REVIEW ARTICLE

Utility of EUS in patients with indeterminate biliary strictures and suspected extrahepatic cholangiocarcinoma (with videos)

Mouen A. Khashab, MD,[1] Paul Fockens, MD,[2] Mohammad A. Al-Haddad, MD[3]

Baltimore, Maryland, USA

Cholangiocarcinoma is the most common malignancy of the biliary system and accounts for about 3% of all GI malignancies.[1,2] Nevertheless, there appears to be a worldwide increase in its incidence and mortality.[3,4] Cholangiocarcinoma is classified into intrahepatic and extrahepatic tumors. Extrahepatic cholangiocarcinoma involves the confluence of the right and left hepatic ducts (perihilar carcinomas) in 70% to 80% of cases. About 20% to 30% of cholangiocarcinomas arise more distally. Distal bile duct tumors are defined as those arising between the junction of the cystic duct-bile duct and the ampulla of Vater.[5] Diffuse involvement of the ducts is rare and occurs in less than 2% of cases.[5] Cholangiocarcinoma usually is diagnosed at an advanced stage, resulting in overall poor prognosis of this tumor. Patients with T1 stage tumor who undergo resection have an excellent prognosis, with a cumulative 5-year survival rate of about 100%.[6] T1 stage tumors are confined to the bile-duct wall and are limited to the mucosa or fibromuscular layer of the bile duct and do not usually present with lymph node metastases. Therefore, a detection of bile duct carcinoma in T1 stage is critical for long-term survival. Serum alkaline phosphatase and gamma glutamyl transferase levels are elevated in only 40% of these patients, and 40% of patients are not icteric.[6] Cholangiocarcinoma typically presents clinically as biliary strictures. These strictures remain a diagnostic dilemma because a significant proportion of them remain inconclusive for malignancy despite a thorough radiologic, endoscopic, and laboratory evaluation. Biliary strictures are considered indeterminate when basic work-up, including transabdominal imaging and ERCP with routine cytologic brushing and/or endoscopic biopsy, are nondiagnostic.

Early and accurate diagnosis impacts not only patients' outcomes and possible surgical candidacy but also potential targeted chemotherapies.

EUS has become a valuable tool in the evaluation of lesions in the GI tract as well as in the pancreaticobiliary system. It has the advantage of being able to provide real-time imaging of the GI tract and adjacent organs as well as to obtain tissue through FNA. EUS-guided FNA (EUS-FNA) has a sensitivity of about 85% and a specificity approaching 100% for the diagnosis of pancreatic tumors.[7,8] The role of EUS in evaluating patients with indeterminate biliary strictures and suspected extrahepatic cholangiocarcinoma is still not well-defined. This review outlines the work-up recommended to investigate such patients, with a focus on the role of EUS to provide a definitive diagnosis.

RADIOLOGIC WORK-UP

Transabdominal US usually is the initial diagnostic modality used to investigate suspected biliary pathology but does not reliably examine the distal common bile duct because of the interference of bowel gas.[9] Abdominal CT is useful for work-up of patients with suspected cholangiocarcinoma. However, it has suboptimal sensitivity for the detection of early tumors.[10,11] In addition, other shortcomings of CT are its suboptimal sensitivity of 54% for detection of regional lymph nodes and its tendency to underestimate the extent of proximal tumors.[12,13] Since its introduction in 1991,[14] MRCP has emerged as an accurate, noninvasive modality for biliary imaging.[15,16] However, its specificity and positive predictive values are suboptimal because it cannot reliably distinguish malignant strictures from other strictures caused by benign etiologies.[17,18] Moreover, the accuracy of MRCP in the assessment of vascular involvement and hepatic parenchyma involvement is only 67% to 73% and 78% to 80%, respectively.[19,20] Nevertheless, some ductal features on MRCP may suggest

Abbreviations: DIA, digital imaging analysis; EUS-FNA, EUS-guided FNA; FISH, fluorescence in situ hybridization; IDUS, intraductal US; pCLE, probe-based confocal laser endomicroscopy; SOC, single-operator cholangioscopy.

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malignant or benign etiology of biliary strictures. Malignancy is suggested by long (>10 mm), asymmetric, and irregular strictures. However, these criteria are not particularly sensitive or specific.[21] Therefore, unless abdominal imaging detects biliary mass lesions, further endoscopic work-up is usually warranted to determine the etiology of biliary strictures.

ERCP

Intraductal brushing during ERCP remains the first-line approach for tissue sampling of biliary strictures because of its wide availability and technical ease in most cases. However, most studies report a poor sensitivity of 27% to 56%.[22-29] Multiple strategies have been used to improve the sensitivity, with marginal benefit. These have included novel brushing devices,[30] biliary stricture dilation with subsequent brushings,[31] repeated brushings,[31] endoscopic needle aspiration,[26] immunohistochemistry testing,[32] and mutational analysis.[32] Inadequate biliary cytology specimens remains the main reason for nondiagnostic samples during ERCP. This may be overcome by the presence of an on-site cytopathologist or technician, which allows real-time assessment of cytology samples and may decrease the likelihood of inadequate samples and improper sample preparation (similar to the practice with EUS-FNA).[33]

Endobiliary forceps biopsy of biliary strictures during ERCP is another endoscopic technique used in routine clinical practice for sampling biliary strictures. In general, forceps biopsies have had the highest yield when compared with brush cytology and percutaneous biopsy. Cancer detection rates by using endobiliary forceps range from 44% to 89% for cholangiocarcinoma and 33% to 71% for pancreatic cancer.[34-37] However, endobiliary biopsy remains technically challenging (especially for proximal biliary strictures), and complications, including bleeding and biliary perforation, have been described.

ANCILLARY CYTOLOGY TECHNIQUES

Chromosomal abnormalities are typically seen in biliary tract malignancies. New ancillary cytologic techniques, such as fluorescence in situ hybridization (FISH) and digital imaging analysis (DIA), have been used recently to improve the sensitivity of routine cytology for the diagnosis of malignancy in pancreatobiliary strictures. FISH analysis detects chromosomal polysomy by using fluorescent probes, whereas DIA technique quantifies nuclear DNA via special stains to assess for the presence of aneuploidy.[32,38,39] Only 80% of pancreaticobiliary malignancies manifest these cellular alterations. Therefore, the sensitivity of these advanced techniques is still not optimal. Levy et al[38] found that FISH improves sensitivity 14% to 24% when routine cytology is negative. Fritcher et al[32] found that patients with abnormal FISH results were 77 times more likely to have carcinoma than those with normal FISH results. They also found that DIA had a higher sensitivity (44.8%) than cytology; however, specificity was significantly lower at 89.1%, and DIA was not found to be a significant independent predictor of malignancy.[32] Therefore, FISH seems to be a more valuable ancillary cytologic technique for the evaluation of indeterminate biliary strictures. It is particularly useful in biliary malignancy because it requires fewer cells for analysis than routine cytology or flow cytometry. A recent report studied the additional value of including deletion of 9p21 (p16) in the diagnostic criteria of FISH for malignant biliary strictures.[40] This addition significantly improved the sensitivity of FISH from 47% to 84%.

It is crucial to realize that benign strictures in patients with primary sclerosing cholangitis may manifest chromosomal abnormalities and, thus, the specificity of FISH in this setting is lower than that of routine cytology, ranging from 67% to 88%.[41] However, the sensitivity of FISH for malignancy in this setting is still higher than that of routine cytology at 72%.[41] In conclusion, FISH increases the sensitivity of brush cytology of indeterminate biliary strictures at the expense of a lower specificity. Therefore, FISH should be reserved for patients with high pretest probability for malignant strictures (eg, primary sclerosing cholangitis patients with new dominant strictures, patients with persistent elevation of CA 19-9 levels despite biliary decompression).

CHOLANGIOSCOPY

Percutaneous cholangioscopy is effective in visualizing the biliary tree but requires percutaneous biliary access and repeated dilations for acceptance of the cholangioscope. The use of "mother-baby" cholangioscopes has fallen out of favor because of the requirement for two operators, fragility, suboptimal irrigation systems, and lack of 4-way tip deflection.[42]

WIRE-GUIDED DIRECT CHOLANGIOSCOPY

The Spyglass direct visualization system (Boston Scientific, Natick, Mass) allows for single-operator cholangioscopy (SOC).[43-45] Chen et al[46] conducted a large-scale, multicenter, prospective, observational study of SOC procedures in 297 patients with biliary strictures and/or stones and aimed to provide confirmatory evidence that direct visualization by using the SOC system can aid in the diagnosis of biliary disease and facilitate stone therapy. The overall procedure success rate was 89%. SOC visual impression had a sensitivity, specificity, positive predictive value and negative predictive value for diagnosing malignancy of 78%, 82%, 80%, and 80%, respectively. For SOC-directed biopsy, the respective results were 49%, 98%, 100%, and 72%. Sensitivity was higher for intrinsic bile duct malignancies as compared with nonintrinsic malignancies (84% and 66%, respectively). Diagnostic SOC procedures altered clinical man-

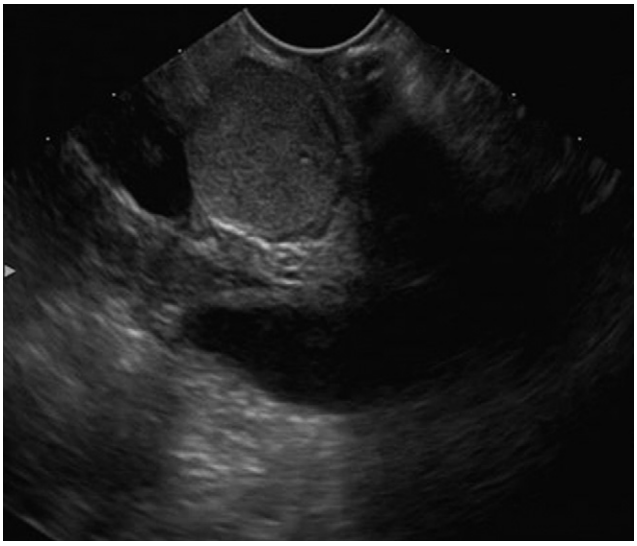

Figure 1. EUS demonstrating hypoechoic bile duct mass suggestive of cholangiocarcinoma. EUS-FNA was diagnostic of cholangiocarcinoma.

agement in 64% of patients. The incidence of serious procedure-related adverse events was 7.5% for diagnostic SOC. Ramchandani et al[47] recently described a sensitivity of 95% and specificity of 79% for visual impression during SOC in 36 patients with indeterminate biliary strictures. Both sensitivity and specificity were 82% after using cholangioscopic biopsies.[47] These results suggest a benefit of SOC in patients with indeterminate biliary strictures. Visual impression of malignancy is an integral part of cholangioscopy, especially when the yield of biopsies is suboptimal. The presence of "tumor vessels" within biliary strictures during cholangioscopy was found to indicate biliary malignancy.[48] These irregular, dilated vessels are due to neovascularization at the site of the stricture because of tumor growth. Their presence has specificity up to 100% for malignancy.[49] However, the interobserver variability and reproducibility of such visual criteria are not known. Intraductal nodules and masses can be visualized during cholangioscopy and are indicative of malignancy.[48] However, these ductal findings are visualized in only a fraction of patients with cholangiocarcinoma.

SUPRAVITAL DYE-ASSISTED CHOLANGIOSCOPY

Biliary mucosal changes can be further delineated by using methylene blue-aided cholangioscopy. In a feasibility study, Hoffman et al[50] showed that normal and nondysplastic mucosa were characterized by a homogenous light blue staining pattern, whereas inflamed and dysplastic mucosa were characterized by intense and inhomogeneous dark blue staining. More studies are needed to depict the utility of chromoendoscopy during cholangioscopy.

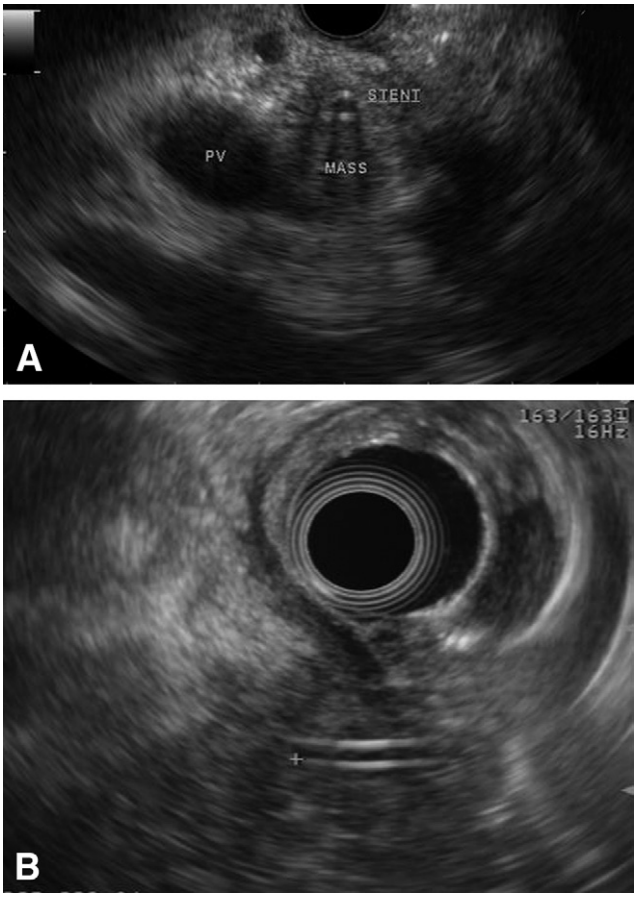

Figure 2. A, EUS revealing a small distal bile duct mass with a stent seen in the bile duct. The mass abuts the portal vein. The superior mesenteric artery is not involved and is seen posterior to the portal vein. **B,** EUS demonstrating a hypoechoic distal bile duct mass invading the duodenal wall. *PV,* portal vein.

PROBE-BASED CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy permits real-time histologic evaluation during endoscopy. Probe-based confocal laser endomicroscopy (pCLE) can be used to generate microscopic information during ERCP.[51] The CholangioFlex probe (Mauna Kea Technologies, Paris, France) is specially designed for pCLE during ERCP procedures. In a feasibility prospective study on 14 patients with indeterminate biliary strictures, Meining et al[52] predicted neoplasia with a sensitivity of 83%, specificity of 88%, and accuracy of 86%. In a larger study of 102 patients with indeterminate pancreaticobiliary strictures, the overall diagnostic accuracy of pCLE was 81%.[53,54] Accuracy for combination of ERCP and pCLE was significantly higher compared with ERCP with tissue acquisition alone (90% vs 73%; $P = .001$). Biliary pCLE is still in its infancy and requires further study before its routine use in the work-up of indeterminate biliary strictures is recommended. The effect of prior stenting on the accuracy of pCLE and the intraobserver

TABLE 1. Summary of published studies on the role of preoperative EUS morphology in staging of cholangiocarcinoma

First author	Publication year	No. patients	Accuracy of tumor staging (%)	Accuracy of node staging (%)	Accuracy of predicting portal vein invasion (%)
Mukai[55]	1992	16	81	81	88
Tio[56]	1993	46	66	64	Not reported
Sugiyama[57]	1997	19	Not reported	Not reported	100

and interobserver agreement of pCLE in the evaluation of biliary strictures need further study.

EUS

EUS allows detailed examination of the extrahepatic biliary tree because of the proximity of the US probe in the proximal duodenum to the bile duct. Examination of the bile duct is typically started with the echoendoscope situated at the ampulla. By slowly withdrawing and rotating the echoendoscope toward the pylorus region, the entire bile duct can be examined. A second position to examine the bile ducts is a long endoscope position in the duodenal bulb, where it is often possible to obtain a longitudinal image of the duct. Both the bile duct bifurcation into the left and right main intrahepatic ducts and bile duct insertion into the ampulla should be identified to ensure complete examination of the extrahepatic bile duct. Bile duct masses typically appear as hypoechoic lesions on EUS (Fig. 1). The relationship of the mass to the hepatic parenchyma, portal vasculature, and hepatic arteries should be scrutinized to stage the tumor and assess for resectability (Fig. 2A and B).

EUS STAGING OF CHOLANGIOCARCINOMA

EUS is an important addition to the armamentarium of available imaging techniques used to stage and assess resectability of cholangiocarcinoma. Endosonographic staging of cholangiocarcinoma is based on the tumor, nodes, metastasis system. Several studies evaluated the use of EUS for preoperative staging of extrahepatic bile duct tumors (Table 1).[55-57] EUS has high accuracy (88%-100%) for predicting portal vein invasion and performs better than transabdominal US, CT, and angiography in this aspect.[55,57] In a recent, large, single-center study, EUS was more sensitive in predicting surgical unresectability than was CT scanning (53% vs 33%), but combining the two modalities increased this sensitivity to 73%.[58]

In terms of nodal staging, EUS has the highest sensitivity for the assessment of regional lymph nodes and allows for FNA of suspicious lymph nodes.[1,59] Gleeson et al[60] performed EUS-FNA on 47 patients with hilar cholangiocarcinoma being considered for liver transplantation. The goals of this study were to examine the performance of EUS-FNA for lymph node detection in this setting as compared with CT/magnetic resonance imaging and to identify features of malignant nodes in patients with cholangiocarcinoma.[60] EUS identified lymph nodes in all patients, and a total of 70 regional lymph nodes were found, with 9 (in 8 patients) of 70 (18%) confirmed as malignant by pathologic examination. Therefore, 17% of patients were spared the cost and morbidity of an unnecessary staging laparotomy. There was no significant relationship between the echogenic and morphologic features of lymph nodes and final cytologic results. EUS detected 12 more patients with lymph nodes than did standard imaging studies (CT or magnetic resonance imaging). Two patients who had negative nodes by EUS were found to have malignant perigastric lymph nodes on surgical exploration. Thus, known features of metastatic nodal disease (round shape, well-demarcated borders, hypoechoic texture, and enlarged size)[61] are inaccurate in predicting malignant nodes in the setting of cholangiocarcinoma. The authors suggested that EUS-FNA of all visualized lymph nodes irrespective of appearance is advised because morphologic and echo features do not predict malignant involvement. It is worth mentioning that metastasis to regional lymph nodes does not change the surgical resection plan in patients not considered for liver transplantation. However, it remains to be seen whether EUS-FNA of lymph nodes may play a role in better selection of patients who may benefit from neoadjuvant chemoradiation therapy before curative resection.[62,63]

Other studies showed lower sensitivity of EUS for detecting nodal metastasis in cholangiocarcinoma.[58] This is likely because FNA of benign-appearing lymph nodes was not performed. EUS elastography may play a role in better targeting nodes with high-risk elastographic features and in reducing the number of false-negative cases and puncture times (Video 1, available online at www.giejournal.org).[64,65] However, the role of EUS elastography in the setting of cholangiocarcinoma remains to be studied and is unlikely to completely replace FNA.

EUS-FNA FOR DIAGNOSIS OF CHOLANGIOCARCINOMA

Approximately 13% to 24% of patients with presumed hilar cholangiocarcinoma are found to have benign dis-

TABLE 2. Summary of published studies on EUS-FNA of indeterminate biliary strictures*

First author	Publication year	Study design	All biliary strictures (no.)	Hilar strictures (no.)	Mass seen on radiologic imaging (%)	Mass seen on EUS (%)	Sensitivity of EUS-FNA for all biliary strictures (%)	Sensitivity of EUS-FNA for proximal extrahepatic biliary strictures (%)	Sensitivity of EUS-FNA for distal biliary strictures (%)
Fritscher-Ravens[72]	2000	Prospective	10	10	NR	100	80	80	NA
Fritscher-Ravens[73]	2004	Prospective	44	44	NR	98	89†	89†	NA
Eloubeidi[74]	2004	Prospective	28	15	33	89	75	NR	NR
Byrne[75]	2004	Retrospective	35	3	NR	71	86	NR	NR
Lee[76]	2004	Retrospective	40	1	0	25	47	NR	NR
Rösch[77]	2004	Prospective	50	11	NR	NR	43	25	60
Meara[78]	2006	Prospective	46	NR	NR	NR	87‡	NR	NR
Dewitt[79]	2006	Prospective	24	24	39	96	77	77	NA
Mohamadnejad[58]	2011	Prospective	81	30	30 (CT), 42 (MRI)	94	73§	59§	81

NR, Not reported; *NA*, not applicable.
*No complications in any studies.
†Includes the 10 patients reported in reference 72.
‡Includes 28 patients reported in reference 74
§Includes 24 patients reported in reference 79.

ease after surgical resection.[66,67] Therefore, accurate preoperative diagnosis is paramount to avoiding unnecessary surgery, and patients with suspected cholangiocarcinoma should preferably have a confirmatory cytopathologic diagnosis before curative radical resection is attempted. Although pancreaticoduodenectomy (Whipple resection) is required for surgical resection of distal cholangiocarcinoma, partial hepatectomies are frequently performed for treatment of perihilar (Klatskin) tumors.[68] These procedures are associated with significant morbidity rate of 37% to 64% and mortality of 8% to 10%.[69-71] The difficulty is amplified when there is an attempt to discern malignant from nonmalignant strictures in patients with primary sclerosing cholangitis, because this affects transplantation decisions.

EUS-FNA of suspected extrahepatic cholangiocarcinoma can be technically difficult, especially in Klatskin tumors. These tumors are best visualized from the prepyloric or postpyloric position, which is difficult to maintain during the puncture process. Performing FNA in the "long position" may help prevent this problem because the gastric greater curvature provides support against the force exerted by needle puncture of the tumor. Multiple studies have reported on the use of EUS-FNA for the diagnosis of extrahepatic cholangiocarcinoma (Table 2).[58,72-79] Advantages of EUS-FNA in this setting are multiple and are summarized in Table 3. The reported sensitivity of EUS-FNA for the diagnosis of cholangiocarcinoma in patients with indeterminate extrahepatic biliary strictures ranges between 43% and 89%, with most studies reporting sensitivities greater than 70% (Table 2). This relatively high sensitivity actually represents an incremental yield above prior imaging and ERCP, because most of these studies included patients with nonrevealing imaging and nondiagnostic ERCP (ie, negative routine cytology). A definite mass is seen on radiologic imaging in only a third of patients with extrahepatic cholangiocarcinoma.[58,74,79] In contrast, most studies reported visualization of biliary mass lesions during EUS in the majority of patients (Table 2) (Video 2, available online at www.giejournal.org). EUS-FNA is, thus, feasible in most cases because a mass can be visualized (Fig. 3A-F) (Video 2). Occasionally, bile duct wall thickening rather than a mass is visualized by EUS. In

TABLE 3. Advantages of EUS-FNA in patients with suspected extrahepatic cholangiocarcinoma

High sensitivity for diagnosis of cholangiocarcinoma in patients with prior negative imaging and nondiagnostic ERCP with brushing
Ability to visualize bile duct mass lesions not previously seen on abdominal imaging
Ability to visualize regional and distant lymph nodes not previously seen on abdominal imaging
Avoid unwarranted surgical interventions by diagnosing metastatic spread to distant lymph nodes
Avoid unwarranted surgical interventions by diagnosing benign disease
Avoid liver transplantation by diagnosing metastatic spread to regional or distant lymph nodes
Provide alternative diagnoses not treatable by surgical resection (eg, lymphoma, metastasis)
Aid in triaging patients to alternative therapies (eg, photodynamic therapy, chemoradiation therapy)

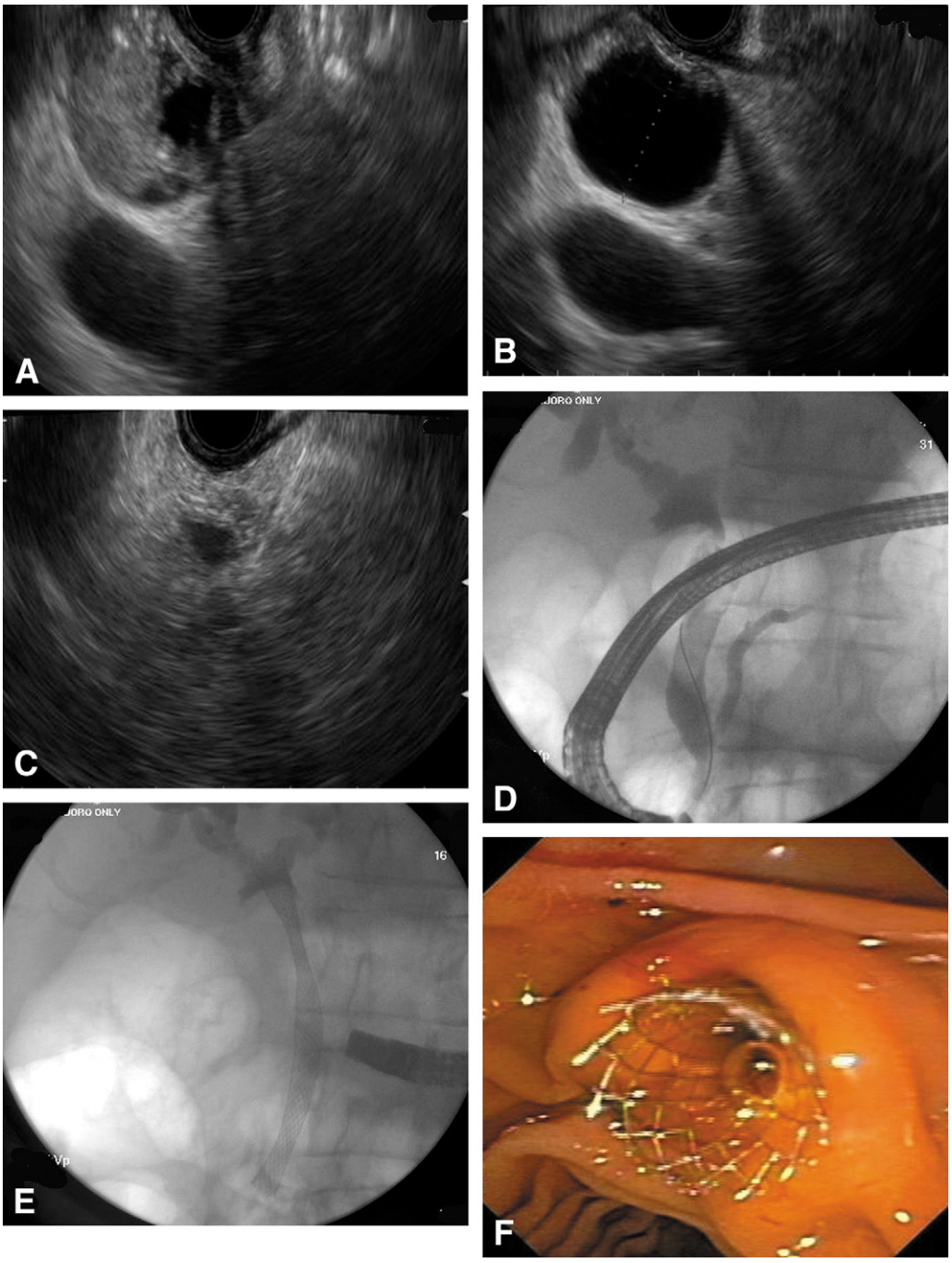

Figure 3. A, EUS showing a bile duct mass that was missed by a CT scan and magnetic resonance imaging. **B,** Biliary dilation was present proximal to the stenosis. **C,** EUS-FNA was performed and was diagnostic of cholangiocarcinoma. **D,** ERC was performed during the same session, and cholangiography revealed a distal biliary stricture. **E, F,** A self-expandable metal biliary stent was placed.

these instances, careful FNA of the thickened duct wall can be attempted by using a 22-gauge or a 25-gauge FNA needle.

Two clinical aspects may impact the sensitivity of EUS-FNA of indeterminate extrahepatic biliary strictures: location of stricture (proximal vs distal) and the presence of a bile duct stent. Mohamadnejad et al[58] compared sensitivity of EUS-FNA of proximal and distal cholangiocarcinoma and found significantly lower sensitivity for proximal tumors (59% vs 81%; $P = .04$, respectively). This could be explained by the relative ease of visualizing and sampling distal bile duct lesions. In contrast, proximal lesions are further from the tip of the echoendoscope and are closer to the liver parenchyma, rendering their diagnosis and sampling more challenging. Although the presence of a bile duct stent could provide a point of reference and may

facilitate identification of a bile duct tumor, the stent itself may produce significant acoustic shadowing that interferes with sonographic imaging of the tumor. In addition, the presence of the stent through a bile duct tumor limits access to and FNA of the contralateral side of the tumor.[58] In a closely related tumor, the impact of biliary stents on the accuracy of staging of pancreatic head cancers remains controversial.[80,81] Some studies found that the presence of a biliary stent did not negatively impact the yield of EUS-FNA where high diagnostic sensitivity was reported.[74]

From a practical standpoint, most patients who present for EUS-FNA for suspected cholangiocarcinoma would have undergone ERCP with biliary stenting for diagnosis (ie, brushing) and treatment of biliary obstruction (ie, stenting). Therefore, most patients will have a biliary stent in place. Whenever feasible, EUS-FNA should be performed immediately before placement of biliary stents to improve diagnostic and staging accuracy of suspected biliary tumors and eliminate the subsequent risk of cholangitis arising from inadvertently contaminating the obstructed biliary system during FNA.

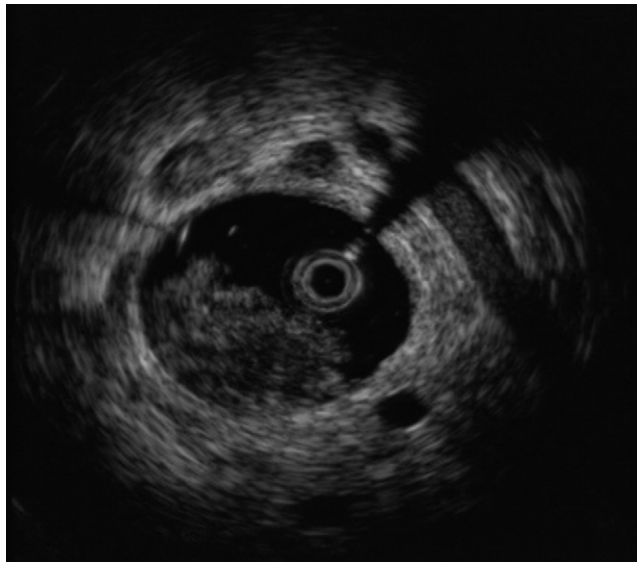

Figure 4. Intraductal US showing a bile duct mass and surrounding lymph nodes.

SAFETY OF EUS-FNA IN PATIENTS WITH SUSPECTED EXTRAHEPATIC CHOLANGIOCARCINOMA

EUS-FNA has been reported to be relatively safe and without significant adverse events reported (Table 2). The risk of cholangitis is decreased by establishing biliary drainage with stent placement before or immediately after the EUS procedure. Nevertheless, some experts discourage percutaneous or EUS-FNA of primary biliary lesions in patients who are potential candidates for curative-intent surgery because of the potential for tumor spread.[1,60] For example, the Mayo Clinic protocol for liver transplantation of cholangiocarcinoma considers aspiration of the primary tumor as a contraindication to proceeding with neoadjuvant therapy and liver transplantation.[60,82] Tumor seeding has been reported in hepatocellular carcinoma after transabdominal FNA.[83] In addition, there have been a few reports of tumor seeding to the peritoneum and the skin from percutaneous biliary catheters.[84] However, no cases of tumor seeding because of EUS-FNA of extrahepatic cholangiocarcinoma have been reported. This is obviously less of an issue in cases of distal tumors because the site of puncture (proximal duodenum) is usually resected during pancreaticoduodenectomy. For proximal tumors, the small theoretical risk of tumor seeding should be carefully considered before FNA of a potentially resectable cholangiocarcinoma until further data become available.

INTRADUCTAL US

ERCP with intraductal US (IDUS) also has been used to improve the diagnostic yield of biliary strictures.[85-87] IDUS is performed by over-the-wire insertion of a small and high-frequency US probe into the biliary system through a standard duodenoscope under fluoroscopic guidance.[88] IDUS provides local staging required to select patients who would benefit from surgical resection when a malignancy is identified.[89] IDUS has consequently emerged as an adjunct to ERCP in the evaluation of biliary strictures. Sonographic features seen during IDUS that are suggestive of malignancy include eccentric wall thickening with an irregular surface, a hypoechoic mass, heterogeneity of the internal echo pattern, a papillary surface, disruption of the normal 3-layer sonographic structure of the bile duct, the presence of lymph nodes, and vascular invasion (Fig. 4).[90] The accuracy of these criteria in patients with biliary strictures ranges from 83% to 90%.[88,91,92] IDUS has been shown to improve the diagnostic accuracy of ERCP (with routine cytology) to 58% to 90%.[87,91,93] The main limitation of IDUS is that it does not provide tissue diagnosis, which guides therapeutic interventions, especially in inoperable patients. In addition, the benefit of IDUS is limited in the repeated evaluation of strictures, because the presence of a previously placed biliary stent affects its diagnostic yield.[76] Lee et al[76] favored EUS to IDUS, given that their patients typically had prior stents placed for the treatment of indeterminate strictures. Despite the cost and fragility of IDUS probes, IDUS may still have a role in concert with EUS, especially in patients without prior stent placement or in those with proximal biliary (eg, hilar strictures) lesions, where EUS has shown suboptimal accuracy.[58,87]

EUS AND CHOLANGIOCARCINOMA: MOVING FORWARD

Indeterminate biliary strictures should be considered malignant until proven otherwise. Accurate preoperative

diagnosis of extrahepatic cholangiocarcinoma is difficult. Although new endoscopic (eg, SOC) and cytologic (eg, FISH) techniques have improved the sensitivity for diagnosing suspected cholangiocarcinoma, differentiation between benign and malignant biliary strictures remains challenging. EUS-FNA plays a major role in improving the diagnostic yield in these patients and should be incorporated in the evaluation of patients with indeterminate biliary strictures. EUS visualizes bile duct mass in a majority of patients. Although endosonographic examination of the bile duct is challenging, EUS-FNA has multiple advantages, including providing a definitive cytologic diagnosis, predicting surgical resectability, and triaging of patients to alternative treatments (eg, liver transplantation, photodynamic therapy, chemoradiation therapy). The notional risk of tumor seeding should be taken into consideration before FNA of a potentially resectable tumor. Larger and long-term prospective studies are needed to assess the risk of seeding after EUS-FNA. Last, all studies reporting on EUS-FNA of cholangiocarcinoma have come from expert centers. It is important to study how EUS-FNA of suspected cholangiocarcinoma performs in community practices, especially given the expertise needed to localize and sample such tumors.

REFERENCES

1. Blechacz B, Komuta M, Roskams T, et al. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 2011;8:512-22.
2. Charbel H, Al-Kawas FH. Cholangiocarcinoma: epidemiology, risk factors, pathogenesis, and diagnosis. Curr Gastroenterol Rep 2011;13: 182-7.
3. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33:1353-7.
4. Mouzas IA, Dimoulios P, Vlachonikolis IG, et al. Increasing incidence of cholangiocarcinoma in Crete 1992-2000. Anticancer Res 2002;22:3637-41.
5. Nakeeb A, Pitt HA, Sohn TA, et al. Cholangiocarcinoma: a spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463-73; discussion 473-5.
6. Mizumoto R, Ogura Y, Kusuda T. Definition and diagnosis of early cancer of the biliary tract. Hepatogastroenterology 1993;40:69-77.
7. Gress F, Gottlieb K, Sherman S, et al. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. Ann Intern Med 2001;134:459-64.
8. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol 2002;97:1386-91.
9. Songur Y, Temucin G, Sahin B. Endoscopic ultrasonography in the evaluation of dilated common bile duct. J Clin Gastroenterol 2001;33:302-5.
10. Sugiyama M, Atomi Y, Kuroda A, et al. Bile duct carcinoma without jaundice: clues to early diagnosis. Hepatogastroenterology 1997;44:1477-83.
11. Xu AM, Cheng HY, Jiang WB, et al. Multi-slice three-dimensional spiral CT cholangiography: a new technique for diagnosis of biliary diseases. Hepatobiliary Pancreat Dis Int 2002;1:595-603.
12. Vilgrain V. Staging cholangiocarcinoma by imaging studies. HPB (Oxford) 2008;10:106-9.
13. Lee HY, Kim SH, Lee JM, et al. Preoperative assessment of resectability of hepatic hilar cholangiocarcinoma: combined CT and cholangiography with revised criteria. Radiology 2006;239:113-21.
14. Wallner BK, Schumacher KA, Weidenmaier W, et al. Dilated biliary tract: evaluation with MR cholangiography with a T2-weighted contrast-enhanced fast sequence. Radiology 1991;181:805-8.
15. Taylor AC, Little AF, Hennessy OF, et al. Prospective assessment of magnetic resonance cholangiopancreatography for noninvasive imaging of the biliary tree. Gastrointest Endosc 2002;55:17-22.
16. Fulcher AS, Turner MA. MR cholangiopancreatography. Radiol Clin North Am 2002;40:1363-76.
17. Rösch T, Meining A, Fruhmorgen S, et al. A prospective comparison of the diagnostic accuracy of ERCP, MRCP, CT, and EUS in biliary strictures. Gastrointest Endosc 2002;55:870-6.
18. Sai JK, Suyama M, Kubokawa Y, et al. Early detection of extrahepatic bile-duct carcinomas in the nonicteric stage by using MRCP followed by EUS. Gastrointest Endosc 2009;70:29-36.
19. Manfredi R, Barbaro B, Masselli G, et al. Magnetic resonance imaging of cholangiocarcinoma. Semin Liver Dis 2004;24:155-64.
20. Masselli G, Manfredi R, Vecchioli A, et al. MR imaging and MR cholangiopancreatography in the preoperative evaluation of hilar cholangiocarcinoma: correlation with surgical and pathologic findings. Eur Radiol 2008;18:2213-21.
21. Park MS, Kim TK, Kim KW, et al. Differentiation of extrahepatic bile duct cholangiocarcinoma from benign stricture: findings at MRCP versus ERCP. Radiology 2004;233:234-40.
22. Kipp BR, Stadheim LM, Halling SA, et al. A comparison of routine cytology and fluorescence in situ hybridization for the detection of malignant bile duct strictures. Am J Gastroenterol 2004;99:1675-81.
23. Lee JG, Leung JW, Baillie J, et al. Benign, dysplastic, or malignant—making sense of endoscopic bile duct brush cytology: results in 149 consecutive patients. Am J Gastroenterol 1995;90:722-6.
24. Glasbrenner B, Ardan M, Boeck W, et al. Prospective evaluation of brush cytology of biliary strictures during endoscopic retrograde cholangiopancreatography. Endoscopy 1999;31:712-7.
25. Coté GA, Sherman S. Biliary stricture and negative cytology: What next? Clin Gastroenterol Hepatol 2011;9:739-43.
26. Howell DA, Beveridge RP, Bosco J, et al. Endoscopic needle aspiration biopsy at ERCP in the diagnosis of biliary strictures. Gastrointest Endosc 1992;38:531-5.
27. Jailwala J, Fogel EL, Sherman S, et al. Triple-tissue sampling at ERCP in malignant biliary obstruction. Gastrointest Endosc 2000;51:383-90.
28. Ponchon T, Gagnon P, Berger F, et al. Value of endobiliary brush cytology and biopsies for the diagnosis of malignant bile duct stenosis: results of a prospective study. Gastrointest Endosc 1995;42:565-72.
29. Pugliese V, Conio M, Nicolo G, et al. Endoscopic retrograde forceps biopsy and brush cytology of biliary strictures: a prospective study. Gastrointest Endosc 1995;42:520-6.
30. Fogel EL, deBellis M, McHenry L, et al. Effectiveness of a new long cytology brush in the evaluation of malignant biliary obstruction: a prospective study. Gastrointest Endosc 2006;63:71-7.
31. de Bellis M, Fogel EL, Sherman S, et al. Influence of stricture dilation and repeat brushing on the cancer detection rate of brush cytology in the evaluation of malignant biliary obstruction. Gastrointest Endosc 2003; 58:176-82.
32. Fritcher EG, Kipp BR, Halling KC, et al. A multivariable model using advanced cytologic methods for the evaluation of indeterminate pancreatobiliary strictures. Gastroenterology 2009;136:2180-6.
33. Athanassiadou P, Grapsa D. Value of endoscopic retrograde cholangiopancreatography-guided brushings in preoperative assessment of pancreaticobiliary strictures: what's new? Acta Cytol 2008;52: 24-34.
34. de Bellis M, Sherman S, Fogel EL, et al. Tissue sampling at ERCP in suspected malignant biliary strictures (Part 2). Gastrointest Endosc 2002;56: 720-30.
35. De Bellis M, Sherman S, Fogel EL, et al. Tissue sampling at ERCP in suspected malignant biliary strictures (Part 1). Gastrointest Endosc 2002;56: 552-61.
36. Higashizawa T, Tamada K, Tomiyama T, et al. Biliary guidewire facilitates bile duct biopsy and endoscopic drainage. J Gastroenterol Hepatol 2002;17:332-6.
37. Mansfield JC, Griffin SM, Wadehra V, et al. A prospective evaluation of cytology from biliary strictures. Gut 1997;40:671-7.

38. Levy MJ, Baron TH, Clayton AC, et al. Prospective evaluation of advanced molecular markers and imaging techniques in patients with indeterminate bile duct strictures. Am J Gastroenterol 2008;103:1263-73.
39. Baron TH, Harewood GC, Rumalla A, et al. A prospective comparison of digital image analysis and routine cytology for the identification of malignancy in biliary tract strictures. Clin Gastroenterol Hepatol 2004;2: 214-9.
40. Gonda TA, Glick MP, Sethi A, et al. Polysomy and p16 deletion by fluorescence in situ hybridization in the diagnosis of indeterminate biliary strictures. Gastrointest Endosc 2012;75:74-9.
41. Bangarulingam SY, Bjornsson E, Enders F, et al. Long-term outcomes of positive fluorescence in situ hybridization tests in primary sclerosing cholangitis. Hepatology 2010;51:174-80.
42. Monga A, Ramchandani M, Reddy DN. Per-oral cholangioscopy. J Interv Gastroenterol 2011;1:70-7.
43. Chen YK, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). Gastrointest Endosc 2007; 65:832-41.
44. Chen YK. Preclinical characterization of the Spyglass peroral cholangiopancreatoscopy system for direct access, visualization, and biopsy. Gastrointest Endosc 2007;65:303-11.
45. Chathadi KV, Chen YK. New kid on the block: development of a partially disposable system for cholangioscopy. Gastrointest Endosc Clin N Am 2009;19:545-55.
46. Chen YK, Parsi MA, Binmoeller KF, et al. Single-operator cholangioscopy in patients requiring evaluation of bile duct disease or therapy of biliary stones (with videos). Gastrointest Endosc 2011;74:805-14.
47. Ramchandani M, Reddy DN, Gupta R, et al. Role of single-operator peroral cholangioscopy in the diagnosis of indeterminate biliary lesions: a single-center, prospective study. Gastrointest Endosc 2011;74:511-9.
48. Parsi MA. Peroral cholangioscopy in the new millennium. World J Gastroenterol 2011;17:1-6.
49. Kim HJ, Kim MH, Lee SK, et al. Tumor vessel: a valuable cholangioscopic clue of malignant biliary stricture. Gastrointest Endosc 2000;52:635-8.
50. Hoffman A, Kiesslich R, Bittinger F, et al. Methylene blue-aided cholangioscopy in patients with biliary strictures: feasibility and outcome analysis. Endoscopy 2008;40:563-71.
51. Loeser CS, Robert ME, Mennone A, et al. Confocal endomicroscopic examination of malignant biliary strictures and histologic correlation with lymphatics. J Clin Gastroenterol 2011;45:246-52.
52. Meining A, Frimberger E, Becker V, et al. Detection of cholangiocarcinoma in vivo using miniprobe-based confocal fluorescence microscopy. Clin Gastroenterol Hepatol 2008;6:1057-60.
53. Meining A, Chen YK, Pleskow D, et al. Direct visualization of indeterminate pancreaticobiliary strictures with probe-based confocal laser endomicroscopy: a multicenter experience. Gastrointest Endosc 2011;74: 961-8.
54. Meining A, Shah RJ, Slivka A, et al. Classification of probe-based confocal laser endomicroscopy findings in pancreaticobiliary strictures. Endoscopy 2012;44:251-7.
55. Mukai H, Nakajima M, Yasuda K, et al. Evaluation of endoscopic ultrasonography in the pre-operative staging of carcinoma of the ampulla of Vater and common bile duct. Gastrointest Endosc 1992;38:676-83.
56. Tio TL, Reeders JW, Sie LH, et al. Endosonography in the clinical staging of Klatskin tumor. Endoscopy 1993;25:81-5.
57. Sugiyama M, Hagi H, Atomi Y, et al. Diagnosis of portal venous invasion by pancreatobiliary carcinoma: value of endoscopic ultrasonography. Abdom Imaging 1997;22:434-8.
58. Mohamadnejad M, DeWitt JM, Sherman S, et al. Role of EUS for preoperative evaluation of cholangiocarcinoma: a large single-center experience. Gastrointest Endosc 2011;73:71-8.
59. Gores GJ. Early detection and treatment of cholangiocarcinoma. Liver Transpl 2000;6:S30-4.
60. Gleeson FC, Rajan E, Levy MJ, et al. EUS-guided FNA of regional lymph nodes in patients with unresectable hilar cholangiocarcinoma. Gastrointest Endosc 2008;67:438-43.
61. Catalano MF, Sivak MV, Jr, Rice T, et al. Endosonographic features predictive of lymph node metastasis. Gastrointest Endosc 1994;40:442-6.
62. Pollack MJ, Gholam PM, Chak A. EUS-FNA in unresectable cholangiocarcinoma: a novel indication. Gastrointest Endosc 2008;67:444-5.
63. Katayose Y, Rikiyama T, Motoi F, et al. Phase I Trial of Neoadjuvant Chemoradiation with Gemcitabine and Surgical Resection for Cholangiocarcinoma Patients (NACRAC Study). Hepatogastroenterology 2011; 58:1866-72.
64. Xu W, Shi J, Zeng X, et al. EUS elastography for the differentiation of benign and malignant lymph nodes: a meta-analysis. Gastrointest Endosc 2011;74:1001-9; quiz 1115 e1-4.
65. Giovannini M, Thomas B, Erwan B, et al. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. World J Gastroenterol 2009;15:1587-93.
66. Clayton RA, Clarke DL, Currie EJ, et al. Incidence of benign pathology in patients undergoing hepatic resection for suspected malignancy. Surgeon 2003;1:32-8.
67. Gerhards MF, Vos P, van Gulik TM, et al. Incidence of benign lesions in patients resected for suspicious hilar obstruction. Br J Surg 2001;88:48-51.
68. Varadarajulu S, Eloubeidi MA. The role of endoscopic ultrasonography in the evaluation of pancreatico-biliary cancer. Surg Clin North Am 2010; 90:251-63.
69. Ortner MA, Liebetruth J, Schreiber S, et al. Photodynamic therapy of nonresectable cholangiocarcinoma. Gastroenterology 1998;114:536-42.
70. Neuhaus P, Jonas S, Bechstein WO, et al. Extended resections for hilar cholangiocarcinoma. Ann Surg 1999;230:808-18; discussion 819.
71. Kosuge T, Yamamoto J, Shimada K, et al. Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. Ann Surg 1999;230:663-71.
72. Fritscher-Ravens A, Broering DC, Sriram PV, et al. EUS-guided fineneedle aspiration cytodiagnosis of hilar cholangiocarcinoma: a case series. Gastrointest Endosc 2000;52:534-40.
73. Fritscher-Ravens A, Broering DC, Knoefel WT, et al. EUS-guided fineneedle aspiration of suspected hilar cholangiocarcinoma in potentially operable patients with negative brush cytology. Am J Gastroenterol 2004;99:45-51.
74. Eloubeidi MA, Chen VK, Jhala NC, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy of suspected cholangiocarcinoma. Clin Gastroenterol Hepatol 2004;2:209-13.
75. Byrne MF, Gerke H, Mitchell RM, et al. Yield of endoscopic ultrasound-guided fine-needle aspiration of bile duct lesions. Endoscopy 2004;36: 715-9.
76. Lee JH, Salem R, Aslanian H, et al. Endoscopic ultrasound and fineneedle aspiration of unexplained bile duct strictures. Am J Gastroenterol 2004;99:1069-73.
77. Rösch T, Hofrichter K, Frimberger E, et al. ERCP or EUS for tissue diagnosis of biliary strictures? A prospective comparative study. Gastrointest Endosc 2004;60:390-6.
78. Meara RS, Jhala D, Eloubeidi MA, et al. Endoscopic ultrasound-guided FNA biopsy of bile duct and gallbladder: analysis of 53 cases. Cytopathology 2006;17:42-9.
79. DeWitt J, Misra VL, Leblanc JK, et al. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. Gastrointest Endosc 2006;64:325-33.
80. Fusaroli P, Manta R, Fedeli P, et al. The influence of endoscopic biliary stents on the accuracy of endoscopic ultrasound for pancreatic head cancer staging. Endoscopy 2007;39:813-7.
81. Shami VM, Mahajan A, Sundaram V, et al. Endoscopic ultrasound staging is adversely affected by placement of a self-expandable metal stent: fact or fiction? Pancreas 2008;37:396-8.
82. Rosen CB, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. Transpl Int 2010;23:692-7.
83. Nakamuta M, Tanabe Y, Ohashi M, et al. Transabdominal seeding of hepatocellular carcinoma after fine-needle aspiration biopsy. J Clin Ultrasound 1993;21:551-6.
84. Chapman WC, Sharp KW, Weaver F, et al. Tumor seeding from percutaneous biliary catheters. Ann Surg 1989;209:708-13; discussion 713-5.

85. 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.
86. 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.
87. Farrell RJ, Agarwal B, Brandwein SL, et al. Intraductal US is a useful adjunct to ERCP for distinguishing malignant from benign biliary strictures. Gastrointest Endosc 2002;56:681-7.
88. Chak A, Isenberg G, Kobayashi K, et al. Prospective evaluation of an over-the-wire catheter US probe. Gastrointest Endosc 2000;51:202-5.
89. Tamada K, Ido K, Ueno N, et al. Preoperative staging of extrahepatic bile duct cancer with intraductal ultrasonography. Am J Gastroenterol 1995; 90:239-46.
90. Tamada K, Ueno N, Tomiyama T, et al. Characterization of biliary strictures using intraductal ultrasonography: comparison with percutaneous cholangioscopic biopsy. Gastrointest Endosc 1998;47:341-9.
91. Stavropoulos S, Larghi A, Verna E, et al. Intraductal ultrasound for the evaluation of patients with biliary strictures and no abdominal mass on computed tomography. Endoscopy 2005;37:715-21.
92. Vazquez-Sequeiros E, Baron TH, Clain JE, et al. Evaluation of indeterminate bile duct strictures by intraductal US. Gastrointest Endosc 2002;56: 372-9.
93. 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.

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Current affiliations: Division of Gastroenterology and Hepatology (1), Department of Medicine, The Johns Hopkins Hospital, Baltimore, Maryland, USA; Department of Gastroenterology and Hepatology (2), Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Division of Gastroenterology and Hepatology (3), Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA.

Reprint requests: Mouen A. Khashab, MD, Assistant Professor of Medicine, Director of Therapeutic Endoscopy, Johns Hopkins Hospital, 1830 E. Monument Street, Room 424, Baltimore, MD 21205.

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