The Role of EUS in the Biliary System

Jean-Louis Frossard, MD
and Jean-Marc Dumonceau, MD

CONTENTS

Abstract

Standard endoscopic ultrasound (EUS) and intraductal ultrasonography (IDUS) are, with magnetic resonance, the best techniques currently available to image the extrahepatic bile ducts and the gallbladder. In this chapter, we review current knowledge about gallstone disease, bile duct strictures, and gallbladder lesions.

In patients at high risk of having bile duct stones, endoscopic retrograde cholangio-pancreatography (ERCP) is the most cost-effective procedure, whereas EUS is indicated when the clinical index of suspicion for stones is low or intermediate (to spare costs and morbidity associated with ERCP). Sensitivity and specificity of EUS for the diagnosis of choledocholithiasis are close to 95%. In cases of unexplained acute pancreatitis, EUS provides a diagnosis in a majority of patients; in particular by detecting gallstone disease that had not been suspected at percutaneous ultrasonography.

From: *Clinical Gastroenterology: Endoscopic Ultrasound*,
Edited by: V. M. Shami and M. Kahaleh, DOI 10.1007/978-1-60327-480-7_14,

For the diagnosis of malignant vs. benign biliary strictures, the accuracy of EUS without fine needle aspiration (FNA) is not as high (80%), but EUS-FNA (in particular of lymph nodes) alters patient management in a significant proportion of cases. IDUS is the best technique for assessing the longitudinal tumor extent as well as T (but not N) categories. IDUS may also assist in diagnosing malignant transformation in primary sclerosing cholangitis.

Gallbladder polypoid lesions are frequent and can better be assessed by EUS than by percutaneous ultrasonography. EUS may be useful to examine lesions measuring 5–10 mm in diameter.

Finally, the accuracy of EUS for staging gallbladder cancer is in the range of 80–90%; it is particularly useful to distinguish between T1 and T2 tumors because the therapeutic planning is markedly different between these two categories.

Key Words: Endoscopic ultrasonography, Endoscopic ultrasonography-guided fine needle aspiration, Gallstone disease, Cholangiocarcinoma, Gallbladder cancer, Primary sclerosing cholangitis

TECHNIQUE OF BILIARY IMAGING

Standard Endoscopic Ultrasonography

Endoscopic ultrasonography (EUS) is performed after an overnight fast, usually with the patient in left lateral decubitus position and under intravenous sedation. If a biliary stricture is suspected, it is useful to have previous cross-sectional imaging studies (in particular magnetic resonance cholangiopancreatography [MRCP] if available) to assess the level of biliary obstruction and the presence of a mass or lymph nodes. Whether a radial or a linear scanning echoendoscope is used, the extrahepatic bile ducts can be visualized completely in the majority of the patients by inserting the echoendoscope in two positions, namely the "apical" position and the "kissing the papilla" position. During the introduction of the instrument, little air inflation is required and many echoendoscopists mainly look at the EUS view even at this stage (the endoscopic view may be placed as a "picture in picture" on the main screen if a radial instrument is used). Once a position is achieved, suctioning air and inflating the balloon at the tip of the instrument enhance acoustic coupling. Using high frequencies (7.5, 12, or even 20 MHz), a spasmolytic drug (N-butyl hyoscine or glucagon) and color Doppler are useful to obtain better imaging and to avoid confusion between a nondilated bile duct and adjacent vessels.

The "apical" position is obtained by inserting the transducer into the apex of the duodenal bulb; the balloon is then inflated until it occludes the duodenal lumen and the instrument is maneuvered to visualize five landmarks: (1) the "duodenal fall-off," which corresponds to the duodenal wall; (2) the bile duct, adjacent to the transducer; (3) the Wirsung's duct (deeper); (4) the superior mesenteric/portal veins; and (5) the gallbladder.

The "kissing the papilla" position is obtained by entering the second portion of the duodenum, distal to the papilla, and then pulling back the instrument in the "short-route" position to place the transducer close to the papilla (as is done for endoscopic retrograde cholangio-pancreatography [ERCP]). At this time, it is useful to have a rapid look at the endoscopic view of the papilla. If the papilla is located in a paradiverticular position, abundant water instillation may be useful to avoid artifacts. This position is ideal to detect a stone impacted into the distal portion of the bile duct or into the papilla.

Particularities relative to the radial- and linear-scanning echoendoscope are as follows: with a radial echoendoscope, EUS is always begun in the "apical" position because the bile duct is readily recognized (usually within 30 s) by delicately pressing the instrument, balloon inflated, against the apex of the duodenal bulb and slightly moving the up/down and right/left knobs. The bile duct courses immediately adjacent to the transducer, presents as a three-layer wall (not always detectable), and may be tracked up to the hilum by slightly withdrawing the instrument while applying counterclockwise torque (inverse movements to track the bile duct down to the papilla) (Fig. 1). If the bile duct is thin, it may be difficult to visualize its full course in a single view; in this case, partly deflating the balloon may be useful to avoid compressing the bile duct. The gallbladder appears as an anechoic crescent when pulling the instrument from the apical position to the pylorus. In the "kissing the papilla" position, the instrument is slightly withdrawn while moving the up/down and right/left knobs to follow the convergence of the biliary and pancreatic ducts into the papilla (Fig. 2).

With a linear echoendoscope, in the "apical" position, the main maneuver performed to track the bile duct consists in torquing the instrument (advancing/withdrawing the instrument is less useful). Some echoendoscopists directly start the examination in the "kissing the papilla" position, and track the bile duct proximally up to the liver hilum by withdrawing the instrument into the duodenal bulb/pyloric region while simultaneously applying counterclockwise torquing (balloon inflation and a relatively long endoscope position may help to prevent it from slipping into the stomach). As complete imaging of the bile duct with a linear instrument requires more experience than with a radial instrument, it may be

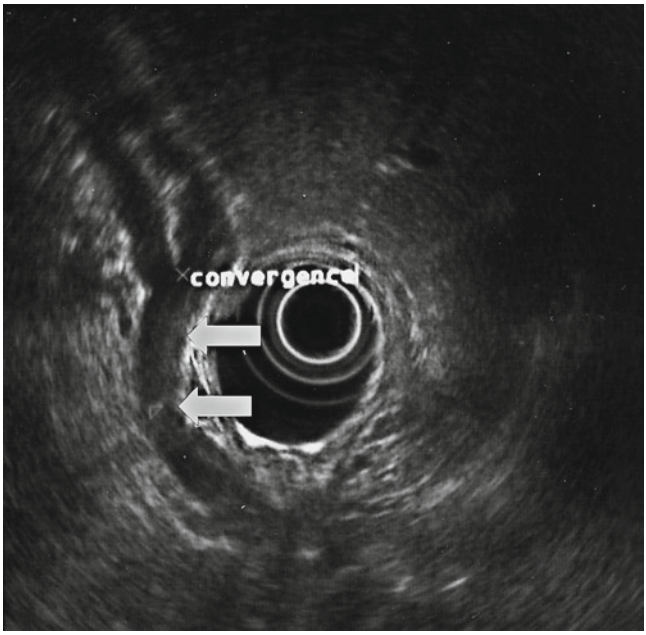

Fig. 1. Radial EUS image (5 MHz) showing the normal anatomy of the common hepatic duct (arrows) emerging from the convergence.

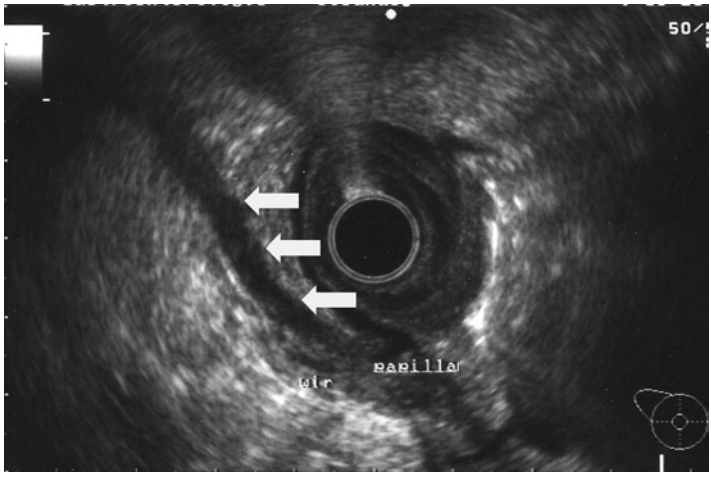

Fig. 2. Radial EUS image (7.5 MHz) showing the normal anatomy of the common bile duct (arrows) and Wirsung's duct down to the ampulla of Vater.

useful to perform the first examinations in patients who have a biliary stent in place. The liver hilum is usually imaged at the lowest frequency available (5 MHz) because it is located at 4–5 cm from the transducer. As in other gastrointestinal locations, EUS-guided fine needle aspiration (EUS-FNA) is performed after color Doppler examination of the anticipated needle tract. EUS-FNA in the region of the liver hilum is more demanding than in other segments of the bile duct; it is usually performed from the post pyloric (or, infrequently, the prepyloric) region while advancing the instrument to lean against the greater curvature of the stomach.

The principal limitations of biliary EUS include (1) difficulties in performing a biliary examination after Billroth II gastrectomy; (2) poor visualization of the right hepatic duct (plus the hilum in some cases, as well as the distal portion of the bile duct in case of chronic calcified pancreatitis); (3) limited accuracy in case of pneumobilia (e.g., previous biliary sphincterotomy); and (4) operator-dependency.

Intraductal Ultrasonography

Intraductal ultrasonography (IDUS) provides high-resolution images of the biliary tree because high-frequency (20–30 MHz) probes are generally used. These probes may be inserted into the bile ducts during endoscopic or percutaneous cholangiography. Wire-guided IDUS probes are strongly advised because they can be inserted without biliary sphincterotomy in virtually all cases (and without dilation in many cases of biliary stricture [stricture dilation or sampling is preferably performed after IDUS]) (1). In practice, for two-dimensional IDUS, a high-frequency, 20-MHz, wire guided, probe (e.g., UM-G20-29R, Olympus, Tokyo, Japan) is inserted "over-the-wire" with the minimal use of the elevator to avoid damaging this fragile and costly probe (Fig. 3). Continuous imaging is obtained during slow withdrawal of the probe, with the elevator in low position to minimize friction (fluoroscopy may be used to locate the radiopaque tip of the probe). IDUS adds a mean of 5 min to ERCP (2).

Three-dimensional IDUS (3D-IDUS) has emerged as an interesting alternative to two-dimensional IDUS. Probes that allow 3D-IDUS present an outer, immobile, sheath and an inner, mobile, radial transducer; they must be connected to a specific driving unit. The most recent models of 3D-IDUS probes (e.g., UM-DG20-31R, Olympus) are wire guided. After inserting the probe up to the hilum, the driving unit is activated and the ultrasonic transducer is progressively withdrawn inside the immobile outer sheath at a constant speed (generally, over a 40-mm length). Two or

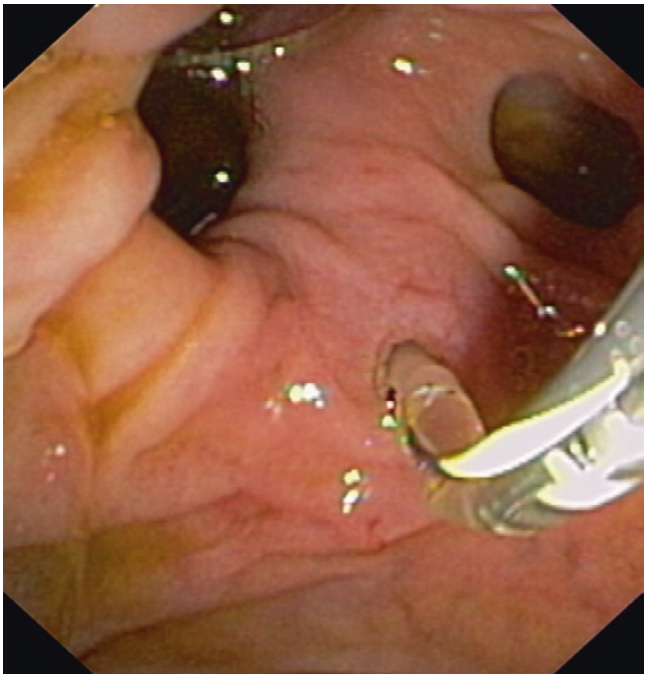

Fig. 3. Endoscopic view of the insertion into the bile duct of a three-dimensional IDUS probe (outer diameter, 2.9 mm). Probe insertion is performed over-the-wire and without previous biliary sphincterotomy (papilla below two diverticulae).

three passes are generally required to image the whole bile duct. Various types of 3D reconstructions, including dual plane, oblique, and surface rendering reconstructions may be performed in real-time. Electronic storage of data acquired during all passes allows, together with the standardization of the procedure, to interpret 3D-IDUS after completing ERCP. Data acquisition is thus quicker than with conventional IDUS and images may be interpreted with an experienced echoendoscopist even if he/she has not attended the procedure.

Complications specifically attributable to IDUS are exceptional, likely because no fluid irrigation is required owing to the presence of bile (in contrast, cholangioscopy requires fluid irrigation and has been associated with increased complication rates) (3). However, IDUS requires ERCP with its associated morbidity (plus biliary stenting to relieve obstruction after biliary contamination if a stricture is present).

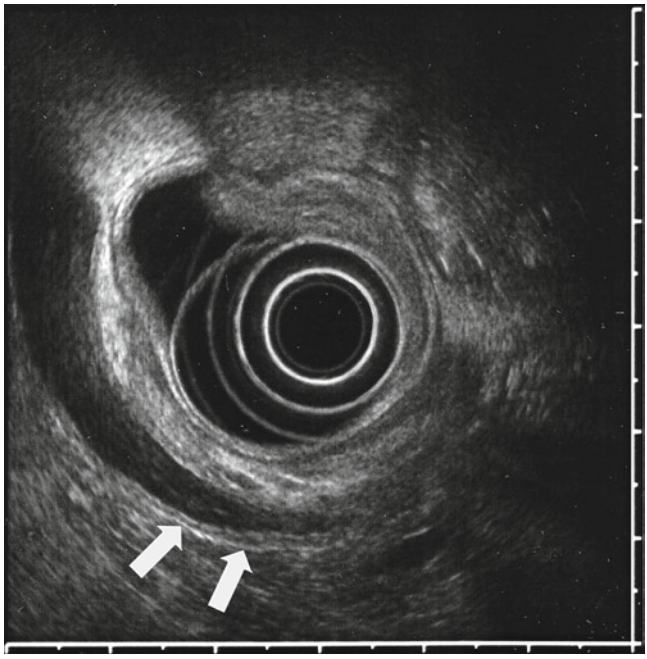

Fig. 4. Radial EUS image (12 MHz) showing the three endosonographic layers of the common bile duct, best identified at high frequencies (arrows).

Normal Findings

Two or three endosonographic layers are identified in the normal bile duct wall (Fig. 4) (4–7). The inner hyperechoic layer corresponds to biliary mucosa and the interface between the bile duct wall and bile (this layer may not be visible); the middle hypoechoic layer corresponds to the fibromuscular layer, and the outer hyperechoic layer corresponds to the adipose layer of the subserosa, the serosa, and the interface echo between the serosa and surrounding organs (thus, it is not part of the bile duct itself). In some patients, the fibromuscular layer cannot be distinguished from the perimuscular connective tissue, particularly in the intrapancreatic portion of the bile duct, and these appear as a single hypoechoic layer (6). The bile duct wall thickness is measured at the level of the middle hypoechoic layer; it is 0.6 mm in normal subjects, and the upper limit of normal is 1.8 mm (7, 8). The thickness of the normal bile duct wall is not significantly different when measured upstream from an obstruction or in case of choledocholithiasis, but it is

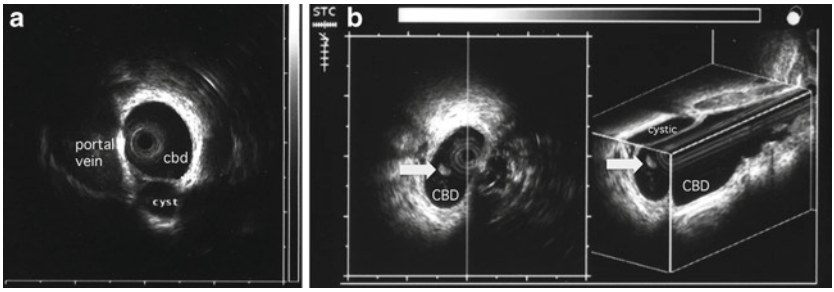

Fig. 5. Normal anatomy of the common bile duct (CBD) as shown by a two-dimensional or a three-dimensional 20 MHz IDUS probe. (**a**) Two-dimensional IDUS probe; the cystic duct (Cyst) and the portal vein are seen in cross-section; (**b**) three-dimensional IDUS probe (composite image, as rendered in real-time); the cystic duct runs parallel to the CBD (note the presence in the CBD of a hyperechoic spot without postacoustic shadow (arrow) that corresponds to a microlithiasis).

increased when a biliary drain is left in place for >2 weeks or in case of primary sclerosing cholangitis (PSC) (mean thickness, 2.0 and 2.5 mm, respectively) (8, 9).

Imaging of the right hepatic artery, portal vein, and hepatoduodenal ligament are easier to obtain with IDUS compared to EUS. During probe withdrawal, the following peribiliary structures can be identified: right hepatic artery (longitudinal, vascular structure crossing behind the common hepatic duct), portal vein (longitudinal vascular structure behind the right hepatic artery that is larger and presents a thinner wall), the cystic duct (in continuity with the CBD) (Fig. 5), the main pancreatic duct and surrounding pancreatic parenchyma, the inferior vena cava (posterior to the pancreatic parenchyma), and the sphincter of Oddi (circular, hypoechoic thickening within the duodenal wall). Demonstration of the common and left hepatic arteries is most often not possible because probes commonly used for biliary imaging work at high frequencies and have a limited penetration depth.

GALLSTONE DISEASE

Introduction

Symptomatic gallstone disease may be related to sludge, microlithiasis and calculi. Biliary sludge is considered to be a suspension of various items, including crystals, mucin, and cellular debris within bile while

Table 1
Risk factors for common bile duct (CBD) stones in patients awaiting cholecystectomy

Low risk (0–5%)	*Intermediate risk (5–50%)*	*High risk (>50%)*
Normal ultrasonography	Hyperbilirubinemia (>30 μmol/L)	Cholangitis
Normal liver tests	Increased alkaline phosphatase	Jaundice
	Increased ALAT	Dilated CBD
	Pancreatitis	
	Cholecystitis	
	Age >55 years	

microlithiasis is defined as stones <3 mm in diameter (10, 11). Many authors use the term microlithiasis or sludge interchangeably, likely because sludge is considered to be a precursor to microlithiasis and both have the same clinical significance.

Gallstone disease is one of the most prevalent digestive diseases in Western countries, but only 2–4% of patients become symptomatic each year (12, 13). CBD lithiasis is found in 10–15% of patients undergoing cholecystectomy (14), and is associated with potentially severe complications, including pancreatitis and cholangitis. ERCP is the preferred procedure to treat CBD stones, but it is being abandoned as a diagnostic test due to its attendant morbidity (5–10%) and imperfect sensitivity (85–90%) (15, 16). In a prospective cost-minimization study that enrolled 485 patients with suspected CBD stones investigated by EUS, EUS followed by ERCP in case of positive finding was the least costly strategy (ERCP was avoided in about half patients) (17). However, "ERCP first" became the least costly strategy if the risk of CBD stones were >60% (e.g., cholangitis). However, this requires the ability to accurately assess the risk of CBD stone based on non-invasive tests (Table 1), and may vary according to local costs.

Technique

Biliary sludge produce low-amplitude echoes without a postacoustic shadow that layer in the dependent portion of the gallbladder or CBD and shift with positional changes (Fig. 6); microlithiasis is observed as tiny hyperechoic materials (0.5–3 mm) without a postacoustic shadow, and stones produce echoes of high amplitude ≥3 mm with a postacoustic

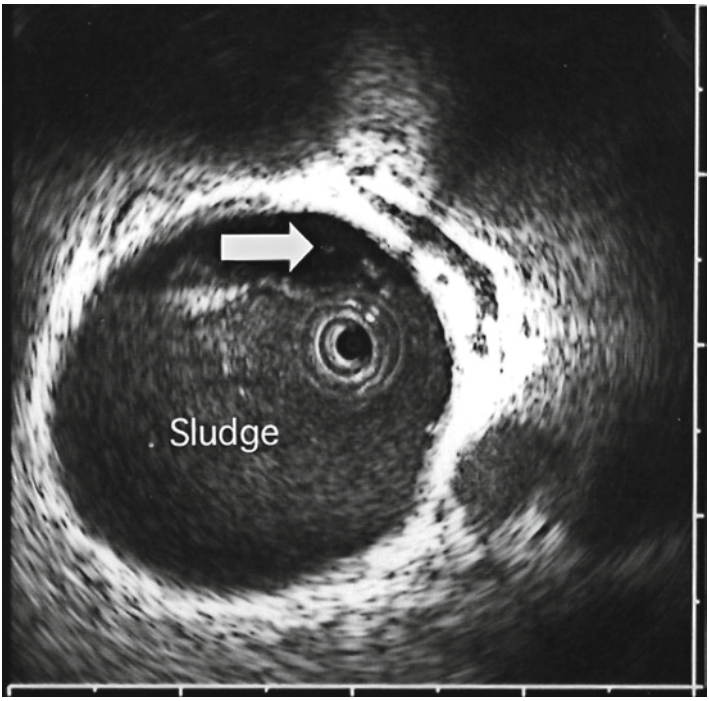

Fig. 6. Two-dimensional IDUS image (20 MHz) showing abundant sludge (low-amplitude echoes without a postacoustic shadow), plus microlithiasis that floats above the bile-sludge level in the common bile duct (tiny hyperechoic materials without a postacoustic shadow, arrow).

shadow and may move within the gallbladder or the CBD (Fig. 7). Mirizzi's syndrome is a condition that should be diagnosed preoperatively because it is associated with an increased risk of bile duct injury at laparoscopic cholecystectomy (18). It is identified as a compression of the CBD by a cystic stone or a large gallbladder stone responsible for upstream dilation of the common hepatic duct (Fig. 8).

Results

A meta-analysis assessed the results of EUS specifically for the diagnosis of CBD stones (19). Twenty-seven prospective cohort studies were included, totaling 2,673 patients with suspected choledocholithiasis (mean prevalence, 36% [15–86%]). Pooled sensitivity and specificity for the diagnosis of choledocholithiasis by EUS were 94% (95%

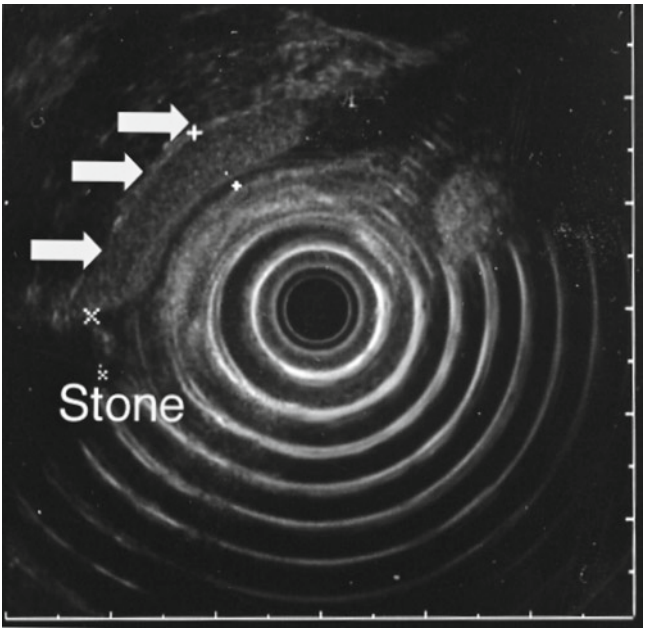

Fig. 7. Radial EUS image (12 MHz) showing an obstructing stone in the common bile duct (high amplitude echo with a postacoustic shadow), associated with an upstream accumulation of dense, sedimented, sludge (arrows).

confidence interval, 93–96%) and 95% (95% confidence interval, 94–96%), respectively. These results concur with those of a previous meta-analysis that showed that EUS had higher sensitivity (89%) and specificity (94%) for the diagnosis of choledocholithiasis compared to malignancy (sensitivity, 78%; specificity, 84%) (20). In the most recent meta-analysis (19), the quality of the 27 studies that qualified for inclusion was generally judged as low because only 33% of studies satisfied all of three predefined criteria to qualify as a high-quality study. In that meta-analysis, three variables were associated with a better accuracy of EUS. These included a clinical context of suspected biliary pancreatitis (as compared to contexts of suspected biliary obstruction or of suspected CBD stones), a time interval between EUS and gold-standard that was <72 h (stones spontaneously pass into the duodenum as time elapses) (21), and the presence of a verification bias (i.e., if patients with stones detected at EUS only were verified by the gold-standard, other patients being verified by clinical follow-up). A limitation of this meta-analysis is that all studies that were included had been performed in tertiary care

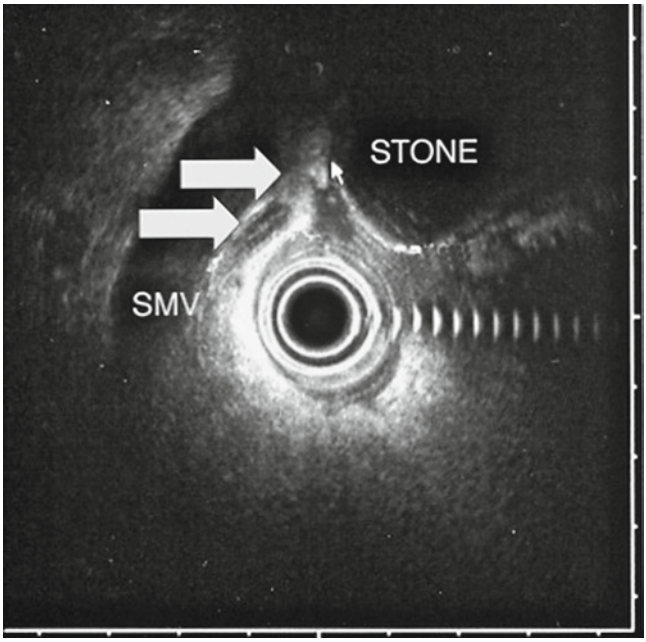

Fig. 8. Radial EUS image (12 MHz) showing a Mirizzi's syndrome. Note the presence of a high amplitude echo with a postacoustic shadow in the gallbladder, corresponding to a large stone that compresses the common bile duct (arrows). SMV superior mesenteric vein.

settings so that it is unknown if these results can be transferred to the community.

Contrary to EUS, MRCP is completely noninvasive, and it also presents an excellent accuracy for the detection of CBD stones (Table 2) (22–29). A systematic review of five prospective randomized blinded trials that compared EUS with MRCP for the detection of CBD stones found no significant differences between both tests (30). The authors concluded that clinicians should choose between tests based on local resource availability (that is much larger for MRCP compared to EUS), experience and costs. An advantage specific to EUS is that, in properly organized endoscopy units, therapeutic ERCP may immediately follow diagnostic EUS. This approach allows saving costs as compared to the "MRCP followed by ERCP" approach in low-to-moderate risk patients (31). EUS is also recommended for the detection of small stones or stones impacted into the papilla in case of negative

Table 2
Comparison of EUS vs. magnetic resonance cholangiopancreatography for the detection of common bile duct stones

		EUS			*Magnetic resonance cholangiopancreatography*		
First author	*No patients*	*Sensitivity*	*Specificity*	*Accuracy*	*Sensitivity*	*Specificity*	*Accuracy*
Ainsworth (22)	163	0.89	0.98	0.93	0.90	0.92	0.91
Aubé (23)	47	0.94	0.97	0.94	0.88	0.97	–
De Lédinghen (24)	32	1	0.95	0.91	1	0.73	0.82
Fernández-Esparrach (29)	72	0.93	0.81	0.86	0.87	0.95	0.92
Kondo (25)	28	1	0.50	0.93	0.88	0.75	0.86
Materne (26)	50	0.97	0.88	0.94	0.91	0.94	0.92
Scheiman (27)	30	0.80	0.95	–	0.40	0.96	–
Schmidt (28)	57	0.97	0.94	0.97	0.95	0.95	0.95

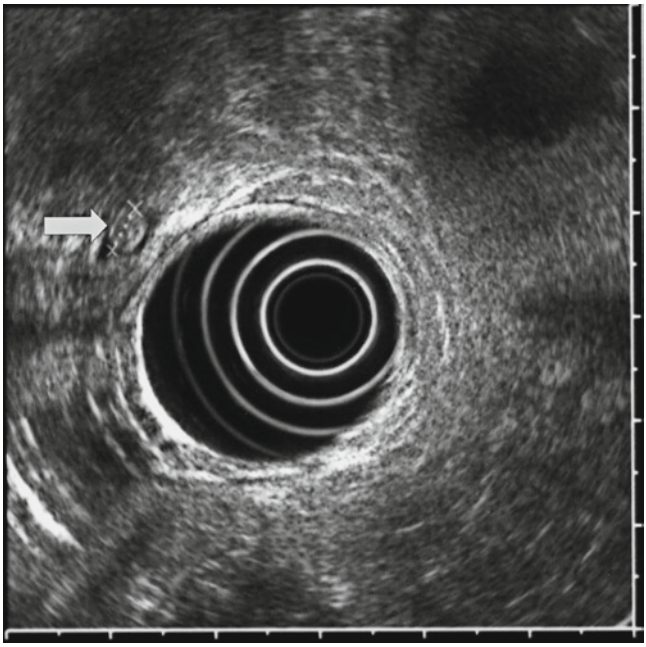

Fig. 9. Radial EUS image (12 MHz) showing a 4-mm in diameter stone impacted into the ampulla (arrow). Note the absence of postacoustic shadow.

MRCP because the spatial resolution of MRCP is lower than that of EUS (1.5 mm vs. 0.1 mm), and the ampullary region is more difficult to examine at MRCP (Figs. 9 and 10) (32).

Finally, (1) the accuracy of MRCP is dependent on experience in image interpretation and on magnetic resonance imaging techniques (similar to EUS), and (2) MRCP is contraindicated in patients with incompatible material such as pacemakers (and it is very difficult to perform in case of claustrophobia) (27, 32).

Particular Case: "Idiopathic" Acute Pancreatitis

EUS is particularly useful to investigate "idiopathic" acute pancreatitis. Standard investigation of acute pancreatitis, including percutaneous ultrasonography (US) and CT scan, does not find the cause of acute pancreatitis in 10–20% of cases (33). A significant proportion of these cases are unrecognized biliary pancreatitis. This is supported, among other factors (33), by the identification, at microscopic examination, of

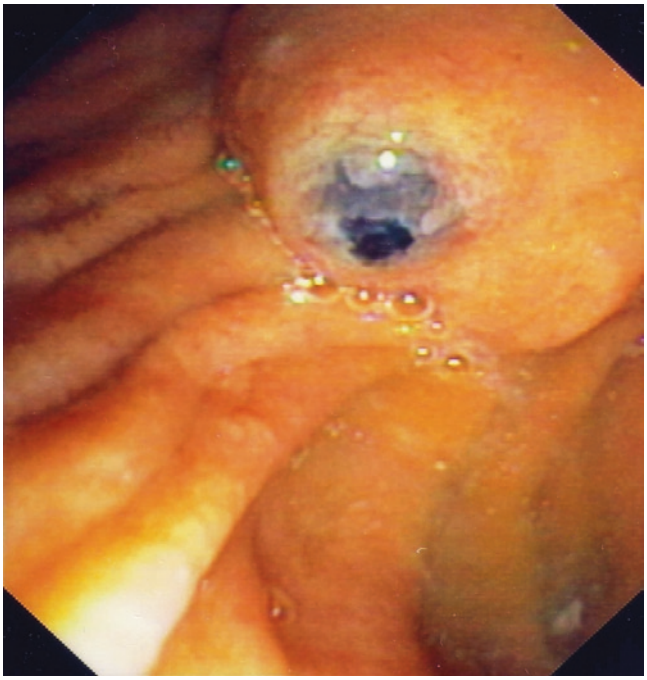

Fig. 10. Endoscopic view of a stone impacted into the papilla, as seen when entering the second portion of the duodenum (black pigment stone related to hemolytic disease in a patient with sickle cell anemia).

crystals in bile sampled from the bile duct or gallbladder in up to 80% of cases (34).

In five studies that have analyzed the results of EUS for acute pancreatitis diagnosed as "idiopathic" after a standard work-up, gallstones were found in 170 (27%) of 631 patients (Fig. 11) (35–39). In addition to this, other lesions were detected in another 220 patients, for an overall yield of EUS of 62%. The likelihood of finding gallstone disease at EUS in idiopathic pancreatitis is similar for a first attack or in case of relapsing disease, but it is low in case of previous cholecystectomy (39).

Recognizing the biliary origin of acute pancreatitis is critical as recurrences develop in 33–61% of cases in the absence of treatment (40, 41). To this end, Wilcox et al. recently concluded that EUS should be considered to evaluate patients with a first attack of "idiopathic" acute pancreatitis (33).

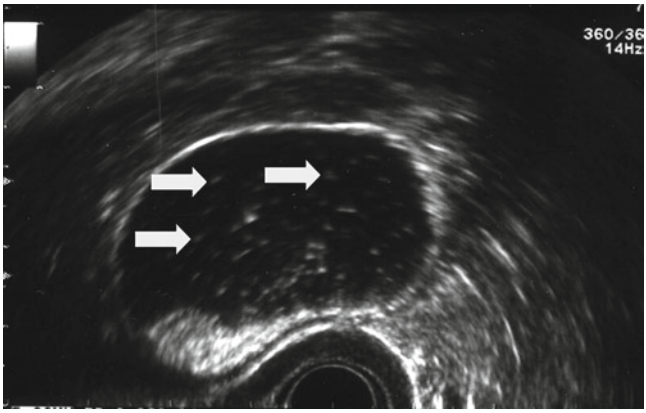

Fig. 11. Linear EUS image (7.5 MHz) showing a microlithiasis of the gallbladder (hyperechoic spots without postacoustic shadow, arrows). Note that hyperechoic spots accumulate in the lower part of the gallbladder and form a hyperechoic pseudopolyp (left hand side). Percutaneous ultrasonography had revealed no abnormality in this obese patient after a first attack of acute pancreatitis, and this had been diagnosed as "idiopathic" acute pancreatitis.

BILIARY STRICTURES

Standard Endoscopic Ultrasonography

Detection and Characterization of Biliary Strictures and Lymph Nodes

In the absence of a pancreatic mass, two characteristics of the bile duct wall are used to discriminate malignant from benign biliary strictures at EUS (42). These are (1) a maximal thickness ≥3 mm and (2) the presence of irregular outer margins. In a prospective study of 40 patients with a bile duct stricture of unknown origin, Lee et al. found that a bile duct wall thickness ≥3 mm had sensitivity and specificity for diagnosing malignancy of 79% each (Fig. 12) (42). An irregular outer edge of the bile duct wall is also indicative of malignancy but, in contrast, echo features are similar for both benign and malignant strictures (most lesions are hypoechoic compared to the liver) (43).

In a recent meta-analysis (20), Garrow et al. reviewed 36 studies that analyzed the ability of EUS (without FNA) to detect the presence and etiology of a biliary obstruction in 3,532 patients. Accuracy of EUS was high for the detection of a biliary obstruction (sensitivity, 88%; specificity, 90%), but lower for differentiating benign from malignant causes (sensitivity, 78%; specificity, 84%). Linear and radial EUS were

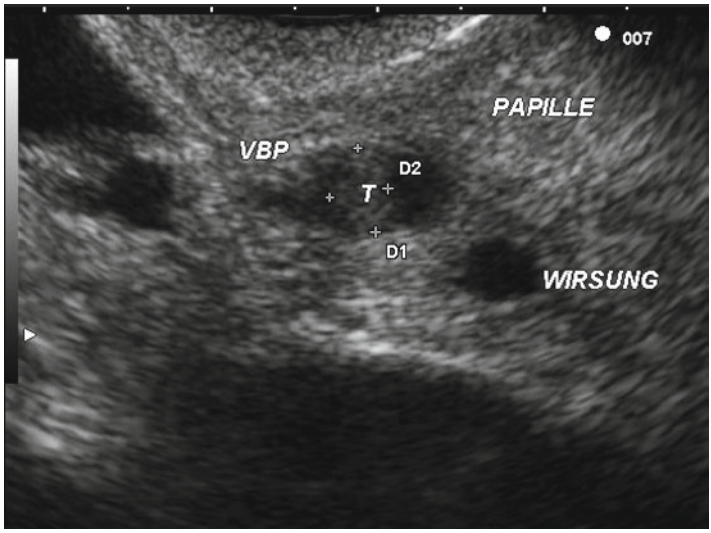

Fig. 12. Linear EUS image (7.5 MHz) showing a T1 cholangiocarcinoma as a hypoechoic mass (T) that measures 3.5 mm×5.1 mm in diameter and obstructs the common bile duct (VBP). Photograph courtesy from M. Giovannini.

found to have similar performances. Of note, the results of standard EUS (without FNA) were slightly inferior to those reported with magnetic resonance in another meta-analysis, with regard to both the detection of biliary obstruction (sensitivity, 97%; specificity, 98%) and the differentiation between benign and malignant biliary obstruction (sensitivity, 88%; specificity, 95%) (44).

Regarding lymph nodes, Faigel et al. have shown for pancreaticobiliary malignancies the size of lymph nodes was not associated with malignant involvement, while other commonly used parameters (i.e., a short distance between the tumor and the lymph node, a round shape and a hypoechoic, homogeneous, texture of the lymph node) were indicative of malignancy (45). For cholangiocarcinomas located at the hilum, Gleeson et al. have found that malignant and benign lymph nodes had a similar aspect, including size, roundness, echogenicity, and homogeneity (46). FNA is therefore necessary if the status of the visualized lymph nodes would alter clinical management.

Sampling

Table 3 summarizes the main results reported with EUS-FNA for suspected cholangiocarcinomas. Compared to pancreatic carcinomas,

Table 3
Results of EUS-FNA for suspected cholangiocarcinoma

First author	*Study design*	N	*On-site cytopathological examination*	*Proximal location*[a]	*Mass at previous imaging*	*Sensitivity*
Fritscher-Ravens (43)	Prospective	44	NR	44 (hilum)	NR	0.89
Byrne (51)	Retrospective	35	Yes	3	NR	0.60
Eloubeidi (48)	Prospective	28	Yes	15	33%	0.86
DeWitt (47)	Retrospective	24	Yes	24	39%	0.77
Meara (49)	Prospective	44	Yes	NR	NR	0.87
Lee (42)	Prospective	40[b]	Yes	1	0	0.47

NR not reported
[a]Lesions located at the hilum or common hepatic duct (those located in the common bile duct, distal to the cystic duct implantation, were defined as distal) (48)
[b]A previously undiagnosed pancreatic head mass was evidenced at EUS in ten patients

cholangiocarcinomas may be more difficult to locate and to sample because they are usually smaller (mean size at the time of FNA, 19–24 mm) (42, 43, 47–49), and many of them are located in the proximal bile duct, including the hilum. Biliary stents may help to locate stricture-associated lesions, and usually pose no significant problem during FNA. Reported sensitivities for the detection of malignancy were ≥70% in four out of six studies, and no sampling-related complications were reported in any of them. Factors that contributed to these results included the operators' expertise and the availability of an "on-site" cytopathologist. However, the interpretation of cytopathological reports and case selection were also likely important contributing factors. Generalizability of these results is uncertain because none of the studies listed in Table 3 reported the total number of patients who were eligible for inclusion during the investigation period, and these studies were performed in referral centers (a single operator performed all EUS-FNAs in at least one study) (48). Moreover, only three studies reported the number of failed attempts at FNA, a figure that is needed to calculate the sensitivity in an "intention to diagnose" analysis (89, 75, and 74% in these three studies) (43, 47, 48). These limitations are likely significant, as the single randomized study that has compared EUS-FNA vs. biliary brushing at ERCP for biliary strictures found that EUS-FNA had a relatively low sensitivity (43% vs. 46% for biliary brushing). However, if punctured lesions only were considered in that study (n = 28), the sensitivity of EUS-FNA for cancer diagnosis was 75%, in line with other reports (50). Finally, in at least four of the studies listed in Table 3, specimens diagnosed as "suspicious for malignancy" were considered as equivalent to "malignant" to calculate the sensitivity for cancer diagnosis (43, 48, 49, 51). From a clinical point of view, this interpretation of cytopathological reports makes sense because no false-positive cases were reported (specificity, 100%). It seems, therefore, desirable that cytopathological reports of biliary FNA specimens include a "highly atypical suspicious for cancer" category, and to locally evaluate the clinical interpretation of this diagnosis (as is performed for biliary brushings in many centers) (52, 53). Finally, a serious drawback of EUS-FNA for cholangiocarcinoma is its low negative predictive value. This attained 70% in two studies only (49, 51), precluding reliable exclusion of malignancy following a negative FNA.

With regard to lymph nodes, these can also be sampled by EUS-FNA to better select patients for surgery (local lymph node metastasis is associated with shorter postresection survival) (54, 55). Gleeson et al. reported a retrospective series of 47 patients with unresectable hilar cholangiocarcinoma considered for liver transplantation who had lymph nodes detected at EUS (including 12 with previously undetec-

ted lymph nodes by CT and/or magnetic resonance) (46). FNA yielded malignant cells in 17% of cases.

Longitudinal Tumor Extent, TNM Stage, and Resectability

Longitudinal spreading is characteristic of cholangiocarcinomas, and tumor extension dictates the possibility (and extent) of surgical resection. Surgical management of cholangiocarcinomas is more problematic if liver hilum is involved compared to the pancreas. Criteria of nonresectability in the hilum classically include: bilateral tumor extension to secondary biliary radicals, encasement or occlusion of the main portal vein, lobar atrophy with contralateral portal vein involvement, advanced nodal disease or spread of tumor to adjacent organs (55, 56). If the tumor is thought to be resectable, negative resection margins should be achieved because this is an independent predictor of survival (54, 55). Depending on tumor extent and liver anatomy, achieving negative resection margins may require partial liver resection, possibly preceded by portal vein embolization to induce compensatory hypertrophy of the future remnant liver. Finally, some patients with an unresectable hilar cholangiocarcinoma <3 cm in diameter and no lymph-node metastases may be eligible for liver transplantation after neoadjuvant therapy, but this is proposed in a few high-volume transplant centers only (46). Accurate assessment of vascular invasion and tumor longitudinal spread is therefore necessary to select the best treatment strategy.

The new 2010 TNM classification of cholangiocarcinomas is different from the previous edition, in that extrahepatic bile duct cancer is now divided into two different staging systems: Perihilar bile ducts (Table 4a) and distal bile duct (Table 4b). This division is as a result of differences in anatomy of the bile duct and consideration of local factors that relate to resectability. Compared to the fifth edition of the TNM classification, the current seventh and previous sixth edition have introduced the T4 category, a modification that has improved the prediction of survival (57). However, several authors have reported that the distinction between the current T2 and T3 categories cannot reliably be performed, even by IDUS or histopathological examination (Fig. 13) (4).

In 1991, Tio et al. reported that the accuracy of EUS staging of carcinomas located in the extrahepatic bile ducts was excellent (84%) (Fig. 14) (58). However, these results were not confirmed and more recent studies have focused on IDUS, which is superior to EUS for T staging (correct T staging in a comparative study, 78% vs. 54%, IDUS vs. EUS, respectively; $P<0.001$), and for the prediction of

Table 4
AJCC TNM classification of cholangiocarcinomas (a) perihilar bile ducts and (b) distal bile duct

a. Perihilar bile ducts	
T category	
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
N category	
N0	No regional lymph-node metastasis
N1	Regional lymph-node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
N2	Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes
b. Distal bile duct	
T category	
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct histologically
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery
T4	Tumor involves the celiac axis, or the superior mesenteric artery
N category	
N0	No regional lymph-node metastasis
N1	Regional lymph-node metastasis

TNM Classification of Gastric Cancer. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC

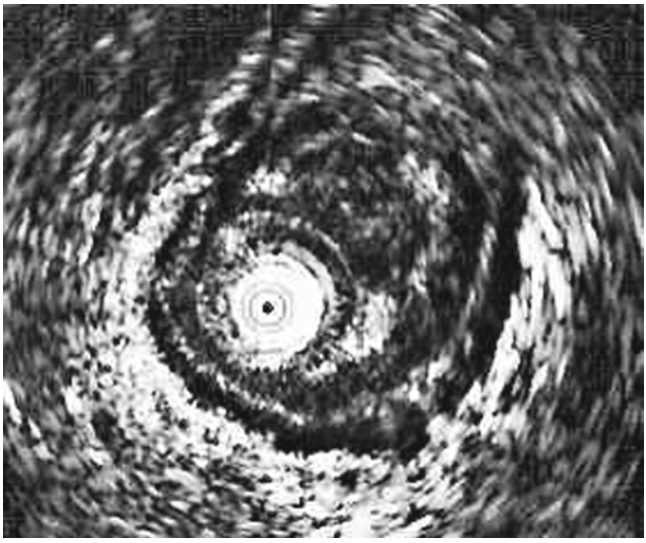

Fig. 13. Two-dimensional IDUS image (30 MHz) showing a T2 cholangiocarcinoma. The edge of the bile duct can often not be distinguished from the edge of the pancreatic parenchyma (2 o'clock position), making the distinction between T2 and T3 categories extremely difficult, even by histopathological means. Photograph courtesy from M. Giovannini.

resectability (59). EUS examination of tumors located at the hilum is limited by the long distance between the transducer and the proximal margin of the tumor. Conversely, its low penetration depth limits IDUS so that lymph nodes cannot be reliably assessed by this technique. Both techniques should therefore be combined in difficult cases.

Impact of EUS-FNA on Patient Management

Pathological diagnosis is required before embarking into neoadjuvant therapy of cholangiocarcinoma (e.g., portal vein embolization to induce compensatory hypertrophy of the future remnant liver), or in patients who are not eligible for surgery if aggressive treatments (e.g., photodynamic therapy) are considered (60, 61). This is critical because many patients who undergo resection for a suspected malignant biliary stricture have a final pathological diagnosis of benign disease (15% for hilar resections, 5–10% for pancreatic head resections) (62, 63). The proportion of inappropriate surgery is even >20% for hilar lesions, due

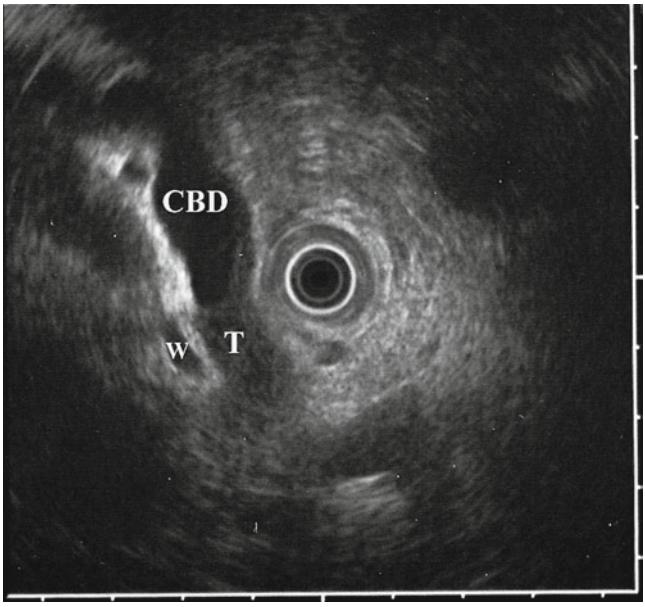

Fig. 14. Radial EUS image (7.5 MHz) showing a T3 cholangiocarcinoma (T) that invades the pancreas and causes upstream dilation of the common bile duct (CBD). The Wirsung's duct (W) is not dilated.

to erroneous preoperative diagnosis of metastases as primary hilar cholangiocarcinomas (64). As bile duct resection incurs 50% morbidity and a significant mortality (5–10% for hilar lesions, less for those treated by pancreaticoduodenectomy) (55), this possibility cannot be neglected.

The results of EUS-FNA have been reported to have a positive impact on patient management in 17–84% of patients in different series (43, 46, 48). Examples of management shift included avoidance of planned surgery in patients with previously undiagnosed Hodgkin's disease or hilar metastases (initially confounded as a primary tumor) or demonstration of malignant lymph node involvement. Conversely, the decision to embark on surgery is facilitated if the malignant etiology of a biliary stricture is demonstrated with FNA sampling. In this regard, the theoretical risk of peritoneal tumor seeding during EUS-FNA of hilar tumors (as has been reported after percutaneous transhepatic biliary drainage of cholangiocarcinomas) should be weighed against the potential benefit (65). Based on their personal experience, Gleeson et al. recommended not performing EUS-FNA in patients with a potentially resectable tumor (46).

Intraductal Ultrasonography

Introduction

Although IDUS does not provide a pathological diagnosis, it is more accurate than ERCP with transpapillary biopsies to distinguish between benign and malignant strictures (accuracy in a comparative study, 90% vs. 67%, respectively; $P<0.02$) (66). In contrast with standard EUS, IDUS obtains high-resolution images of the bile duct stricture. For example, in a prospective comparative study of 56 patients, IDUS provided a diagnosis in 55/56 (98%) cases, as compared to only 45/56 (80%) cases for EUS ($P<0.005$), due to the proximal location and/or to the small size of the tumors (59). This difference translated into a higher accuracy of IDUS for diagnosing biliary malignancy as compared with EUS (89% vs. 76%, $P<0.002$).

Distinction Between Benign and Malignant Strictures

Multiple echoendoscopic features have been proposed to discriminate benign from malignant biliary strictures (67), and this has often created some confusion. By using various combinations of these criteria, the few studies that have evaluated the performance of IDUS in the most relevant population (i.e., patients with a biliary stricture and no culprit mass identified at CT-Scan/magnetic resonance) have found sensitivities between 82 and 89%, and specificities between 64 and 85% (2, 68, 69). However, echoendoscopists were generally unblinded to both clinical data and ERCP findings, and neither the learning curve for biliary IDUS nor the interobserver agreement has been studied. To facilitate the interpretation of IDUS findings, Tamada et al. have identified three features that were independently associated with a malignant diagnosis in a prospective study that included 62 patients (Table 5) (70). If none of these three features were present, the negative predictive value of IDUS for malignancy was close to 90%. On the contrary, when IDUS showed two or three of these features, a final diagnosis of malignancy was made in 97% of cases. This

Table 5
IDUS features independently associated with malignancy in biliary strictures

Presence of a sessile tumor (intraductal or outside of the bile duct)
Tumor size greater than 10.0 mm
Interrupted wall structure

indicates that patients with 2 IDUS features predictive of malignancy should be managed as having a malignancy even if preoperative pathological findings are benign.

Finally, as IDUS is limited by the lack of pathological diagnosis, some investigators have performed IDUS-directed biopsy sampling (with the IDUS probe and a biopsy forceps introduced together in the working channel of the duodenoscope). Using this approach in 21 patients, Moon et al. reported a higher sensitivity for cancer diagnosis with IDUS-guided in comparison with fluoroscopically-guided biopsy (83% vs. 56%, P=0.14) (71). New techniques are being developed to facilitate IDUS-guided bile duct biopsy.

Staging of Cholangiocarcinomas

Criteria used for staging purposes at IDUS in the largest series were as follows:

- Pancreas invasion was diagnosed if the hyperechoic layer between the bile duct and the pancreas was lost (72), or if the margin between the tumor and surrounding pancreatic tissue was not smooth (e.g., digitiform indentations) (73)
- Vessel invasion was diagnosed if the vessel-parenchymal sonographic interface was lost or if the tumor was detected within the vessel lumen (72, 73)
- Lymph nodes were considered as malignant if ≥2 of the following criteria were present: hypoechogenicity relative to periductal connective tissue, a round configuration, and conspicuous margins (see above comments about the validity of echoendoscopic criteria for assessment of lymph node metastasis) (2)
- Longitudinal tumor extent was assessed by defining tumor limits on the hepatic and duodenal sides as the disappearance of bile duct wall thickening; asymmetric wall thickening was considered a sign of tumor invasion (this should be assessed prior to biliary drainage to avoid stent-induced artifacts) (74).

For T staging, the accuracy of IDUS is superior to that of EUS, with the greatest difference noted for tumors located at the hilum (59). Tamada et al. also reported in pioneer studies, using various types of probes (7.5, 15, 20 and 30 MHz) a very high accuracy for T staging and for the diagnosis of vascular invasion (T staging, 82%; portal vein invasion, 100%; right hepatic artery invasion, 100%) (26, 27). These results were confirmed by other authors who reported accuracies close to 90% for the assessment of pancreas and portal vein invasion (the portal vein and the right hepatic artery are the most frequently invaded vessels, while the left and common hepatic arteries are less frequently invaded)

(72, 75–77). Compared to angiography, IDUS yielded slightly better results for the assessment of hepatic artery and portal vein invasion (nonsignificant differences) (75, 76). Resectability is better predicted by IDUS than by EUS (59).

For N staging, IDUS presents a lower accuracy than EUS, even without FNA (43% vs. 63%; $P<0.05$). Due to the limited penetration depth (<2 cm) of IDUS probes, this technique is currently considered as unreliable for complete lymph node assessment (59, 73). EUS coupled with FNA of lymph nodes is more useful for this purpose (46, 78).

The longitudinal extent of cholangiocarcinomas is a critical factor for the planning of surgical resection. IDUS coupled with biopsy sampling is likely the best technique currently available to assess this parameter. In a prospective study of 19 patients with a cholangiocarcinoma investigated by IDUS immediately after biliary cannulation, longitudinal spread was correctly assessed by IDUS in 84% of cases vs. 47% with ERC ($P<0.05$) (74). Other studies have reported slightly less favorable results with IDUS, including 3D-IDUS (72). To overcome the shortcomings of IDUS, some authors have recently proposed to combine IDUS with transpapillary biopsy sampling: in a prospective study of 44 patients with a cholangiocarcinoma investigated preoperatively, the longitudinal tumor extent was correctly assessed on the hepatic and duodenal sides with IDUS in, respectively, 77 and 61% of cases. In the same patients, the corresponding figures with IDUS plus biopsy sampling were 93 and 82%, respectively (both P values <0.05) (79).

Particular Case: Primary Sclerosing Cholangitis

The risk of developing a cholangiocarcinoma is markedly elevated in patients with PSC compared to the general population (prevalence, 5–36%, depending on the methods used for screening and follow-up duration) (80–82). As the development of a cholangiocarcinoma is not reliably heralded by symptomatic changes, surveillance strategies have been proposed for PSC patients. These include standard liver biochemistries every 3 months and dosage of serum tumor markers (CA 19-9 and CEA) plus magnetic resonance every 6 months. Worsening of liver biochemistries, elevation of the CA 19-9 above 200 IU/mL and/or CEA above 5 ng/mL, or the development of a new dominant stricture at magnetic resonance (i.e., a stricture <1.5 mm on the CBD and/or <1.0 mm on the common hepatic duct within 2 cm of the bifurcation) should prompt referral for ERCP and biliary sampling (56). IDUS may be performed at this time (no large series of PSC patients investigated with EUS has been reported to date).

The interpretation of 2 IDUS images in PSC patients may be difficult because the bile duct wall is thickened (at a mean of 2.5 mm vs. 0.6–0.8 mm in normal subjects) (7, 8), but this thickening is uniform along the extrahepatic bile ducts. In 34 PSC patients (41% of whom had a final diagnosis of malignancy), IDUS had a sensitivity and specificity for cancer detection of 77% and 55%, i.e. lower than those reported in 52 non-PSC patients in the same series (97% [$P<0.05$] and 74% [NS], respectively) (68). In that study, malignancy was diagnosed at IDUS if any one of the three following criteria was met: (1) hypoechoic stricture with irregular outer margin; (2) hypoechoic stricture with regular outer margin and one or both of the following: (a) abnormal stricture morphology (asymmetry, notching, or shelf-like), or (b) suspicious lymph nodes (hypoechoic, round, and smooth-border); or (3) stricture of intermediate echogenicity with irregular outer margin and one or both of following: (a) abnormal stricture morphology (asymmetry, notching, or shelf-like), or (b) suspicious lymph nodes (hypoechoic, round, and smooth border). The authors did not discuss why they chose criteria different from those listed in Table 5, but they explained that the comparison of strictures relative to one another allowed to make subjective diagnoses that were more accurate (sensitivity, 64%; specificity, 95%) than those strictly based on these three criteria.

Hyodo et al. have reported in a small case-series that the US contrast agents could help to differentiate PSC from cholangiocarcinoma (bile duct wall enhancement was observed 2 min after Levovist injection in sclerosing cholangitis but not in cholangiocarcinoma) (83). This approach merits further investigation with the US contrast agents of the current generation.

Therapeutic EUS for Biliary Strictures

Preamble

Although EUS-guided biliary drainage seems promising, comparison with the current standard in case of ERCP failure, i.e., percutaneous drainage, has not yet been reported. Therefore, this technique should be reserved in patients in whom an endoscopist highly skilled at ERCP has failed to deeply cannulate the bile duct. An endoscopist skilled at both EUS and ERCP should perform EUS-guided biliary drainage, with interventional radiologists/biliary surgeons available in case of failure or complications. In hospitals where percutaneous biliary drainages are performed by radiologists, EUS-guided biliary drainage presents the advantage of requiring no coordination between interventional radiologists and endoscopists.

Technique

See Chap. 16.

Results

Eleven case series totaling 70 patients treated by EUS-guided biliary drainage have been published to date, with the largest experience reported by Kahaleh et al. (84–93). Overall, biliary drainage was successful in >90% of cases, with failures mostly related to difficulties in advancing the guidewire through the stricture. In one third of cases, a rendezvous procedure was performed and in two thirds of cases a stent was inserted into the bilioenteric access. Complications were reported in 11% of cases, and included cases of bile leak causing ascites and fever treated by paracentesis (extrahepatic approach), spontaneously resolving pneumoperitoneum, and cholangitis. Hemobilia was remarkably infrequent when the transhepatic route was used; this is likely related to the use of Doppler guidance to access the bile ducts.

GALLBLADDER

Normal Findings

Two or three layers are identified at EUS of the gallbladder wall. The inner hypoechoic layer corresponds to the mucosa, muscularis propria, and connective tissue of the subserosa (in some patients, little connective fibrous tissue is present and this layer mainly represents the muscularis propria); the outer hyperechoic layer represents the subserosal adipose tissue and serosa; if an additional (innermost) hyperechoic layer is visualized, it is associated with an echo interface or with the mucosa (94, 95). The thickness of the gallbladder wall is measured at a right angle to the transducer beam; it varies with its degree of distension but in a fasting patient the upper limit of normal is 3.5 mm (96).

Stones

EUS excels for the detection of gallbladder stones that are difficult to detect at percutaneous US due to their small size (<3 mm in diameter), location in the cystic duct, or because of the interposition of adipose tissue in obese patients. EUS is most beneficial in patients with "idiopathic" pancreatitis: in a study of 18 patients with negative findings at percutaneous US, 14 (78%) patients were found to have gallbladder

stones at EUS (36). In another study performed in patients with suspected gallbladder stones and ≥2 normal percutaneous US examinations, the sensitivity and specificity of EUS for the diagnosis of gallbladder stones were 96 and 86%, respectively (97).

Polypoid Lesions

Description

Gallbladder polypoid lesions (GBP), defined as lesions that protrude from the wall of the gallbladder into its lumen, are devoid from acoustic shadow and do not move with gravity or manipulation. Their presence should be confirmed by a second examination because GBP may be confused with a sludge ball or a blood clot (98, 99). According to two percutaneous US studies conducted in >6,000 subjects, the prevalence of GBP ranges between 4.5 and 6.9% of healthy subjects, with 85% of GBP being ≤5 mm in diameter (99, 100).

Lesions reported as GBP correspond to a spectrum of histopathological findings (Table 6):

- Cholesterol polyps account for the majority of GBP; they have no malignant potential and require no follow-up (101, 102). At pathological examination, they are often multiple and correspond to an accumulation of lipid-laden macrophages covered by a normal epithelium. At EUS, they are typically round or slightly lobulated, homogeneous, hyperechoic relative to liver parenchyma, and <10 mm in diameter.

Table 6
Principal histopathological findings associated with gallbladder polypoid lesions

Neoplastic
Malignant: adenocarcinoma, metastases
Benign: adenoma (rarely, leiomyoma, lipoma, hemangioma, hamartoma, neurofibroma, paragangliomas)
Non-neoplastic
Cholesterol polyp
Adenomyoma
Inflammatory polyp
Heterotopias (gastric, pancreatic)

Adapted from Albores-Saavedra et al. (135)

They may be difficult to distinguish from nonshadowing adherent stones. Large cholesterol polyps are typically pedunculated masses with a granular surface and contain hyperechoic spots corresponding to aggregates of foamy macrophages (103, 104).

- Adenomyomatous polyps, also called adenomyomas, are a variant of adenomyomatosis (an excessive proliferation of the biliary epithelium with invaginations into the thickened muscularis or beyond that may be diffuse, segmental, or focal, forming polyps). Gallbladder adenomyomatosis is common (2–33% of consecutive cholecystectomy specimens) and adenomyomas have been reported in up to 7% of unselected autopsies (105). At EUS, gallbladder adenomyomas appear as fundal masses that contain round anechoic or echogenic foci (corresponding to intramural diverticulae filled with bile or sludge, respectively), and may harbor a typical "comet tail" artifact originating from echogenic foci (106).
- Neoplasms account for up to 15% of all GBP (107). The distinction at EUS between the two most frequent forms, adenoma and adenocarcinoma, is not fundamental because adenomas may follow the adenoma-carcinoma sequence (108) and thus also need to be removed. At EUS, adenomas are typically smoothly marginated, intraluminal, sessile or pedunculated, polypoid masses. They are generally homogeneously hyperechoic (103), but larger polyps tend to be less echogenic and more heterogeneous (109). Adenocarcinomas are pedunculated or sessile, hypo- to isoechoic, homogeneous or heterogeneous masses (110, 111).

Role of EUS in the Management of Gallbladder Polypoid Lesions

Most authors have advocated cholecystectomy for GBP if these were (1) >10 mm in diameter, or (2) associated with gallstones or (3) found in patients >50 years (plus, more recently, in patients with PSC, although this is debated) (112, 113). Even though the morbidity of cholecystectomy is acceptable, findings at surgery argue in favor of a preoperative diagnosis more refined than simply assessing the GBP size and the presence or absence of gallbladder stones. This applies mainly for GBP in the 5–15 mm range because most GBPs <5 mm are non-neoplastic and most GBPs >15 mm are neoplastic (103, 111, 114, 115). In contrast, findings in the 5–15 mm range are mixed: adenomas and adenocarcinomas account for 8–29% of GBP measuring 5–10 mm, and non-neoplastic (mainly cholesterol) polyps account for 53–75% of GBP measuring 11–15 mm (104, 111, 114).

EUS is more effective than percutaneous US to image GBPs because it uses higher frequencies and, hence, has a higher resolution: Sugiyama

et al. have correctly diagnosed neoplastic vs. non-neoplastic GBPs in 97% vs. 71% of cases at EUS vs. percutaneous US, respectively ($P<0.0001$), while using identical diagnostic criteria (115). Sadamoto et al. have identified in a retrospective EUS study three factors that were independently associated with a neoplastic (adenoma or adenocarcinoma) diagnosis in GBP <20 mm in diameter, namely, the absence of internal hyperechoic spot, the presence of a heterogeneous echotexture and a greater maximum size (114). Based on these findings, scores were constructed to help differentiating neoplastic vs. non-neoplastic GBP (as was also done by Choi et al. (111)), but these scores are not very practical to use and have not been validated prospectively.(116) Therefore, it has been suggested that, in cases where GBPs appear different from either a cholesterol polyp (i.e., single tiny echogenic spot or containing at least a partial aggregation of echogenic spots) or an adenomyoma (i.e., containing multiple microcysts or with a comet tail artifact) at EUS, should be removed surgically. Other GBPs should be followed-up by percutaneous US every 6–12 months (104).

Finally, the ethnic origin of patients is likely an important factor that has been overlooked until recently. Gallbladder cancer is known to be more prevalent in Indians, American Indians, Japanese, and in some countries of Central and Eastern Europe (117). Based on a retrospective review of >70,000 reports of percutaneous US, it has been calculated that, for similar gallbladder lesions, cholecystectomy would allow to detect an early cancer in 1/13 Indian patients vs. 1/670 Caucasian patients (117, 118).

Carcinoma

Gallbladder carcinoma (GBC) is the most common malignancy of the biliary tract. It may present as a GBP, a complex mass filling the gallbladder, or a wall thickening; this latter form represents 18% of GBC (119), and is difficult to differentiate from xanthogranulomatous cholecystitis and adenomyomatosis (120). GBC frequently invades the liver because of the continuity between the perimuscular connective tissue of the gallbladder and the interlobular connective tissue of the liver, and it disseminates to lymph nodes early in the course of the disease (even to nodes posterior to the portal vein or pancreatic head) (121, 122). Therefore, GBC is usually detected at an advanced stage and it has long had the reputation of having an extremely poor prognosis (except when it is discovered incidentally on a cholecystectomy specimen). Recently, progresses made in techniques of hepatic resection have allowed proposing a more aggressive surgical approach, and this has translated into

longer survivals. For T2 tumors, extended cholecystectomy (including resection of hepatic segments IV and V) plus extensive lymph node dissection are associated with 90–100% survivals at 3 years, as compared to 20–40% after a simple cholecystectomy. Importantly, simple cholecystectomy is sufficient for T1 tumors (at least T1a), and provides an almost 100% cure rate (123–125). It is thus of paramount importance to distinguish between T1 and T2 tumors preoperatively (i.e., cancer invasion limited to the muscle layer or to the perimuscular connective tissue).

The current, seventh edition of the TNM classification of GBC is shown in Table 7 (126). The main changes from the sixth edition is that the cystic duct is now included in the classification scheme, and the N classification now distinguishes hilar nodes (N1) from other regional nodes (N2). Although the majority of EUS studies have used the previous, fifth edition of the TNM classification, their results remain valid because the two categories that underwent modifications (T3 and T4) had been grouped in these EUS studies. Two retrospective studies have analyzed a total of 80 patients with GBC. Lesions were classified into four types, based on tumor characteristics (shape and surface) and

Table 7
2010 AJCC TNM classification of gallbladder carcinomas

T category	
Tis	Carcinoma in situ
T1a	Tumor invades lamina propria
T1b	Tumor invades muscle layer
T2	Tumor invades perimuscular connective tissue (no extension beyond serosa or into liver)
T3	Tumor perforates serosa and/or invades the liver and/or one other adjacent organ[a]
T4	Tumor invades main portal vein or hepatic artery or invades multiple extrahepatic organs or structures
N category	
N0	No regional lymph-node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic duct, hepatic artery, and/or portal vein
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes

[a]For example, stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts

integrity of the outer hyperechoic layer of the gallbladder (127, 128). In the first study, the interobserver agreement was analyzed, and this was high (92%) (127). Correspondences between the four types of lesions described at EUS and T categories were proposed: type A (pedunculated mass with preserved adjacent wall structures) as pTis, type B (sessile and/or broad-based mass with a preserved outer hyperechoic layer of the gallbladder wall) as pT1, type C (sessile and/or broad-based mass with a narrowed outer hyperechoic layer) as pT2, and type D (sessile and/or broad-based mass with a disrupted outer hyperechoic layer) as pT3-4 (grouped). Using these correspondences, the accuracy of EUS was as follows: Tis, 100%; T1, 76%; T2, 85%; and T3-4, 93% (128). Distinction between T1 and T2 categories may be difficult because the difference between these two categories may be as slim as invasion up to the muscle layer or to the perimuscular connective tissue. As therapeutic planning between these two categories is markedly different, it is important to recognize a thinned outer hyperechoic layer as indicative of a T2 tumor. Fujimoto et al. have described in a case report another US feature that is suggestive of invasion into the subserosa (T2); this sign was confirmed by other authors to be valuable at EUS in patients with a GBC (it was identified in 11 of 13 patients with a type C lesion) (128).

During EUS, one should also look for previously undetected lymph nodes, liver metastases and carcinomatous ascites because up to 50% of the patients thought to have a resectable disease have metastasis at staging laparoscopy (129). Unfortunately, lymph nodes were not assessed in the two studies that have evaluated the accuracy of EUS staging (127, 128). Indeed, the value of EUS-FNA has not been thoroughly studied in patients with a GBC, likely because lesions located in the gallbladder can easily and safely be removed surgically, and it may not be justifiable to incur the risk of biliary peritonitis (a complication reported with both percutaneous and EUS-guided FNA of the gallbladder) or of a false-negative result (130). Two retrospective studies totaling 12 patients have reported the results of EUS-FNA for a suspected malignant gallbladder mass: no complication occurred, sensitivity for cancer detection was 90%, and lymph node involvement was demonstrated by FNA in three of ten malignant cases (131, 132). As always, FNA might be the most useful, when it demonstrates metastatic involvement of distant lymph nodes.

The role of EUS for staging GBC is challenged by recent advances in noninvasive imaging techniques. For example, 10 years ago, the sensitivity of CT-Scan to detect liver infiltration <2 cm in depth and lymph node metastases were 65 and <50%, respectively (133, 134). Recently, the improved spatial resolution of multidetector CT has

allowed to describe new CT criteria for T staging and to improve its overall accuracy (correct T staging, 84% in a recent retrospective study that included 118 patients) (135). In particular, the sensitivity and specificity for distinguishing T1 vs. ≥T2 lesions in that study were 79 and 99%, respectively (68 patients with pT1 or pT2 lesion were included).

In conclusion, EUS and IDUS are excellent imaging techniques to evaluate the biliary system. Because of its lower complication rate, it is preferred over ERCP for ruling out microlithiasis in somebody with low or intermediate clinical suspicion. EUS has become essential in clinical staging and managements of cholangiocarcinoma and gallbladder cancers.

REFERENCES

1. Technology Assessment Committee, Liu J, Carpenter S, Chuttani R, Croffie J, Disario J, et al. Endoscopic ultrasound probes. Gastrointest Endosc. 2006;63:751–4.
2. Stavropoulos S, Larghi A, Verna E, Battezzati P, Stevens P. Intraductal ultrasound for the evaluation of patients with biliary strictures and no abdominal mass on computed tomography. Endoscopy. 2005;37:715–21.
3. Sethi A, Chen KY, Austin GL, Brauer BC, Fukami N, Khan AH, et al. ERCP with cholangiopancreatoscopy (CP) is associated with higher rates of endoscopic complications than ERCP alone. Gastrointest Endosc. 2008;67:AB102–3.
4. Domagk D, Diallo R, Menzel J, Schleicher C, Bankfalvi A, Gabbert HE, et al. Endosonographic and histopathological staging of extrahepatic bile duct cancer: time to leave the present TNM-classification? Am J Gastroenterol. 2005;100:594–600.
5. Noda Y, Fujita N, Kobayashi G, Kimura K, Yago A, Yuki T, et al. Comparison of echograms by a microscanner and histological findings of the common bile duct, in vitro study. Jpn J Gastroenterol. 1997;94:172–9.
6. Tamada K, Kanai N, Ueno N, Ichiyama M, Tomiyama T, Wada S, 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.
7. Tamada K, Tomiyama T, Oohashi A, Aizawa T, Nishizono T, Wada S, et al. Bile duct wall thickness measured by intraductal US in patients who have not undergone previous biliary drainage. Gastrointest Endosc. 1999;49:199–203.
8. Mesenas S, Vu C, Doig L, Meenan J. Duodenal EUS to identify thickening of the extrahepatic biliary tree wall in primary sclerosing cholangitis. Gastrointest Endosc. 2006;63:403–8.
9. Tamada K, Tomiyama T, Ichiyama M, Oohashi A, Wada S, Nishizono T, et al. Influence of biliary drainage catheter on bile duct wall thickness as measured by intraductal ultrasonography. Gastrointest Endosc. 1998;47:28–32.
10. Levy MJ. The hunt for microlithiasis in idiopathic acute recurrent pancreatitis: should we abandon the search or intensify our efforts? Gastrointest Endosc. 2002;55:286–93.

11. Jüngst C, Kullak-Ublick GA, Jüngst D. Gallstone disease: microlithiasis and sludge. Best Pract Res Clin Gastroenterol. 2006;20:1053–62.
12. [No authors listed]. Gallstones and laparoscopic cholecystectomy. NIH Consens Statement. 1992;10:1–28.
13. Everhart J. Digestive diseases in the United States: epidemiology and impact. Bethesda, MD: NIH, NIDDK; 1994. NIH publication no. 94-1447.
14. Soltan HM, Kow L, Toouli J. A simple scoring system for predicting bile duct stones in patients with cholelithiasis. J Gastrointest Surg. 2001;5:434–7.
15. Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc. 2001;54:425–34.
16. Mazen Jamal M, Yoon EJ, Saadi A, Sy TY, Hashemzadeh M. Trends in the utilization of endoscopic retrograde cholangiopancreatography (ERCP) in the United States. Am J Gastroenterol. 2007;102:966–75.
17. Buscarini E, Tansini P, Vallisa D, Zambelli A, Buscarini L. EUS for suspected choledocholithiasis: do benefits outweigh costs? A prospective, controlled study. Gastrointest Endosc. 2003;57:510–8.
18. Solis-Caxaj CA. Treatment of Mirizzi syndrome. J Am Coll Surg. 2007;205:518–9.
19. Tse F, Liu L, Barkun A, Armstrong D, Moayyedi P. EUS: a meta-analysis of test performance in suspected choledocholithiasis. Gastrointest Endosc. 2008;67: 235–44.
20. Garrow D, Miller S, Sinha D, Conway J, Hoffman BJ, Hawes RH, et al. Endoscopic ultrasound: a meta-analysis of test performance in suspected biliary obstruction. Clin Gastroenterol Hepatol. 2007;5:616–23.
21. Frossard JL, Hadengue A, Amouyal G, Choury A, Marty O, Giostra E, et al. Choledocholithiasis: a prospective study of spontaneous common bile duct stone migration. Gastrointest Endosc. 2000;51:175–9.
22. Ainsworth AP, Rafaelsen SR, Wamberg PA, Durup J, Pless TK, Mortensen MB. Is there a difference in diagnostic accuracy and clinical impact between endoscopic ultrasonography and magnetic resonance cholangiopancreatography? Endoscopy. 2003;35:1029–32.
23. Aubé C, Delorme B, Yzet T, Burtin P, Lebigot J, Pessaux P, et al. MR cholangiopancreatography versus endoscopic sonography in suspected common bile duct lithiasis: a prospective, comparative study. AJR Am J Roentgenol. 2005;184: 55–62.
24. de Lédinghen V, Lecesne R, Raymond JM, Gense V, Amouretti M, Drouillard J, et al. Diagnosis of choledocholithiasis: EUS or magnetic resonance cholangiography? A prospective controlled study. Gastrointest Endosc. 1999;49:26–31.
25. Kondo S, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, et al. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. J Hepatobiliary Pancreat Surg. 2008;15:41–54.
26. Materne R, Van Beers BE, Gigot JF, Jamart J, Geubel A, Pringot J, et al. Extrahepatic biliary obstruction: magnetic resonance imaging compared with endoscopic ultrasonography. Endoscopy. 2000;32:3–9.
27. Scheiman JM, Carlos RC, Barnett JL, Elta GH, Nostrant TT, Chey WD, et al. Can endoscopic ultrasound or magnetic resonance cholangiopancreatography replace

ERCP in patients with suspected biliary disease? A prospective trial and cost analysis. Am J Gastroenterol. 2001;96:2900–4.
28. Schmidt S, Chevallier P, Novellas S, Gelsi E, Vanbiervliet G, Tran A, et al. Choledocholithiasis: repetitive thick-slab single-shot projection magnetic resonance cholangiopancreaticography versus endoscopic ultrasonography. Eur Radiol. 2007;17:241–50.
29. Fernandez-Esparrach G, Gines A, Sanchez M, Pages M, Pellise M, Fernandez-Cruz L, et al. Comparison of endoscopic ultrasonography and magnetic resonance cholangiopancreatography in the diagnosis of pancreatobiliary diseases: a prospective study. Am J Gastroenterol. 2007;102:1632–9.
30. Verma D, Kapadia A, Eisen GM, Adler DG. EUS vs MRCP for detection of choledocholithiasis. Gastrointest Endosc. 2006;64:248–54.
31. Arguedas MR, Dupont AW, Wilcox CM. Where do ERCP, endoscopic ultrasound, magnetic resonance cholangiopancreatography, and intraoperative cholangiography fit in the management of acute biliary pancreatitis? A decision analysis model. Am J Gastroenterol. 2001;96:2892–9.
32. McMahon CJ. The relative roles of magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound in diagnosis of common bile duct calculi: a critically appraised topic. Abdom Imaging. 2008;33:6–9.
33. Wilcox CM, Varadarajulu S, Eloubeidi M. Role of endoscopic evaluation in idiopathic pancreatitis: a systematic review. Gastrointest Endosc. 2006;63:1037–45.
34. Kohut M, Nowak A, Nowakowska-Duława E, Kaczor R, Marek T. The frequency of bile duct crystals in patients with presumed biliary pancreatitis. Gastrointest Endosc. 2001;54:37–41.
35. Frossard JL, Sosa-Valencia L, Amouyal G, Marty O, Hadengue A, Amouyal P. Usefulness of endoscopic ultrasonography in patients with “idiopathic” acute pancreatitis. Am J Med. 2000;109:196–200.
36. Liu CL, Lo CM, Chan JK, Poon RT, Fan ST. EUS for detection of occult cholelithiasis in patients with idiopathic pancreatitis. Gastrointest Endosc. 2000;51:28–32.
37. Norton SA, Alderson D. Endoscopic ultrasonography in the evaluation of idiopathic acute pancreatitis. Br J Surg. 2000;87:1650–5.
38. Tandon M, Topazian M. Endoscopic ultrasound in idiopathic acute pancreatitis. Am J Gastroenterol. 2001;96:705–9.
39. Yusoff IF, Raymond G, Sahai AV. A prospective comparison of the yield of EUS in primary vs. recurrent idiopathic acute pancreatitis. Gastrointest Endosc. 2004;60:673–8.
40. Frei GJ, Frei VT, Thirlby RC, McClelland RN. Biliary pancreatitis: clinical presentation and surgical management. Am J Surg. 1986;151:170–5.
41. Goodman AJ, Neoptolemos JP, Carr-Locke DL, Finlay DB, Fossard DP. Detection of gall stones after acute pancreatitis. Gut. 1985;26:125–32.
42. Lee JH, Salem R, Aslanian H, Chacho M, Topazian M. Endoscopic ultrasound and fine-needle aspiration of unexplained bile duct strictures. Am J Gastroenterol. 2004;99:1069–73.
43. Fritscher-Ravens A, Broering DC, Knoefel WT, Rogiers X, Swain P, Thonke F, et al. EUS-guided fine-needle aspiration of suspected hilar cholangiocarcinoma in potentially operable patients with negative brush cytology. Am J Gastroenterol. 2004;99:45–51.

44. Romagnuolo J, Bardou M, Rahme E, Joseph L, Reinhold C, Barkun AN. Magnetic resonance cholangiopancreatography: a meta-analysis of test performance in suspected biliary disease. Ann Intern Med. 2003;139:547–57.
45. Faigel DO. EUS in patients with benign and malignant lymphadenopathy. Gastrointest Endosc. 2001;53:593–8.
46. Gleeson F, Rajan E, Levy M, Clain J, Topazian M, Harewood G, et al. EUS-guided FNA of regional lymph nodes in patients with unresectable hilar cholangiocarcinoma. Gastrointest Endosc. 2008;67:438–43.
47. DeWitt J, Misra VL, Leblanc JK, McHenry L, Sherman S. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. Gastrointest Endosc. 2006;64:325–33.
48. Eloubeidi MA, Chen VK, Jhala NC, Eltoum IE, Jhala D, Chhieng DC, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy of suspected cholangiocarcinoma. Clin Gastroenterol Hepatol. 2004;2:209–13.
49. Meara RS, Jhala D, Eloubeidi MA, Eltoum I, Chhieng DC, Crowe DR, et al. Endoscopic ultrasound-guided FNA biopsy of bile duct and gallbladder: analysis of 53 cases. Cytopathology. 2006;17:42–9.
50. Rösch T, Hofrichter K, Frimberger E, Meining A, Born P, Weigert N, et al. ERCP or EUS for tissue diagnosis of biliary strictures? A prospective comparative study. Gastrointest Endosc. 2004;60:390–6.
51. Byrne MF, Gerke H, Mitchell RM, Stiffler HL, McGrath K, Branch MS, et al. Yield of endoscopic ultrasound-guided fine-needle aspiration of bile duct lesions. Endoscopy. 2004;36:715–9.
52. Dumonceau JM. Biliary ERCP. Endoscopy. 2008;40:50–4.
53. Dumonceau JM, Macias Gomez C, Casco C, Genevay M, Marcolongo M, Bongiovanni M, et al. Grasp or brush for biliary sampling at endoscopic retrograde cholangiography? A blinded randomized controlled trial. Am J Gastroenterol. 2008;103: 333–40.
54. DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg. 2007;245:755–62.
55. Tsao JI, Nimura Y, Kamiya J, Hayakawa N, Kondo S, Nagino M, et al. Management of hilar cholangiocarcinoma: comparison of an American and a Japanese experience. Ann Surg. 2000;232:166–74.
56. Yachimski P, Pratt DS. Cholangiocarcinoma: natural history, treatment, and strategies for surveillance in high-risk patients. J Clin Gastroenterol. 2008;42:178–90.
57. Nishio H, Nagino M, Oda K, Ebata T, Arai T, Nimura Y. TNM classification for perihilar cholangiocarcinoma: comparison between 5th and 6th editions of the AJCC/UICC staging system. Langenbecks Arch Surg. 2005;390:319–27.
58. Tio TL, Cheng J, Wijers OB, Sars PR, Tytgat GN. Endosonographic TNM staging of extrahepatic bile duct cancer: comparison with pathological staging. Gastroenterology. 1991;100:1351–61.
59. Menzel J, Poremba C, Dietl KH, Domschke W. Preoperative diagnosis of bile duct strictures – comparison of intraductal ultrasonography with conventional endosonography. Scand J Gastroenterol. 2000;35:77–82.
60. Kahaleh M, Mishra R, Shami VM, Northup PG, Berg CL, Bashlor P, et al. Unresectable cholangiocarcinoma: comparison of survival in biliary stenting

alone versus stenting with photodynamic therapy. Clin Gastroenterol Hepatol. 2008;6:290–7.
61. Ortner ME, Caca K, Berr F, Liebetruth J, Mansmann U, Huster D, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology. 2003;125:1355–63.
62. Gerhards MF, Vos P, van Gulik TM, Rauws EA, Bosma A, Gouma DJ. Incidence of benign lesions in patients resected for suspicious hilar obstruction. Br J Surg. 2001;88:48–51.
63. Wolfson D, Barkin JS, Chari ST, Clain JE, Bell RH, Alexakis N, et al. Management of pancreatic masses. Pancreas. 2005;31:203–17.
64. Wetter LA, Ring EJ, Pellegrini CA, Way LW. Differential diagnosis of sclerosing cholangiocarcinomas of the common hepatic duct (Klatskin tumors). Am J Surg. 1991;161:57–63.
65. Chapman WC, Sharp KW, Weaver F, Sawyers JL. Tumor seeding from percutaneous biliary catheters. Ann Surg. 1989;209:708–15.
66. Vazquez-Sequeiros E, Baron TH, Clain JE, Gostout CJ, Norton ID, Petersen BT, et al. Evaluation of indeterminate bile duct strictures by intraductal US. Gastrointest Endosc. 2002;56:372–9.
67. Tamada K, Ueno N, Tomiyama T, Oohashi A, Wada S, Nishizono T, et al. Characterization of biliary strictures using intraductal ultrasonography: comparison with percutaneous cholangioscopic biopsy. Gastrointest Endosc. 1998;47:341–9.
68. Levy MJ, Baron TH, Clayton AC, Enders FB, Gostout CJ, Halling KC, 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.
69. Varadarajulu S, Eloubeidi MA, Wilcox CM. Prospective evaluation of indeterminate ERCP findings by intraductal ultrasound. J Gastroenterol Hepatol. 2007;22:2086–92.
70. Tamada K, Tomiyama T, Wada S, Ohashi A, Satoh Y, Ido K, et al. Endoscopic transpapillary bile duct biopsy with the combination of intraductal ultrasonography in the diagnosis of biliary strictures. Gut. 2002;50:326–31.
71. Moon JH, Choi HJ, Kim HK, Kwon KW, Cheon YK, Cho YD, et al. The usefulness of IDUS-guided transpapillary bile duct biopsy for the diagnosis of malignant biliary strictures. Gastrointest Endosc. 2008;67:AB208.
72. Inui K, Yoshino J, Okushima K, Miyoshi H, Nakamura Y. Intraductal EUS. Gastrointest Endosc. 2002;56:S58–62.
73. Tamada K, Ido K, Ueno N, Kimura K, Ichiyama M, Tomiyama T. Preoperative staging of extrahepatic bile duct cancer with intraductal ultrasonography. Am J Gastroenterol. 1995;90:239–46.
74. Tamada K, Nagai H, Yasuda Y, Tomiyama T, Ohashi A, Wada S, et al. Transpapillary intraductal US prior to biliary drainage in the assessment of longitudinal spread of extrahepatic bile duct carcinoma. Gastrointest Endosc. 2001;53:300–7.
75. Tamada K, Ido K, Ueno N, Ichiyama M, Tomiyama T, Nishizono T, et al. Assessment of hepatic artery invasion by bile duct cancer using intraductal ultrasonography. Endoscopy. 1995;27:579–83.

76. Tamada K, Ido K, Ueno N, Ichiyama M, Tomiyama T, Nishizono T, et al. Assessment of portal vein invasion by bile duct cancer using intraductal ultrasonography. Endoscopy. 1995;27:573–8.
77. Inui K, Miyoshi H, Yoshino J. Bile duct cancers: what can EUS offer? Intraductal us, 3d-IDUS? FNA – is it possible? Endoscopy. 2006;38:47–9.
78. Pollack MJ, Gholam PM, Chak A. EUS-FNA in unresectable cholangiocarcinoma: a novel indication. Gastrointest Endosc. 2008;67:444–5.
79. Noda Y, Fujita N, Kobayashi G, Ito K, Horaguchi J, Takasawa O, et al. Prospective study of intraductal ultrasonography before biliary drainage (IDUS-BD), transpapillary biopsy (TPB) and peroral cholangioscopy (POCS) in assessment of the longitudinal extent of bile duct cancer. Gastrointest Endosc. 2008;67:AB156–7.
80. Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. Am J Gastroenterol. 2004;99:523–6.
81. Farrant JM, Hayllar KM, Wilkinson ML, Karani J, Portmann BC, Westaby D, et al. Natural history and prognostic variables in primary sclerosing cholangitis. Gastroenterology. 1991;100:1710–7.
82. Rosen CB, Nagorney DM, Wiesner RH, Coffey RJ, LaRusso NF. Cholangiocarcinoma complicating primary sclerosing cholangitis. Ann Surg. 1991;213:21–5.
83. Hyodo T, Hyodo N, Yamanaka T, Imawari M. Contrast-enhanced intraductal ultrasonography for thickened bile duct wall. J Gastroenterol. 2001;36:557–9.
84. Ang TL, Teo EK, Fock KM. EUS-guided transduodenal biliary drainage in unresectable pancreatic cancer with obstructive jaundice. JOP. 2007;8:438–43.
85. Bories E, Pesenti C, Caillol F, Lopes C, Giovannini M. Transgastric endoscopic ultrasonography-guided biliary drainage: results of a pilot study. Endoscopy. 2007;39:287–91.
86. Burmester E, Niehaus J, Leineweber T, Huetteroth T. EUS-cholangio-drainage of the bile duct: report of 4 cases. Gastrointest Endosc. 2003;57:246–51.
87. Giovannini M, Moutardier V, Pesenti C, Bories E, Lelong B, Delpero JR. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. Endoscopy. 2001;33:898–900.
88. Kahaleh M, Hernandez AJ, Tokar J, Adams RB, Shami VM, Yeaton P. Interventional EUS-guided cholangiography: evaluation of a technique in evolution. Gastrointest Endosc. 2006;64:52–9.
89. Mallery S, Matlock J, Freeman ML. EUS-guided rendezvous drainage of obstructed biliary and pancreatic ducts: report of 6 cases. Gastrointest Endosc. 2004;59:100–7.
90. Puspok A, Lomoschitz F, Dejaco C, Hejna M, Sautner T, Gangl A. Endoscopic ultrasound guided therapy of benign and malignant biliary obstruction: a case series. Am J Gastroenterol. 2005;100:1743–7.
91. Tarantino I, Barresi L, Repici A, Traina M. EUS-guided biliary drainage: a case series. Endoscopy. 2008;40:336–9.
92. Will U, Thieme A, Fueldner F, Gerlach R, Wanzar I, Meyer F. Treatment of biliary obstruction in selected patients by endoscopic ultrasonography (EUS)-guided transluminal biliary drainage. Endoscopy. 2007;39:292–5.

93. Yamao K, Bhatia V, Mizuno N, Sawaki A, Ishikawa H, Tajika M, et al. EUS-guided choledochoduodenostomy for palliative biliary drainage in patients with malignant biliary obstruction: results of long-term follow-up. Endoscopy. 2008;40:340–2.
94. Fujita NY. Analysis of the layer structure of the gallbladder wall delineated by endoscopic ultrasound using the pinning method. Dig Endosc. 1995;7:353–6.
95. Watanabe Y, Goto H, Naitoh Y, Hirooka Y, Itoh A, Taki T, et al. Usefulness of intraductal ultrasonography in gallbladder disease. J Ultrasound Med. 1998;17:33–9.
96. Engel JM, Deitch EA, Sikkema W. Gallbladder wall thickness: sonographic accuracy and relation to disease. AJR Am J Roentgenol. 1980;134:907–9.
97. Dahan P, Andant C, Lévy P, Amouyal P, Amouyal G, Dumont M, et al. Prospective evaluation of endoscopic ultrasonography and microscopic examination of duodenal bile in the diagnosis of cholecystolithiasis in 45 patients with normal conventional ultrasonography. Gut. 1996;38:277–81.
98. Cooperberg P, Golding RH. Advances in ultrasonography of the gallbladder and biliary tract. Radiol Clin N Am. 1982;20:611–33.
99. Jørgensen T, Jensen KH. Polyps in the gallbladder. A prevalence study. Scand J Gastroenterol. 1990;25:281–6.
100. Chen CY, Lu CL, Chang FY, Lee SD. Risk factors for gallbladder polyps in the Chinese population. Am J Gastroenterol. 1997;92:2066–8.
101. Kubota K, Bandai Y, Noie T, Ishizaki Y, Teruya M, Makuuchi M. How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy? Surgery. 1995;117:481–7.
102. Owen CC, Bilhartz LE. Gallbladder polyps, cholesterolosis, adenomyomatosis, and acute acalculous cholecystitis. Semin Gastrointest Dis. 2003;14:178–88.
103. Sugiyama M, Atomi Y, Kuroda A, Muto T, Wada N. Large cholesterol polyps of the gallbladder: diagnosis by means of US and endoscopic US. Radiology. 1995;196:493–7.
104. Sugiyama M, Atomi Y, Yamato T. Endoscopic ultrasonography for differential diagnosis of polypoid gall bladder lesions: analysis in surgical and follow up series. Gut. 2000;46:250–4.
105. Friess H, Holzinger F, Liao Q, Büchler MW. Surveillance of pre-malignant disease of the pancreatico-biliary system. Best Pract Res Clin Gastroenterol. 2001;15: 285–300.
106. Raghavendra BN, Subramanyam BR, Balthazar EJ, Horii SC, Megibow AJ, Hilton S. Sonography of adenomyomatosis of the gallbladder: radiologic-pathologic correlation. Radiology. 1983;146:747–52.
107. Yang HL, Sun YG, Wang Z. Polypoid lesions of the gallbladder: diagnosis and indications for surgery. Br J Surg. 1992;79:227–9.
108. Kozuka S, Tsubone N, Yasui A, Hachisuka K. Relation of adenoma to carcinoma in the gallbladder. Cancer. 1982;50:2226–34.
109. Levy AD, Murakata LA, Abbott RM, Rohrmann CA. From the archives of the AFIP. Benign tumors and tumorlike lesions of the gallbladder and extrahepatic bile ducts: radiologic-pathologic correlation. Armed Forces Institute of Pathology. Radiographics. 2002;22:387–413.
110. Azuma T, Yoshikawa T, Araida T, Takasaki K. Differential diagnosis of polypoid lesions of the gallbladder by endoscopic ultrasonography. Am J Surg. 2001;181: 65–70.

111. Choi WB, Lee SK, Kim MH, Seo DW, Kim HJ, Kim DI, et al. A new strategy to predict the neoplastic polyps of the gallbladder based on a scoring system using EUS. Gastrointest Endosc. 2000;52:372–9.
112. Boulton RA, Adams DH. Gallbladder polyps: when to wait and when to act. Lancet. 1997;349:817.
113. Karlsen TH, Schrumpf E, Boberg KM. Gallbladder polyps in primary sclerosing cholangitis: not so benign. Curr Opin Gastroenterol. 2008;24:395–9.
114. Sadamoto Y, Oda S, Tanaka M, Harada N, Kubo H, Eguchi T, et al. A useful approach to the differential diagnosis of small polypoid lesions of the gallbladder, utilizing an endoscopic ultrasound scoring system. Endoscopy. 2002;34:959–65.
115. Sugiyama M, Xie XY, Atomi Y, Saito M. Differential diagnosis of small polypoid lesions of the gallbladder: the value of endoscopic ultrasonography. Ann Surg. 1999;229:498–504.
116. Chung JP, Lee SJ, Lee KS, Chung JB, Lee SI, Kang JK. EUS and the prediction of gallbladder neoplastic polyps: are polyps of 5 to 15 mm diameter really a homogenous group? Gastrointest Endosc. 2001;54:138–9.
117. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer. 2006;118:1591–602.
118. Aldouri A, Malik H, Waytt J, Khan S, Ranganathan K, Kummaraganti S, et al. The risk of gallbladder cancer from polyps in a large multiethnic series. Eur J Surg Oncol. 2009;35:48–51. doi:10.1016/j-ejso.2008.01.036.
119. Chijiiwa K, Sumiyoshi K, Nakayama F. Impact of recent advances in hepatobiliary imaging techniques on the preoperative diagnosis of carcinoma of the gallbladder. World J Surg. 1991;15:322–7.
120. Guermazi A. Are there other imaging features to differentiate xanthogranulomatous cholecystitis from gallbladder carcinoma? Eur Radiol. 2005;15:1271–2.
121. Levy AD, Murakata LA, Rohrmann CA. Gallbladder carcinoma: radiologic-pathologic correlation. Radiographics. 2001;21:295–314. questionnaire, 549–55.
122. Shirai Y, Yoshida K, Tsukada K, Ohtani T, Muto T. Identification of the regional lymphatic system of the gallbladder by vital staining. Br J Surg. 1992;79:659–62.
123. Bartlett DL. Gallbladder cancer. Semin Surg Oncol. 2000;19:145–55.
124. Bartlett DL, Fong Y, Fortner JG, Brennan MF, Blumgart LH. Long-term results after resection for gallbladder cancer. Implications for staging and management. Ann Surg. 1996;224:639–46.
125. Dixon E, Vollmer CM, Sahajpal A, Cattral M, Grant D, Doig C, et al. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: a 12-year study at a North American center. Ann Surg. 2005;241:385–94.
126. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
127. Fujita N, Noda Y, Kobayashi G, Kimura K, Yago A. Diagnosis of the depth of invasion of gallbladder carcinoma by EUS. Gastrointest Endosc. 1999;50:659–63.
128. Sadamoto Y, Kubo H, Harada N, Tanaka M, Eguchi T, Nawata H. Preoperative diagnosis and staging of gallbladder carcinoma by EUS. Gastrointest Endosc. 2003;58:536–41.
129. Weber SM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Staging laparoscopy in patients with extrahepatic biliary carcinoma. Analysis of 100 patients. Ann Surg. 2002;235:392–9.

130. Jacobson BC, Waxman I, Parmar K, Kauffman JM, Clarke GA, Van Dam J. Endoscopic ultrasound-guided gallbladder bile aspiration in idiopathic pancreatitis carries a significant risk of bile peritonitis. Pancreatology. 2002;2:26–9.
131. Jacobson BC, Pitman MB, Brugge WR. EUS-guided FNA for the diagnosis of gallbladder masses. Gastrointest Endosc. 2003;57:251–4.
132. Varadarajulu S, Eloubeidi MA. Endoscopic ultrasound-guided fine-needle aspiration in the evaluation of gallbladder masses. Endoscopy. 2005;37:751–4.
133. Ootani T, Shirai Y, Tsukada K, Muto T. Relationship between gallbladder carcinoma and the segmental type of adenomyomatosis of the gallbladder. Cancer. 1992;69:2647–52.
134. Rodríguez-Fernández A, Gómez-Río M, Medina-Benítez A, Moral JV-D, Ramos-Font C, Ramia-Angel JM, et al. Application of modern imaging methods in diagnosis of gallbladder cancer. J Surg Oncol. 2006;93:650–64.
135. Kim SJ, Lee JM, Lee JY, Choi JY, Kim SH, Han JK, et al. Accuracy of preoperative T-staging of gallbladder carcinoma using MDCT. AJR Am J Roentgenol. 2008;190:74–80.