Review Article

The role of intraductal ultrasonography in pancreatobiliary diseases

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ABSTRACT

Intraductal ultrasonography (IDUS) provides real-time, cross-sectional imaging of pancreatobiliary ducts and surrounding structures during endoscopic retrograde cholangiopancreatography using a high-frequency ultrasound (US) transducer. Hence, IDUS has been considered a sensitive tool in the evaluation of suspicious choledocholithiasis and neoplasms, to help distinguish between benign and malignant bile duct strictures or wall thickness, and to assess tumor extension and invasion depth. With the rapid development and enriched choices of sensitive diagnostic modalities include but are not limited to endoscopic US, peroral cholangioscopy, and confocal laser endomicroscopy, it is needed to systematically assess the role of IDUS in the investigation of pancreatobiliary diseases. Some new developments and innovative use of IDUS techniques will be discussed in this paper with the review of literature.

Key words: Ampullary tumors, choledocholithiasis, indeterminate bile duct strictures, intraductal papillary mucinous neoplasm, intraductal ultrasonography

INTRODUCTION

Cross-sectional imaging modalities are preferred initial investigation in patients with pancreatobiliary disorders. Endoscopic ultrasound (EUS) plays an important role when transcutaneous ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) fail to provide conclusive diagnosis and is currently recommended to evaluate various pancreatobiliary disorders such as suspected cholangiocarcinoma (CCA), ampullary adenocarcinoma, and idiopathic acute pancreatitis.[1,2] Finally, endoscopic retrograde cholangiopancreatography (ERCP) plays a role when cytohistological diagnosis or therapeutic intervention is required. However, the diagnostic yield of ERCP-directed tissue acquisition methods is suboptimal, which results in emerging of new techniques based on ERCP including peroral cholangioscopy (POC), confocal laser endomicroscopy, and intraductal ultrasonography (IDUS).

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Among these techniques, IDUS can be performed during ERCP and provides real-time, high-quality cross-sectional images of extrahepatic bile duct, pancreatic duct, and periductal structures. Using a high-frequency (12–30 MHz) US probe which can be placed in close proximity to the pancreatobiliary ductal system, it is sensitive and accurate to characterize duct wall thickness and detect microstones that are not shown on cholangiogram. However, it is not widely used because of known limitations and most ERCP practitioners are not well trained in EUS.[3,4] Despite this, the value of IDUS in pancreatobiliary diseases merits further exploration, and some technique modification and novel usage keep emerging in the literature. As a result, we reviewed the literature for the available evidence with regards to the benefits, limitations, and perspectives of IDUS in patients with pancreatobiliary disorders.

EVALUATION OF EXTRAHEPATIC BILIARY MALIGNANCIES

Indeterminate biliary strictures

Accurately differentiating malignant from benign biliary strictures is of significant importance but remains a major clinical challenge.[5] Conventional endoscopic transpapillary tissue acquisition has been considered unsatisfactory in diagnosing indeterminate biliary strictures (IDBSs) with a pooled sensitivity of 45% for brush cytology, 48.1% for forceps biopsy, and 59.4% for the combination of both.[6] As a result, other technologies such as cholangioscopy, confocal endomicroscopy, and IDUS have been developed and used with ERCP to improve the diagnostic yield.[7-10] IDUS can provide high-resolution cross-sectional images of the bile duct and has been considered effective in the evaluation of IDBSs.[1] A technology review published in 2015 by European Society of Gastrointestinal Endoscopy expressed that evaluation of IDBSs and ampullary tumors could be a promising indication for IDUS.[11] This was further supported by several recent study results.[5,12,13] A retrospective trial accessed the diagnostic yield of IDUS in 193 patients with biliary strictures. The sensitivity, specificity, and accuracy for IDUS in distinguishing malignancies from benign biliary strictures were 96.9%, 79.2%, and 88.1%, respectively.[5] Another retrospective study by Meister *et al.* with the largest patient cohort assessed the diagnostic yield of IDUS in 379 patients with IDBSs. The sensitivity, specificity, and accuracy of IDUS, when using histopathology or long-term follow-up results as the gold standard, were 93.2%, 89.5%, and 91.4%, respectively.[4]

Sonographic features of malignant biliary strictures

Sonographic features suggestive of malignancy on IDUS include disruption of normal bile duct wall echo layers, eccentric wall thickening, hypoechoic sessile mass with signs of adjacent tissue or vascular invasion, and the presence of enlarged lymph nodes.[12] Ito *et al.* retrospectively analyzed the IDUS features of early stage CCA in 23 patients. IDUS found a sessile mass in 56.5% of enrolled patients, while polypoid mass or localized duct wall thickening were observed in the rest of patients.[14] In a prospective study of 62 patients, Tamada *et al.* found that the presence of a sessile mass, mass size larger than 10 mm, and bile duct wall interruption were independent variables to predict malignancy.[15] In addition, measurement of duct wall thickness at the stricture site by IDUS also appeared helpful to predict malignancy. In a retrospective, single-center study by Krishna *et al.*, 45 patients with biliary strictures but no visible mass on CT or MRI were evaluated by ERCP and IDUS. A bile duct wall thickness of 7 mm or less at the stricture site without extrinsic compression had a 100% negative predictive value for excluding malignancy.[16] A recent study by Chen *et al.* on a number of 193 patients with biliary strictures showed that bile duct wall thickness >7 mm at the stricture site had a positive predictive value of 100% for diagnosing malignancy in the absence of extrinsic compression.[5]

Intraductal ultrasonography versus other modalities

IDUS is more accurate than EUS, transpapillary biopsy, or brush cytology for identification of biliary malignancy.[1,17] An early study of forty patients by Tischendorf *et al.* prospectively assessed the value of IDUS in primary sclerosing cholangitis (PSC) with dominant bile duct stenoses. Compared with ERCP-guided tissue sampling, IDUS showed significantly better sensitivity (87.5% *vs.* 62.5%, $P = 0.05$), specificity (90.6% *vs.* 53.1%, $P < 0.001$), and accuracy (90% *vs.* 55%, $P < 0.001$) in diagnosing malignancy.[18] Recently, Heinzow *et al.* retrospectively evaluated the diagnostic yield of ERCP, IDUS, EUS, and CT in a cohort of 234 patients with IDBSs. Using histological or long-term follow-up as the gold standard, the authors obtained values for sensitivity, specificity, and accuracy of 93%, 89%, and 91%, respectively, for IDUS combined with ERCP; 94%, 89%, and 92%, respectively, for IDUS combined with

endoscopic transpapillary forceps biopsies (ETP); 37%, 100%, and 59%, respectively, for ETP; 71%, 78%, and 74%, respectively, for EUS; 67%, 82%, and 73%, respectively, for CT. The detection rate of biliary malignancy by combining IDUS with ERCP was superior to ETP, EUS, or CT.[19] On the other hand, when IDUS was combined with transpapillary biopsy, the preoperative diagnostic accuracy for biliary strictures can be significantly improved. In an early prospectively designed study, Domagk *et al.* reported an accuracy rate of 98% when adding IDUS to transpapillary forceps biopsy (TFB) in diagnosing biliary strictures, which was significantly higher than TFB alone (60%).[17] Unlike EUS which has a higher diagnostic accuracy rate for distal common bile duct (CBD) strictures than for proximal biliary strictures,[19] the study of Chen *et al.* showed that IDUS was more accurate in diagnosing proximal ductal obstructions than distal CBD stricture (98.08 *vs.* 82.73%, $P = 0.006$).[5]

Intraductal ultrasonography-guided tissue acquisition

Since fluoroscopy-guided forceps biopsy and brush cytology have low sensitivity in providing histopathological diagnosis for IDBSs, IDUS has been applied to help direct tissue acquisition. This can be mostly achieved by IDUS initially to identify the location of suspected lesion and followed by fluoroscopy-guided forceps biopsy or brush cytology.[15,20,21] Another technique is by placing IDUS probe alongside biopsy forceps in the bile duct to direct biopsy. Limited data showed that IDUS-guided biopsy is feasible for bile duct sampling and obtained higher diagnostic yield (83.3%) than fluoroscopy guided biopsy (55.6%) of IDBSs.[22]

Evaluation of tumor extension

Extrahepatic CCA tends to grow longitudinally along the bile duct, which can be underestimated on cholangiography, magnetic resonance cholangiopancreatography (MRCP), and CT. IDUS, transpapillary or through percutaneous route, appeared effective and superior to cholangiography in the evaluation of longitudinal extension of CCA and thereby may help in the selection of an optimal surgical plan.[23,24] In a prospective study of 42 patients with borderline resectable hilar CCA, IDUS showed an accuracy of 90% in the assessment of tumor extension, which was superior to cholangiogram (60%) and CT (66.6%).[23] Noda *et al.* investigated the diagnostic yield of IDUS in 27 patients with extrahepatic biliary carcinomas, they found that IDUS has a sensitivity of 82% and 85%, a specificity of 70% and 43%, and an accuracy of 78% and 70% in assessment of cancer extension in its hepatic and duodenal side, respectively. Inflammation and collapse of the bile duct on the duodenal side of tumor could cause overestimation of extension.[25] Kim *et al.* combined IDUS with percutaneous transhepatic cholangioscopy (PTCS) in 20 patients with hilar CCA. They found that IDUS had an accuracy of 85% for the evaluation of Bismuth type. When IDUS was combined with PTCS and biopsy, the overall accuracy increased to 95%, and it reached 100% in 18 patients with Bismuth type III and IV cancer.[24] However, IDUS may be more accurate than POC in cancers owning features of submucosal spread.

Staging of biliary malignancy

Study results suggested a suboptimal diagnostic accuracy of IDUS in differentiating between stage T1 and T2 CCA. What appeared to be a stage T1 lesion with an intact outer hyperechoic layer of duct wall on IDUS could actually invade perimuscular loose connective tissue (T2) because the hypoechoic inner layer of bile duct wall contains a part of the perimuscular connective tissue. Tamada *et al.* performed IDUS (20 MHz) on 26 patients with bile duct cancer and *in vitro* on eight resected bile duct specimens. They found that the accuracy of IDUS in T-staging was 77% using histology as the standard.[26] A recent large cohort study by Meister *et al.* on a number of 174 patients with malignant biliary strictures showed that IDUS had an accuracy rate of 84% for stage T1 tumors, 73% for T2, 71% for T3 malignancies, and 69% for N0 and N1.[4]

IDUS is more accurate than EUS for T-staging of hilar CCA but has low accuracy in N staging due to limited ultrasonic penetration depth.[1] This was supported by Menzel *et al.* who prospectively compared the diagnostic accuracy of EUS and IDUS in 56 patients with biliary strictures. The authors concluded that IDUS was more accurate than EUS in preoperative T-staging of biliary malignancies (IDUS, 77.7%; EUS, 54.1%, $P < 0.001$), but there was no significant difference in lymph node staging between EUS and IDUS (IDUS, 60%; EUS, 62.5%).[27]

EVALUATION OF CHOLEDOCHOLITHIASIS

Diagnosis of suspicious choledocholithiasis

Both EUS and IDUS are sensitive and accurate for the detection of CBD stones and sludge. Compared

with IDUS, EUS is less invasive and is mainly used to evaluate idiopathic pancreatitis or unexplained CBD dilatation before ERCP to help guide the management and avoid unnecessary invasive procedures.[28,29] IDUS can be performed at ERCP and enables visualization of small bile duct stones or sludge which is missed on cholangiogram and MRCP; therefore, it has been considered more effective than ERCP, abdominal CT, and MRI in the diagnosis of CBD stones. In a prospective study of 95 patients with suspicious choledocholithiasis, IDUS detected small bile duct stones in 31 patients (32.6%) and sludge in 24 patients (25.2%), which was not detected on cholangiography. Endoscopic extraction confirmed bile duct stones (mean diameter of 2.9 mm) in all 31 patients and sludge in 21 patients.[30] Endo *et al.* conducted a retrospective study of 213 patients with suspected choledocholithiasis, they found that the sensitivity of ERCP in the diagnosis of bile duct stones was significantly affected by the size of stones (100% for stones ≥8 mm, 74% for stones <8 mm) and the diameter of CBD when the stone size was smaller than 8 mm. The authors thus recommended IDUS in suspicious choledocholithiasis when cholangiogram failed to detect bile duct stones, especially in a dilated CBD (≥12 mm in diameter).[31]

Confirmation of ductal clearance after stone extraction

Residue small bile duct stones or sludge is considered a risk factor for later stone recurrence. IDUS can be performed conveniently at ERCP to detect remnant CBD stones and sludge, to confirm bile duct clearance after stone extraction, and thus, decrease the recurrence rate of CBD stones.[32,33] In a prospectively study of 70 patients, Ang *et al.* evaluated the role of IDUS in the detection of residue bile duct stones after stone extraction. IDUS found bile duct stones (mean size 2.6 mm) in all 32 patients with initial normal cholangiography. After stone extraction with negative balloon occlusion cholangiogram, IDUS was able to show residue stones (mean size 2.2 mm) in 28 (40%) patients, which were all flushed out by saline solution irrigation.[33] Another prospective study by Tsuchiya *et al.* investigated whether performing IDUS after stone extraction could decrease the rate of stone recurrence. IDUS detected small residue CBD stones in 23.7% (14/59) of enrolled patients, which was not observed on cholangiogram. The authors found a significant lower stone recurrence rate in those underwent IDUS (3.4%) than those without (13.2%) ($P < 0.05$).[34]

Evaluation of idiopathic pancreatitis

The ability of IDUS to detect small CBD stones makes it a sensitive tool to evaluate acute or recurrent idiopathic pancreatitis. Although EUS has been currently recommended before ERCP to detect possible CBD stones or sludge, IDUS plays a role at ERCP when cholangiogram fails to detect CBD stones, especially when a spontaneous stone passage is suspected. In addition, IDUS can be used to confirm bile duct clearance right after stone extraction and thereby to reduce the recurrence rate of acute biliary pancreatitis, which is difficult for EUS mainly due to the interference by air bubbles in the bile duct after endoscopic sphincterotomy or balloon dilation of the papilla.

A small, prospective study of 31 patients by Kim *et al.* reported using IDUS to evaluate the etiology of idiopathic recurrent pancreatitis. IDUS found small bile duct stones (≤3 mm in diameter) in five patients (16.1%) and sludge in three (9.7%) patients. Pancreatitis did not recur in seven of these patients after stone and sludge extraction.[35] Another recently conducted, prospective study with a larger cohort by Yoon *et al.* evaluated the usefulness of IDUS in suspicious acute biliary pancreatitis. A total of 92 patients with initial negative cholangiogram underwent wire-guided IDUS during ERCP. IDUS was able to detect bile duct stones in 33 (35.9%) patients, which was all confirmed by stone extraction. Acute pancreatitis did not recur in the majority (97.9%) of patients during follow-up.[36] These study results support the usefulness of IDUS in the detection of suspicious bile duct stones in idiopathic acute pancreatitis, as well as its role in the prevention of recurrence of acute biliary pancreatitis.

Methods to overcome pneumobilia

Pneumobilia is commonly encountered after endoscopic sphincterotomy or balloon sphincteroplasty and is a known obstacle for conventional IDUS to provide accurate cross-sectional imaging of the biliary system and might increase the possibility of residual CBD stones after stone extraction. To overcome this limitation, Varadarajulu reported an effective technique in 2008 by flushing the bile duct with normal saline through an ERCP catheter placed alongside an IDUS probe to remove intraductal air bubble and to perform IDUS simultaneously.[37] Recently, Kim *et al.* reported another technique using a balloon-sheathed catheter IDUS system in 16 patients with CBD stones and

extensive pneumobilia. During the procedure, the balloon at the tip of US probe was inflated to facilitate US scan of the bile duct and successfully detected remnant stones after stone extraction and asymmetrical wall thickening without interference by pneumobilia. The major limitations of this balloon-sheathed IDUS system include difficult manipulation during probe insertion because of a wireless character, requirement of a therapeutic duodenoscope with a working channel of larger than 3.4 mm, relatively small and fixed balloon size (10 mm in diameter) which might compromise its utility in extremely dilated bile duct. Therefore, the authors suggested that a guidewire assisted, larger balloon-tipped mini-probe would be more effective and attractive.[38]

DIAGNOSIS OF OTHER BENIGN BILIARY DISORDERS

Portal hypertensive biliopathy

Portal hypertensive biliopathy (PHB) is described as bile duct wall abnormalities secondary to portal hypertension, which typically presents with CBD stricture caused by periductal or intraductal varices compression, choledocholithiasis, ischemic ductal change, and cholangitis.[39-41] IDUS allows high-resolution imaging of bile duct wall and its surrounding structures, which makes it helpful in diagnosing PHB by detecting and characterizing the anatomy of biliary varices.[42] On IDUS, biliary varices typically present with multiple, hypoechoic structures in the duct wall or surrounding the bile duct.[42]

In a recent cohort study by Takagi *et al.* in 377 patients with biliary abnormalities, IDUS detected biliary varices in 11 cases (2.9%) including all four patients with extrahepatic portal vein obstruction, two of ten patients with PSC, 1 of 13 patients with chronic pancreatitis, 3 of 41 patients with pancreatic cancer, and 1 of 149 patients with bile duct cancer. Authors concluded that IDUS was superior to percutaneous US, CT, and MRI in diagnosing biliary varices.[42] However, there has been no study to compare the diagnostic ability between IDUS and EUS which was reported effective in the evaluation of PHB in case series.[43,44] On the other hand, combining IDUS with other modalities may add more diagnostic information for evaluation of PHB. Ramchandani *et al.* first reported a case series of five patients with PHB underwent evaluation by IDUS and single-operator POC (SOPOC). IDUS helped to reveal large periductal varices in two patients, which caused extrinsic compression of the bile duct and presented as biliary stricture on cholangiogram. IDUS and SOPOC helped to exclude intra- and extra-ductal varices in one patient with ischemic bile duct stricture. Combining IDUS with cholangioscopy could help to avoid severe bleeding by detecting intraductal varices and avoiding blind invasive therapeutic procedures.[45]

IgG4-related sclerosing cholangitis and primary sclerosing cholangitis

IgG4-related sclerosing cholangitis (IgG4-SC) has been increasingly recognized in the past few years.[46-49] Its cholangiographic features resemble those of CCA, PSC, and pancreatic cancer.[50] Transpapillary biopsy appeared not useful for histological diagnosis of IgG4-SC since the fibroinflammatory change mainly involves the submucosa of bile duct wall. IDUS allows visualization of the morphology of bile duct wall in detail, and therefore can provide further information for differentiation of IgG4-SC from CCA and PSC.[51-54]

A recent retrospective study by Naitoh *et al.* compared IDUS findings between patients with IgG4-SC and those with PSC. Several IDUS features were found to be more encountered in PSC than in IgG4-SC ($P < 0.001$) including circular asymmetric wall thickening, irregular inner margin, unclear outer margin, heterogeneous internal echo, diverticulum-like ductal wall outpouching, and disappearance of three normal echo layers of duct wall. Among these features, irregular inner margin, diverticulum-like outpouching, and disappearance of three echo layers of duct wall were specific for PSC compared to IgG4-SC. Furthermore, IDUS is more sensitive than ERCP for the early detection of diverticulum-like outpouching.[52] The sonographic features of IgG4-SC on IDUS, quite opposite to those of PSC, include circular symmetrical wall thickening with smooth outer and inner margin, and homogeneous internal echo at the stenotic area.[55] A small scale study by Kubota *et al.* reviewed and compared IDUS features among six patients with autoimmune pancreatitis-associated sclerosing cholangitis (SC-AIP), ten patients with PSC, and 12 patients with hilar CCA. They found that patients with SC-AIP presented more often on IDUS than PSC and CCA ($P < 0.05$) with features of symmetrical wall thickness, the presence of homogeneous internal foci and lateral mucosal lesions continuous to the hepatic hilum.[53] In a retrospective study, Naitoh *et al.* found that the bile duct wall in the nonstenotic area was thicker in IgG4-SC than CCA on IDUS.

A wall thickness of more than 0.8 mm in the region of normal duct on cholangiogram can be used to differentiate IgG4-SC from CCA with the sensitivity, specificity, and accuracy of 95%, 100%, and 93.5%, respectively.[51]

INTRADUCTAL ULTRASONOGRAPHY DIRECTED ENDOSCOPIC BILIARY PROCEDURES

IDUS is traditionally performed in combination with radiocontrast cholangiography, but several recent studies replaced radiocontrast cholangiogram with IDUS in the management of biliary disease in the rational to prevent contrast injection-related ascending cholangitis, post-ERCP pancreatitis, and adverse reactions to iodine-containing contrast media and to reduce the time of radiation exposure.[20,55,56] Some investigators have reported using IDUS rather than fluoroscopy to perform emergent bedside ERCP in critically ill patients.[57]

In a small case series by Lee *et al.*, IDUS was used to direct endoscopic biliary stenting by measuring the insertion length of the probe between the major papilla and the lesion to determine the length of the plastic stent. Successful endoscopic biliary drainage was achieved in all nine enrolled patients without complications, and no fluoroscopy was required.[55] A prospective, single-armed study by Park *et al.* reported a 100% success rate of IDUS assisted stone removal in 35 patients with CBD stones (median size of 9 mm) without significant immediate or delayed complications. Stones were removed successfully after endoscopic sphincterotomy without biliary radiocontrast injection and only guided by IDUS to confirm the existence and clearance of stones. However, those with larger (≥20 mm in diameter) or multiple CBD stones were not included in the study.[56] Lim *et al.* conducted a retrospective study with a larger cohort of 105 patients using IDUS to diagnose and management of extrahepatic biliary disease without the assistance of radiocontrast cholangiography. The technical success, defined by the placement of the US probe into the confluent of left and right hepatic duct, was 100% without significant associated complications. The mean diameter of CBD stones detected on IDUS was 6.4 ± 3.5 mm. A total of 91 (86.6%) enrolled patients underwent biliary drainage, stone removal, bile duct biopsy, or brush cytology following IDUS as a single-step intervention, and most of the patients (82.9%, 87/105) underwent therapeutic procedures without contrast cholangiogram. Fluoroscopy was only used in a small number of patients to assist biliary cannulation (10, 9.5%), stone capture (9, 8.5%), biliary drainage (4, 3.8%), and clearance of remnant stones (8, 7.6%).[20] Although IDUS-directed endoscopic biliary drainage and stone removal appeared effective and safe in experienced hands in these studies, further investigations are needed to compare its efficacy, feasibility, and safety with traditional radiocontrast cholangiogram-guided endoscopic biliary procedures.

ROLE IN PANCREATIC DISORDERS

EUS offers the highest resolution of pancreas, allows direct cytopathological diagnosis and cystic fluid analysis through EUS-guided fine-needle aspiration. Therefore, EUS has been recommended as a valuable tool in the diagnosis and management of solid and cystic pancreatic lesions including intraductal papillary mucinous neoplasm (IPMN).[58-61] The role of IDUS is now mainly on detection the extension of IPMN preoperatively and helps to determine the extent of surgical resection.[62,63] In a randomized, prospective study, Cheon *et al.* evaluated forty patients with IPMN who underwent surgical resection. The study results showed that IDUS was more accurate than other imaging modalities (85% *vs.* 50%, $P = 0.018$) in preoperative assessment of tumor extension. In five patients with disease recurrence, only one was assessed by IDUS and four by other imaging tests preoperatively.[62] In another retrospective study of 24 patients with branch type IPMN, Kobayashi *et al.* concluded that the lateral spreading of tumor was associated with the dilation of main pancreatic duct (≥6 mm) ($P < 0.05$). IDUS showed a sensitivity, specificity, and accuracy of 92%, 91%, and 92%, respectively, in the assessment of tumor extension along the main pancreatic duct.[63] The usefulness of IDUS also needs to be compared with other methods such as preoperative or intraoperative peroral pancreatoscopy with narrow-band imaging or biopsy which appeared helpful in identifying the occult or skip IPMN lesions, evaluate the resection margin, and modify the surgical plan.[60,64,65]

EVALUATION OF TUMORS OF AMPULLA OF VATER

Endoscopic snare papillectomy for duodenal papilla tumors has been established as an alternative treatment

to surgical resection in selected cases. Signs now have been accepted as endoscopic resectable include intraductal extension <1 cm for adenoma, absence of invasion of duodenal muscular propria, pancreas, CBD, and progressive disease (PD) for malignancy. The recent published American Society for Gastrointestinal Endoscopy guideline recommended EUS evaluation for large ampullary lesion before treatment.[66] However, IDUS showed similar diagnostic accuracy for ampullary tumors and in the evaluation of intraductal tumor extension and is valuable in triage of patients to surgical resection or endoscopic papillectomy. Okano *et al.* performed EUS and IDUS on 48 patients with ampulla tumors before surgical resection or endoscopic papillectomy. They found no significant difference in the accuracy of both modalities for evaluation of focal extension of tumors into the ducts (90% and 88%, respectively, for infiltration into the CBD and 92% and 88%, respectively, for extension into the PD). The overall accuracy of EUS and IDUS was 85% and 80% for T-staging, 97% and 94% for adenoma and pTis, 73% and 73% for pT1, 50% and 50% for pT2, and 50% and 100% for pT3–T4, respectively. Echo attenuation due to the high frequency of mini-probe may explain the lower accuracy in advanced stage tumors.[67]

TECHNIQUE LIMITATIONS AND PERSPECTIVES

Ductal cannulation is prerequisite to perform IDUS. Introduction of the mini-probe into the bile duct or pancreatic duct can be achieved by guidewire assistance. However, the US probe is still easy to be damaged by cannulation maneuvers and permanent access to the bile duct is not promising. To overcome this limitation, Vila *et al.* reported an alternative technique to protect the probe and facilitate US scan. They initially cannulated the bile duct with a guidewire followed by placement of an Oasis (11.5 F, Wilson-Cook) stent delivery system through the guidewire into the bile duct. Then, the guidewire and the introducer catheter were removed leaving the positioning sleeve of the system in the bile duct, through which the miniprobe (2.5 mm in diameter) was inserted and achieve US examination even within the positioning sleeve.[68] However, it is difficult to maintain the mini-probe in the central position of duct even with guidewire assistance, especially in a dilated duct, which could compromise the image quality. In addition, the ultrasound scan can be affected significantly by air inside the duct as described before.[39] As a result, a novel, guidewire-assisted, and balloon-sheathed mini-probe with a water injection function may facilitate intraductal ultrasonographic exam and will be attractive and highly desirable.

CONCLUSION

IDUS is a safe and more sensitive diagnostic tool than conventional tissue acquisition methods in the evaluation of extrahepatic biliary neoplasms. Detailed echo features of bile duct wall can be obtained on IDUS with a high-frequency ultrasound transducer, which makes IDUS a nonignored method in differentiating malignancies from benign biliary strictures. By combining IDUS with other techniques, preoperative diagnostic accuracy can be improved substantially through IDUS-guided target biopsy, precise assessment of mucosal or submucosal tumor extension, and providing additional information with regard to cancer infiltration depth and vascular invasion. IDUS is the modality of choice to confirm possible spontaneous stone passage during ERCP, to ensure a clean bile duct after stone extraction and helps to reduce the stone recurrence. Emerging success of IDUS-directed therapeutic endoscopic biliary procedures in selected cases is appealing but warrants further evaluation. Not without limitations, some modifications of the US probe is expected to ease its delivery, facilitate position maintenance, and acquire better visualization of the pancreatobiliary ductal system.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee, Anderson MA, Appalaneni V, *et al.* The role of endoscopy in the evaluation and treatment of patients with biliary neoplasia. *Gastrointest Endosc* 2013;77:167-74.
2. ASGE Standards of Practice Committee, Chandrasekhara V, Chathadi KV, *et al.* The role of endoscopy in benign pancreatic disease. *Gastrointest Endosc* 2015;82:203-14.
3. Singh A, Gelrud A, Agarwal B. Biliary strictures: Diagnostic considerations and approach. *Gastroenterol Rep* (*Oxf*) 2015;3:22-31.
4. Meister T, Heinzow HS, Woestmeyer C, *et al.* Intraductal ultrasound substantiates diagnostics of bile duct strictures of uncertain etiology. *World J Gastroenterol* 2013;19:874-81.
5. Chen L, Lu Y, Wu JC, *et al.* Diagnostic utility of endoscopic retrograde cholangiography/intraductal ultrasound (ERC/IDUS) in distinguishing malignant from benign bile duct obstruction. *Dig Dis Sci* 2016;61:610-7.
6. Navaneethan U, Njei B, Lourdusamy V, *et al.* Comparative effectiveness of

biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: A systematic review and meta-analysis. *Gastrointest Endosc* 2015;81:168-76.
7. García-Cano J. Endoscopic management of benign biliary strictures. *Curr Gastroenterol Rep* 2013;15:336.
8. Siddiqui AA, Mehendiratta V, Jackson W, *et al*. Identification of cholangiocarcinoma by using the Spyglass Spyscope system for peroral cholangioscopy and biopsy collection. *Clin Gastroenterol Hepatol* 2012;10:466-71.
9. Rey JW, Hansen T, Dümcke S, *et al*. Efficacy of SpyGlass (TM)-directed biopsy compared to brush cytology in obtaining adequate tissue for diagnosis in patients with biliary strictures. *World J Gastrointest Endosc* 2014;6:137-43.
10. Singh A, Siddiqui UD. The role of endoscopy in the diagnosis and management of cholangiocarcinoma. *J Clin Gastroenterol* 2015;49:725-37.
11. Tringali A, Lemmers A, Meves V, *et al*. Intraductal biliopancreatic imaging: European Society of Gastrointestinal Endoscopy (ESGE) technology review. *Endoscopy* 2015;47:739-53.
12. Khashab MA, Fockens P, Al-Haddad MA. Utility of EUS in patients with indeterminate biliary strictures and suspected extrahepatic cholangiocarcinoma (with videos). *Gastrointest Endosc* 2012;76:1024-33.
13. Ito Y, Kenmochi T, Egawa T, *et al*. Clinicopathological features of early distal cholangiocarcinoma. *Hepatogastroenterology* 2013;60:673-7.
14. Ito Y, Shibutani S, Egawa T, *et al*. Utility of intraductal ultrasonography as a diagnostic tool in patients with early distal cholangiocarcinoma. *Hepatogastroenterology* 2015;62:782-6.
15. Tamada K, Tomiyama T, Wada S, *et al*. Endoscopic transpapillary bile duct biopsy with the combination of intraductal ultrasonography in the diagnosis of biliary strictures. *Gut* 2002;50:326-31.
16. Krishna NB, Saripalli S, Safdar R, *et al*. Intraductal US in evaluation of biliary strictures without a mass lesion on CT scan or magnetic resonance imaging: Significance of focal wall thickening and extrinsic compression at the stricture site. *Gastrointest Endosc* 2007;66:90-6.
17. Domagk D, Poremba C, Dietl KH, *et al*. Endoscopic transpapillary biopsies and intraductal ultrasonography in the diagnostics of bile duct strictures: A prospective study. *Gut* 2002;51:240-4.
18. Tischendorf JJ, Meier PN, Schneider A, *et al*. Transpapillary intraductal ultrasound in the evaluation of dominant bile duct stenoses in patients with primary sclerosing cholangitis. *Scand J Gastroenterol* 2007;42:1011-7.
19. Heinzow HS, Kammerer S, Rammes C, *et al*. Comparative analysis of ERCP, IDUS, EUS and CT in predicting malignant bile duct strictures. *World J Gastroenterol* 2014;20:10495-503.
20. Lim SU, Park CH, Kee WJ, *et al*. Intraductal ultrasonography without radiocontrast cholangiogramin patients with extrahepatic biliary disease. *Gut Liver* 2015;9:540-6.
21. Liu F, Li F, Zhou Y, *et al*. Intraductal ultrasound improves diagnostic yield for ERCP and cytology brushing in detecting malignant bile duct strictures for patients without biliary mass lesions on CT or MRI. *Gastrointest Endosc* 2008;67:Ab228.
22. Moon JH, Choi HJ, Kim HK, *et al*. The usefulness of IDUS-guided transpapillary bile duct biopsy for the diagnosis of malignant biliary strictures. *Gastrointest Endosc* 2008;67:Ab208.
23. Choi ER, Chung YH, Lee JK, *et al*. Preoperative evaluation of the longitudinal extent of borderline resectable hilar cholangiocarcinoma by intraductal ultrasonography. *J Gastroenterol Hepatol* 2011;26:1804-10.
24. Kim HM, Park JY, Kim KS, *et al*. Intraductal ultrasonography combined with percutaneous transhepatic cholangioscopy for the preoperative evaluation of longitudinal tumor extent in hilar cholangiocarcinoma. *J Gastroenterol Hepatol* 2010;25:286-92.
25. Noda Y, Fujita N, Kobayashi G, *et al*. Intraductal ultrasonography before biliary drainage and transpapillary biopsy in assessment of the longitudinal extent of bile duct cancer. *Dig Endosc* 2008;20:73-8.
26. Tamada K, Kanai N, Ueno N, *et al*. Limitations of intraductal ultrasonography in differentiating between bile duct cancer in stage T1 and stage T2: *In-vitro* and *in-vivo* studies. *Endoscopy* 1997;29:721-5.
27. Menzel J, Poremba C, Dietl KH, *et al*. Preoperative diagnosis of bile duct strictures – Comparison of intraductal ultrasonography with conventional endosonography. *Scand J Gastroenterol* 2000;35:77-82.
28. Bang BW, Hong JT, Choi YC, *et al*. Is endoscopic ultrasound needed as an add-on test for gallstone diseases without choledocholithiasis on multidetector computed tomography? *Dig Dis Sci* 2012;57:3246-51.
29. Fusaroli P, Lisotti A, Syguda A, *et al*. Reliability of endoscopic ultrasound in predicting the number and size of common bile duct stones before endoscopic retrograde cholangiopancreatography. *Dig Liver Dis* 2016;48:277-82.
30. Kim DC, Moon JH, Choi HJ, *et al*. Usefulness of intraductal ultrasonography in icteric patients with highly suspected choledocholithiasis showing normal endoscopic retrograde cholangiopancreatography. *Dig Dis Sci* 2014;59:1902-8.
31. Endo T, Ito K, Fujita N, *et al*. Intraductal ultrasonography in the diagnosis of bile duct stones: When and whom? *Dig Endosc* 2011;23:173-5.
32. Lu J, Guo CY, Xu XF, *et al*. Efficacy of intraductal ultrasonography in the diagnosis of non-opaque choledocholith. *World J Gastroenterol* 2012;18:275-8.
33. Ang TL, Teo EK, Fock KM, *et al*. Are there roles for intraductal US and saline solution irrigation in ensuring complete clearance of common bile duct stones? *Gastrointest Endosc* 2009;69:1276-81.
34. Tsuchiya S, Tsuyuguchi T, Sakai Y, *et al*. Clinical utility of intraductal US to decrease early recurrence rate of common bile duct stones after endoscopic papillotomy. *J Gastroenterol Hepatol* 2008;23:1590-5.
35. Kim HS, Moon JH, Choi HJ, *et al*. The role of intraductal US in the management of idiopathic recurrent pancreatitis without a definite cause on ERCP. *Gastrointest Endosc* 2011;73:1148-54.
36. Yoon LY, Moon JH, Choi HJ, *et al*. Clinical usefulness of intraductal ultrasonography for the management of acute biliary pancreatitis. *J Gastroenterol Hepatol* 2015;30:952-6.
37. Varadarajulu S. A modified technique to overcome the limitations of intraductal ultrasound for diagnosis of common bile duct stones. *Endoscopy* 2008;40 Suppl 2:E152.
38. Kim HN, Park CH, Cho EA, *et al*. Role of balloon-sheathed intraductal ultrasonography for patients with extensive pneumobilia. *Gut Liver* 2015;9:561-5.
39. Suárez V, Puerta A, Santos LF, *et al*. Portal hypertensive biliopathy: A single center experience and literature review. *World J Hepatol* 2013;5:137-44.
40. Rana SS, Bhasin DK, Rao C, *et al*. Portal hypertensive biliopathy developing after acute severe pancreatitis. *Endosc Ultrasound* 2013;2:228-9.
41. Macaluso FS, Maida M, Dioguardi Burgio M, *et al*. Education and Imaging. Hepatobiliary and pancreatic: Portal hypertensive biliopathy presenting as acute cholangitis. *J Gastroenterol Hepatol* 2013;28:1257.
42. Takagi T, Irisawa A, Shibukawa G, *et al*. Intraductal ultrasonographic anatomy of biliary varices in patients with portal hypertension. *Endosc Ultrasound* 2015;4:44-51.
43. Rana SS, Bhasin DK, Rao C. Communication of duodenal varix with pericholedochal venous plexus demonstrated by endoscopic ultrasound in a patient of portal biliopathy. *Endosc Ultrasound* 2012;1:165-6.
44. Umphress JL, Pecha RE, Urayama S. Biliary stricture caused by portal biliopathy: Diagnosis by EUS with Doppler US. *Gastrointest Endosc* 2004;60:1021-4.
45. Ramchandani M, Nageshwar Reddy D, Lakhtakia S, *et al*. Role of single-operator per-oral cholangioscopy and intraductal US in assessment of portal biliopathy (with videos). *Gastrointest Endosc* 2014;79:1015-9.
46. Nakazawa T, Ikeda Y, Kawaguchi Y, *et al*. Isolated intrapancreatic IgG4-related sclerosing cholangitis. *World J Gastroenterol* 2015;21:1334-43.
47. Kuwatani M, Kawakami H, Zen Y, *et al*. Difference from bile duct cancer and relationship between bile duct wall thickness and serum IgG/IgG4 levels in IgG4-related sclerosing cholangitis. *Hepatogastroenterology* 2014;61:1852-6.
48. Huggett MT, Culver EL, Kumar M, *et al*. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. *Am J Gastroenterol* 2014;109:1675-83.
49. Ohara H, Nakazawa T, Kawa S, *et al*. Establishment of a serum IgG4

cut-off value for the differential diagnosis of IgG4-related sclerosing cholangitis: A Japanese cohort. *J Gastroenterol Hepatol* 2013;28:1247-51.
50. Zen Y, Kawakami H, Kim JH. IgG4-related sclerosing cholangitis: All we need to know. *J Gastroenterol* 2016;51:295-312.
51. Naitoh I, Nakazawa T, Ohara H, *et al.* Endoscopic transpapillary intraductal ultrasonography and biopsy in the diagnosis of IgG4-related sclerosing cholangitis. *J Gastroenterol* 2009;44:1147-55.
52. Naitoh I, Nakazawa T, Hayashi K, *et al.* Comparison of intraductal ultrasonography findings between primary sclerosing cholangitis and IgG4-related sclerosing cholangitis. *J Gastroenterol Hepatol* 2015;30:1104-9.
53. Kubota K, Kato S, Uchiyama T, *et al.* Discrimination between sclerosing cholangitis-associated autoimmune pancreatitis and primary sclerosing cholangitis, cancer using intraductal ultrasonography. *Dig Endosc* 2011;23:10-6.
54. Nakazawa T, Naitoh I, Hayashi K, *et al.* Diagnosis of IgG4-related sclerosing cholangitis. *World J Gastroenterol* 2013;19:7661-70.
55. Lee JM, Park CH, Rew SJ, *et al.* Intraductal ultrasonography-directed endoscopic retrograde biliary drainage without fluoroscopy. *Endoscopy* 2014;46 Suppl 1:E495.
56. Park SY, Park CH, Lim SU, *et al.* Intraductal US-directed management of bile duct stones without radiocontrast cholangiography. *Gastrointest Endosc* 2015;82:939-43.
57. Stavropoulos S, Larghi A, Verna E, *et al.* Therapeutic endoscopic retrograde cholangiopancreatography without fluoroscopy in four critically ill patients using wire-guided intraductal ultrasound. *Endoscopy* 2005;37:389-92.
58. Arnelo U, Siiki A, Swahn F, *et al.* Single-operator pancreatoscopy is helpful in the evaluation of suspected intraductal papillary mucinous neoplasms (IPMN). *Pancreatology* 2014;14:510-4.
59. Nagayoshi Y, Aso T, Ohtsuka T, *et al.* Peroral pancreatoscopy using the SpyGlass system for the assessment of intraductal papillary mucinous neoplasm of the pancreas. *J Hepatobiliary Pancreat Sci* 2014;21:410-7.
60. Kachaamy T, Salah W, Dzeletovic I, *et al.* Intraoperative laparoscopic-assisted pancreatoscopy and its role in differentiating main duct intraductal papillary mucinous neoplasm from chronic pancreatitis. *Gastrointest Endosc* 2015;81:459-60.
61. Krishna SG, Swanson B, Conwell DL, *et al. In vivo* and *ex vivo* needle-based confocal endomicroscopy of intraductal papillary mucinous neoplasm of the pancreas. *Gastrointest Endosc* 2015;82:571-2.
62. Cheon YK, Cho YD, Jeon SR, *et al.* Pancreatic resection guided by preoperative intraductal ultrasonography for intraductal papillary mucinous neoplasm. *Am J Gastroenterol* 2010;105:1963-9.
63. Kobayashi G, Fujita N, Noda Y, *et al.* Lateral spread along the main pancreatic duct in branch-duct intraductal papillary-mucinous neoplasms of the pancreas: Usefulness of intraductal ultrasonography for its evaluation. *Dig Endosc* 2011;23:62-8.
64. Navez J, Hubert C, Gigot JF, *et al.* Impact of intraoperative pancreatoscopy with intraductal biopsies on surgical management of intraductal papillary mucinous neoplasm of the pancreas. *J Am Coll Surg* 2015;221:982-7.
65. Yelamali A, Mansard MJ, Dama R, *et al.* Intraoperative pancreatoscopy with narrow band imaging: A novel method for assessment of resection margins in case of intraductal papillary mucinous neoplasm. *Surg Endosc* 2012;26:3682-5.
66. ASGE Standards of Practice Committee, Chathadi KV, Khashab MA, *et al.* The role of endoscopy in ampullary and duodenal adenomas. *Gastrointest Endosc* 2015;82:773-81.
67. Okano N, Igarashi Y, Hara S, *et al.* Endosonographic preoperative evaluation for tumors of the ampulla of vater using endoscopic ultrasonography and intraductal ultrasonography. *Clin Endosc* 2014;47:174-7.
68. Vila JJ, Jiménez J, Prieto C, *et al.* A novel technique to perform intraductal ultrasonography with the aid of a biliary stent introduction system: A new application for an old device. *Gastrointest Endosc* 2006;64:297-8.