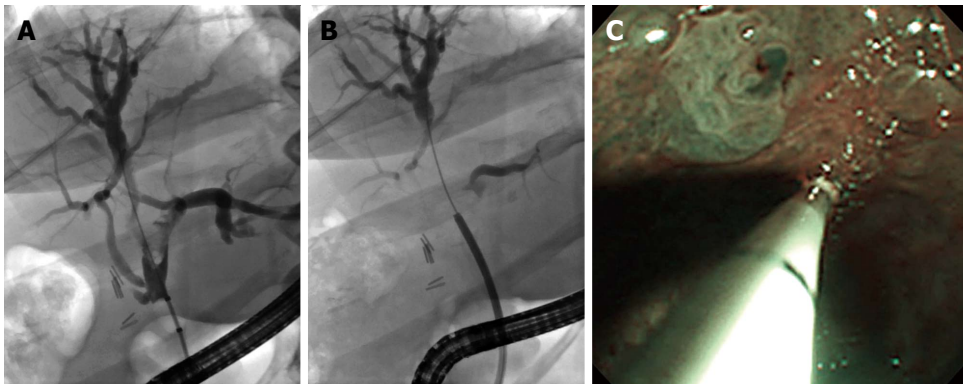

Figure 3 Passage of a SypGlass digital cholangioscope through a therapeutic duodenoscope to better evaluate hilar strictures and filling defects. A: Hilar (primarily right anterior hepatic duct) stricture and filling defects seen during endoscopic retrograde cholangiography pancreatography; B: SypGlass cholangioscope being passed through the working channel of therapeutic duodenoscope to better assess biliary stricturing and filling defects; C: SpyGlass cholangioscopy with narrow band imaging revealing villiform biliary mucosal changes; targeted biopsies were obtained and revealed low grade dysplasia concerning for early cholangiocarcinoma.

forceps biopsy were as follows: 5.8% and 39%, 29% and 54%, and 77% and 85%, respectively; mini-forceps biopsy was significantly more sensitive and accurate than cytology (P = 0.0001) or forceps biopsy (P = 0.0215) alone. Chen *et al*[64] reported the sensitivity and specificity of ERCP, cholangioscopy, and cholangioscopy-directed tissue biopsies to be 51% and 54%, 78% and 82%, and 49% and 98%, respectively, thus demonstrating much greater sensitivity and specificity for cholangioscopy with or without biopsy compared to ERCP alone.

The benefit of cholangioscopy over ERCP in patients with PSC and for distinguishing malignant from benign dominant strictures has also been demonstrated. In a study of 53 patients with PSC and dominant stricture, Tischendorf *et al*[52] used cholangioscopic findings of a polypoid or villous mass or irregularly shaped ulcer to classify malignancy before confirmation with standard tissue acquisition. This cholangioscopic finding provided greater sensitivity (92% *vs* 66%) and specificity (93% *vs* 51%) with a better NPV (97% *vs* 84%) than ERCP alone[52]. Cholangioscopy in the setting of PSC is often severely hampered by the number and severity of biliary stenosis. Cholangioscopy is performed predominantly under water immersion; alternatively, carbon dioxide gas insufflation can be used (predominantly during direct peroral cholangioscopy) and provides a distinctly different appearance to the biliary mucosa. Differences between the two imaging approaches may have individual value, *e.g.,* interpreting subtle surface mucosal change *vs* mucosal surface vascular pattern changes.

Video chip-based cholangioscopes are also equipped with narrow band imaging (NBI) (Figure 3C). NBI is based on the observation that the depth of light penetration depends on wavelength; the longer the wavelength, the deeper the penetration. Standard color video chips provide images based on sequential red-green- and blue illumination. The image is passed directly through selective band filters which highlight the red and blue bands. Blue light penetrates only superficially, whereas red light penetrates into deeper layers. The selective color imaging enhancement highlights mucosal surface detail and more so, mucosal vascular patterns[65-67]. An initial feasibility study involving 21 patients with biliary lesions found visualization of 57% of lesions to be "excellent" using NBI *vs* 9.5% using conventional white-light imaging[68]. A recent, small series of patients with PSC also led to the conclusion that NBI allowed better determination of tumor margins and increased detection of suspicious lesions compared to white-light imaging; the authors could not demonstrate an improved dysplasia detection rate, but this may have been consequent to methodological issues[69].

Relatively few studies have compared the diagnostic yield of cholangioscopy *vs* EUS. In one retrospective series of 66 patients undergoing evaluation of IDBSs with cholangioscopy combined with EUS, sensitivity and specificity for combined modalities was greater than for either modality alone[70]. In another study, 39 patients with negative brush cytology underwent EUS-FNA first and only proceeded to cholangioscopy if EUS was negative; EUS-FNA was diagnostic in 23 patients (58%), and the remainder of the patients required cholangioscopy, thus leading the authors to conclude that cholangioscopy could be reserved for cases where EUS-FNA is nondiagnostic[71].

Potential adverse events of cholangioscopy include pancreatitis, cholangitis, perforation, hemobilia, and sphincterotomy bleeding. A recent retrospective study found that patients undergoing ERCP with cholangioscopy had significantly higher rates of pancreatitis (2.2% *vs* 1.3%), cholangitis (1.0% *vs* 0.2%), and perforation (1.0% *vs* 0.3%) than ERCP alone[72]. However, multivariable analysis did not find cholangioscopy to be associated with an increased rate of adverse events compared to ERCP[73].

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) is an emerging imaging modality that permits high-resolution, *in vivo* assessment of the biliary epithelium. It provides real-time contact imaging at a cellular and sub-cellular

level, offering a lateral resolution of 3.5 μm, optical slice thickness of 30 μm, and optical penetration of 40-70 μm. CLE is based upon the principle of illuminating a tissue with a low-power laser and then detecting reflected fluorescent light. The laser is focused at a specific depth, and only light which is reflected back from that plane is refocused and able to pass through the pinhole confocal aperture; the term "confocal" hence refers to the fact that the reflected light is refocused onto the detection system by the same lens through which the laser light was initially emitted. As a result, scattered light from above and below the plane of interest is not detected, thereby increasing spatial resolution. A focused, scanning light source (*i.e.,* laser) and processor then generate reconstructed grayscale images of the target area, enabling epithelial and subepithelial visualization. Notably, CLE requires administration of intravenous or topical contrast (typically fluorescein) to highlight tissue features and better differentiate normal architecture or inflammatory changes from neoplastic tissue.

A CLE imaging probe (pCLE) can be passed through various ERCP catheters or through the working channel of a cholangioscope. In the first study of pCLE for the evaluation of IDBSs, Meining *et al*[74] reported that the visualization of irregular, dilated ("angiogenic") vessels predicted malignancy with a sensitivity of 83% (compared to 50% for standard histopathology), specificity of 88%, and accuracy of 86% among 14 patients. A subsequent study with 37 patients revealed similar findings[75]. In an effort to more uniformly identify pCLE imaging findings associated with malignancy, a standardized classification system (*i.e.,* Miami classification) was proposed consisting of: (1) the presence of thick, white bands (> 20 pm); (2) thick dark bands (> 40 μm); (3) dark clumps; (4) epithelial structures; and (5) fluorescein leakage[76]. Suggested criteria for benign strictures were: (1) thin, dark (branching) bands; and (2) thin, white bands. In a blinded consensus review that validated this classification schema, combining two or more of the criteria suggestive for malignancy (except fluorescein leakage) provided a sensitivity, specificity, positive predictive value (PPV), and NPV of 97%, 33%, 80%, and 80%, respectively, compared with 48%, 100%, 100%, and 41% for standard tissue acquisition[77]. Interobserver variability was moderate for most of the criteria. A prospective, multicenter study assessing the role of pCLE in the evaluation of 89 patients with IDBSs reported a sensitivity, specificity, PPV, and NPV of 98%, 67%, 71%, and 97% for the detection of malignancy, respectively, compared with 45%, 100%, 100%, and 69% for index pathology[78]. Moreover, when combined with ERCP, pCLE was significantly more accurate than ERCP with tissue acquisition (90% *vs* 73%). Among the subset of patients with PSC, a small retrospective study found that pCLE detected malignancy with a sensitivity, specificity, PPV, and NPV of 100%, 61%, 22.2% and 100%, respectively, compared to 0%, 94.4%, 0% and 89% with standard tissue sampling[79]. Given its high sensitivity and NPV, pCLE may ideally be used to exclude malignancy in this high-risk population. The technique is limited by the need for point contact and by movement. Additional study is needed to optimize image interpretation and to determine the cost benefit.

A limitation of the Miami classification is the suboptimal interobserver agreement. In contrast to the initially reported moderate interobserver variability with most criteria, a subsequent study among 6 experienced endoscopists from 5 institutions reviewed 25 de-identified pCLE video clips of IDBSs and found interobserver agreement for individual criteria to range from poor to fair and for final diagnosis to be slight[80]. Further training and standardization is needed to improve interobserver reliability, as may be expected with most evolving techniques[81].

In an effort to improve the low specificity of pCLE, which has been attributed to inflammatory changes (*e.g.,* chronic inflammation, stent-related changes, previous endoscopic procedures), descriptive criteria (*i.e.,* Paris classification) have recently been proposed[82]. These criteria aim to distinguish benign inflammatory strictures by assessing for vascular congestion, dark glandular patterns, increased interglandular space, and thickened reticular structures, and reportedly have increased the specificity from 64% to 76%[82]. A prospective, multicenter study evaluating 112 patients with IDBSs incorporating the Paris classification found pCLE to be 89% sensitive, 71% specific, and 82% accurate compared with 56%, 100% and 72% with standard tissue sampling alone[83].

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is analogous to ultrasound but relies on low-intensity infrared light (700 to 1500 nm wavelength range) instead of sound to generate high-resolution, cross-sectional tissue imaging. The delay in time of light back-scattered by the various tissues is measured using a technique known as low coherence interferometry, which has a depth of penetration of 1-3 mm and lateral and axial resolution down to 10 μm. This technology provides much greater spatial resolution than IDUS and, unlike endomicroscopy, does not require contrast administration. OCT achieves visualization of layer architecture similar to histologic sections[84,85]. In doing so, OCT allows visualization of microscopic structures such as blood vessels, lymphoid aggregates, crypts, and submucosal glands and can aid in differentiating malignant from benign tissue in real-time[86-88]. Miniaturization of early OCT probes has enabled insertion into a transparent biliary catheter that can be passed through the working channel of an ERCP scope for biliary cannulation and *in vivo* imaging[89].

OCT has been shown to increase the sensitivity for detecting malignant biliary strictures as compared to biliary brushing cytology alone. Arvanitakis *et al*[90] evaluated 2 OCT criteria, namely unrecognizable layer architecture and presence of large nonreflective areas compatible with tumor vessels, for diagnosing malignant

strictures when compared to the gold standard of tissue acquisition in 35 patients undergoing ERCP for evaluation of IDBSs. Nineteen patients ultimately had malignant strictures, and these 2 OCT criteria were associated with a sensitivity, specificity, PPV, NPV and accuracy of 53%, 100%, 100%, 64% and 74%, respectively. The sensitivity of biliary mucosal brushings and/or biopsy improved from 67% to 84% when at least 1 criterion was added. In another study, the diagnostic utilities of OCT and ERCP-guided brush cytology were compared while evaluating 12 patients with main pancreatic duct stricture. Six patients ultimately had malignancy and OCT demonstrated greater sensitivity (100% *vs* 67%) than cytology while maintaining equal specificity (100%)[91]. OCT, unlike confocal imaging, permits larger surfaces areas to be examined. Improved resolution is paramount. The limited existing data are encouraging, but additional studies are awaited to better define the potential role of OCT in evaluating IBDSs, particularly among patients with high-risk conditions such as PSC.

FUTURE DIRECTIONS

Other technologies may be amenable to use in the evaluation of IDBSs. These include high-resolution endomicroscopy, Raman spectroscopy, EUS elastography, and CLE with chromocholangioscopy or autofluorescence. Each will be challenged by the need for miniaturization and must satisfy value in the face of added cost.

CONCLUSION

IDBSs pose a diagnostic challenge for which more accurate diagnostic tests are critically needed. Although ERCP offers therapeutic options for biliary obstruction, conventional methods of tissue acquisition remain generally insensitive, albeit to a lesser degree with use of advanced cytologic techniques such as FISH. EUS can be of additional benefit in evaluating distal strictures and staging, though concerns remain regarding tumor seeding. IDUS may supplement ERCP and EUS and aid in local staging but, despite its longstanding availability, is seldom employed. Cholangioscopy permits direct visualization and directed sampling; design enhancements may simplify its use and improve performance. Emerging techniques such as pCLE and OCT enable real-time, *in vivo*, endohistologic assessment, but additional study is needed to standardize interpretation, improve inter-rater reliability, and validate performance. The challenges in diagnosis often result in multimodal testing that marginally enhances diagnosis but substantially increases cost. While application of new and innovative technologies is of interest to endoscopists, their use must be tempered by the realization of only marginal improvements in diagnostic sensitivity and frequent decrement in specificity, their potential for adverse events, associated cost, and often limited availability to a small number of diagnostic centers. In addition, more research is needed to determine how to best guide important clinical decisions using these and other established and emerging modalities.

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