Patients with Biliary Stricture

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Introduction

The differentiation of biliary strictures remains a diagnostic dilemma in clinical practice because a significant proportion of strictures are inconclusive for malignancy despite a thorough radiologic, endoscopic, and laboratory evaluation. As an abnormal narrowing of the bile duct, biliary strictures can be caused by diverse benign and malignant processes. These are designated as indeterminate when basic work-up, including cross-sectional imaging and ERCP with routine brush cytology and/or forceps biopsy are nondiagnostic.

Recently, the major technical advance in the field of diagnostic endoscopy has been the development of improved systems to directly visualize and assess intraductal mucosa. In this review, recent advances in endoscopic and diagnostic techniques will be outlined, and their application in the diagnosis of biliary strictures will be discussed.

Conventional diagnostic work-up

Transabdominal ultrasonography is usually used as an initial diagnostic modality to evaluate the dilated bile duct. However, it does not reliably examine the distal common bile duct due to the interference of bowel gas. Cross sectional image such as MDCT had provided little definitive diagnostic information in the setting of indeterminate structures without a mass lesion and its tendency to underestimate the extent of proximal tumors. Since its introduction in 1991, MRCP has emerged as an accurate and noninvasive modality for biliary imaging. However, its specificity and positive predictive values are suboptimal because it cannot reliably distinguish malignant strictures from other strictures caused by benign etiologies. Moreover, the accuracy of MRCP in the assessment of vascular and hepatic parenchymal involvements is only 67% to 73% and 78% to 80%, respectively. Although some ductal features on MRCP such as long (>10 mm), asymmetric, and irregular strictures may suggest malignancy, these criteria are not particularly sensitive or specific. Therefore, unless radiologic imaging detects biliary mass lesions, further endoscopic work-up is usually warranted to determine the etiology of biliary strictures.

For more than last 35 years, endoscopic retrograde cholangiopancreatography (ERCP) has been the standard procedure that used to evaluate disorders of the biliary tract and pancreatic duct; it combines endoscopy and fluoroscopy to diagnose and treat problems of the biliary or pancreatic ductal systems. Accompanying biliary brush cytology during ERCP remains the initial approach for tissue sampling of biliary strictures because of its wide availability and technical ease. However, most studies reported a poor sensitivity of 27% to 56%. Different techniques or additional procedures for increasing the sensitivity were reported in several articles. These included novel brushing devices, biliary stricture dilation with subsequent brushings, repeated brushings, endoscopic needle aspiration, additional immunohistochemical staining, and mutational analysis. But most data revealed marginal benefit. Endobiliary forceps biopsy for biliary strictures during ERCP is another endoscopic technique for histologic diagnosis. In general, forceps biopsies had the highest yield when compared with brush cytology and percutaneous biopsy. Cancer detection rates using endobiliary forceps range from
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44% to 89% for cholangiocarcinoma. However, forceps biopsy for biliary strictures remains technically challenging, especially for proximal biliary strictures and complications, including bleeding and biliary perforation, have been described.

Advances in endoscopic procedures for differentiation of biliary strictures

1. Peroral cholangioscopy

Direct visualization of the bile duct is the principal advantage of cholangioscopy compared with other modalities. Cholangioscopy provides more thorough examination of the biliary tract and targeted biopsies of suspected malignancies. Peroral cholangioscopy is appealing to endoscopists because of those desires. 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. These irregular and dilated vessels are due to neovascularization at the site of the stricture because of tumor growth.

Direct peroral cholangioscopy was first described in 1970s, but original “mother-baby” endoscope has failed to gain wider clinical use due to several obstacles, including poor image quality, the requirement of two-skilled endoscopists, limitation of scope tip deflection, and easy fragility. Despite all its shortcomings, it proved the feasibility of peroral cholangioscopy. In the mid-1980s, second generation cholangioscopy had added up tip deflection and an accessory channel that could be used either for irrigation or instrumentation. In the late 1990s and early in the new millennium, advanced imaging technology led to the introduction of video cholangioscopy with improved image quality that enabled satisfactory views of the biliary mucosa. Furthermore, cholangioscopy-guided visually targeted tissue sampling was shown to significantly improve the differentiation of biliary strictures comparing with ERCP alone.

In late 2006, renewed interest in a single operator cholangioscopy (SOC) system has arisen from the introduction of SpyGlass Direct Visualization System (Boston Scientific Corp, Natick, MA, USA), which overcomes some of limitations. Currently, the two main indications for its use are evaluation of indeterminate biliary strictures and lithotripsy for difficult-to-remove biliary stones. Recently published prospective data reveals that the overall success rates for adequate tissue sampling and bile duct stone clearance are around 90%, with an acceptable safety profile. Chen et al reported a multicenter prospective experience of SOC procedures in 15 tertiary centers of USA and Europe. Of 297 patients enrolled, procedural success was achieved in 89%. Of 140 patients undergoing SOC to investigate an indeterminate biliary stricture, sufficient material for histological examination was obtained in 88%, and a definitive diagnosis was achieved in 85%. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for diagnosing malignancy based on visual impression alone was 78%, 82%, 80%, and 80%, respectively. For SOC directed biopsy, the respective results were 49%, 98%, 100%, and 72%. Especially, sensitivity of malignancy on visual impression was higher for intrinsic bile duct malignancies as compared with extrinsic malignancies (84% and 62%, respectively). Diagnostic SOC procedures altered clinical management in 64% of patients. The incidence of procedure-related adverse events for diagnostic SOC was 7.5% including cholangitis, pancreatitis, transient events of bacteremia and hypotension, and abdominal pain/distension.

Another single center study by Ramchandani et al in 36 patients with indeterminate biliary strictures described sensitivity and specificity for visual impression of SOC as 95% and 79%, respectively. These results suggest a benefit of SOC in patients with indeterminate biliary strictures because of visual impression of tumor vessels showed specificity up to 100% for malignancy. Although intraductal nodules and masses can be visualized during cholangioscopy and are indicative of malignancy, these ductal findings are visualized in only a fraction of patients with cholangiocarcinoma.
Overall, the sensitivity of SpyGlass for detecting cancer in intrinsic biliary strictures is superior to that of standard ERCP sampling modalities. The two main limitations are image quality that is impeded by the use of fiberoptic technology and a relatively small accessory channel providing passage only for dedicated miniaccessories. Also, the interobserver variability and reproducibility of such visual criteria are not known. An upgraded digital imaging version is currently in development.

Recently, new video baby endoscope (Olympus Optical Co. Ltd, Tokyo, Japan) with narrow band image (NBI) system was developed. It is based on modifying/narrowing the bandwidth of spectral transmittance resulting in optical color separation. The filter is placed in the optical illumination system and removes all light wavelengths except for two narrow wavelengths, 415 nm and 540 nm. The shorter band gives information about the capillary and pit patterns of the superficial mucosa, whilst the longer wavelength does about thicker capillaries in slightly deeper tissues. Addition of narrow band imaging (NBI) capability led to further improvements in detection of abnormal vascularization of biliary mucosa, which is important to diagnose biliary malignancies.

To date, published literatures regarding to NBI cholangioscopy are limited to case reports and small caser series.36-38 The largest case series evaluated 21 lesions in 12 patients who underwent peroral cholangioscopy with NBI.36 The authors evaluated the clinical feasibility and ability using peroral cholangioscopy with NBI to identify biliary lesions comparing to conventional peroral cholangioscopy. In this small case series, only two lesions with conventional white light cholangioscopies were rated as excellent visualization in comparison with 12 lesions with NBI. Also, NBI identified four strictures not seen with standard peroral cholangioscopy. They suggested that observation of biliary mucosa and its related vessels was as good as or better than conventional observation and video cholangioscopy with NBI may be helpful in differentiating benign from malignant strictures. A limitation of NBI cholangioscopy is that bile and blood both appear as dark red fluid, possibly limiting views.

As an alternative approach to biliary access, ultrathin videoendoscopes (5-6mm diameter tip, with 2mm working channel) provides excellent digital imaging of the biliary mucosa, but the challenge remains as to how best to access the biliary tree, and maintain endoscope position. Direct peroral intubation of the biliary tree using ultrathin gastroscopes has been reported,39,40 but is technically challenging, mainly due to the need for sharp angulation in the duodenum. The most widely used technique involves initial wire placement within the biliary tree at standard ERCP, removal of the duodenoscope, leaving the wire in place, and subsequent insertion of the ultrathin endoscope over the wire. As well as being labor intensive, this two-step procedure carries a failure rate of nearly 50%.40 One-step pernasal cholangioscopy using ultrathin gastroscopes has also been reported in a study of 25 patients from a specialist unit, with success rate of 72% and no significant complications.41 The use of an overtube to maintain endoscope stability in the duodenum has also been reported to improve procedural success to more than 80%.42,43 Improved ultrathin endoscope insertion and stability may be achieved with a recently devised anchoring balloon, but this system has been withdrawn due to cases of fatal embolism associated with hepatic trauma.44 As well as issues related to biliary access, SOC with ultrathin endoscopes hampered by the need for prior biliary sphincterotomy in the great majority (e.g. via conventional ERCP), and the inability to insert adequate diameter biliary stents of more than 5F diameter through the working channel.

2. Endoscopic ultrasonography (EUS)

Although common hepatic duct and hilar strictures cannot be visualized well, EUS allows detailed examination of the extrahepatic biliary tree because of the proximity of the US probe to the course of the bile duct.45 Endosonographic examination of the bile duct is typically started at the level of ampulla.46 By slowly withdrawing and counterclockwise rotating the scope toward the pylorus region, the entire bile duct can be evaluated. A longitudinal image of the bile duct can be
The utility of EUS findings in evaluating unexplained biliary strictures was mentioned by Lee et al.47 The presence of a pancreatic head mass, an irregular bile duct wall, or a bile duct wall thickness of >3 mm on EUS were associated with malignancy in indeterminate biliary strictures. The sensitivity, specificity, PPV, and NPV of EUS for detecting malignancy were 88%, 100%, 100%, and 84%, respectively. However, these findings did not firmly establish the presence or absence of cancer.

Using EUS-guided fine needle aspiration (EUS-FNA), EUS has an advantage of establishing the diagnosis of indeterminate biliary strictures. In the two series that reported patients with prior negative ERCP-guided intraductal tissue sampling, sensitivity of EUS was 77% and 89%, highlighting the ability of EUS-FNA to diagnose malignancy with negative ERCP-guided tissue sampling. Another advantages of EUS-FNA have (1) high sensitivity for diagnosis of cholangiocarcinoma in patients with prior negative imaging and nondiagnostic ERCP with brushing, (2) ability to visualize bile duct mass lesions and regional lymph nodes not previously seen on abdominal imaging, (3) avoid unwarranted surgical interventions by diagnosing benign disease or metastatic spread to distant lymph nodes, and (4) aid in triaging patients to alternative therapies (eg, photodynamic therapy, chemoradiation therapy).46 However, EUS-FNA of suspected extrahepatic cholangiocarcinoma can be technically difficult, especially in Klatskin tumors.

Multiple studies have reported on the use of EUS-FNA for the diagnosis of biliary strictures.45,47-54 The reported sensitivity of EUS-FNA for the diagnosis of cholangiocarcinoma in patients with indeterminate extrahepatic biliary strictures ranges between 43% and 89%. 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. EUS-FNA is feasible in most cases because a mass or bile duct wall thickening can be visualized.

Two clinical aspects such as the location of stricture and the presence of a bile duct stent may impact the sensitivity of EUS-FNA for biliary strictures. Mohamadnejad et al48 compared sensitivity of EUS-FNA of proximal and distal cholangiocarcinoma and found significantly lower sensitivity for proximal tumors (59% vs. 81%). This could be explained by the relative ease of visualizing and sampling distal bile duct lesions. In contrast, diagnosis and sampling for more proximal lesions are challenging, because proximal lesions are further from the tip of the echoendoscope and are closer to the liver parenchyma. 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 to perform FNA of the contralateral side of the tumor.48 Some studies found that the presence of a bile duct stent did not negatively impact the yield of EUS-FNA where high diagnostic sensitivity was reported.45 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. EUS-FNA has been reported to be relatively safe and without significant adverse events reported. The risk of cholangitis is decreased by establishing biliary drainage with stent placement before or immediately after the EUS procedure.

A major concern with EUS-FNA of bile duct strictures is the potential for needle track tumor seeding, or the implantation of cancer cells along the pathway of a needle. Some experts discourage EUS-FNA of primary biliary lesions in patients who are potential candidates for curative-intent surgery because the EUS needle traverses peritoneum and omental fat that will not be resected.55 However, no cases of tumor seeding have been reported in EUS-FNA of extrahepatic cholangiocarcinoma. 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 be-
come available.

3. Intraductal ultrasonography (IDUS)

Intraductal ultrasonography (IDUS) is a promising imaging modality for the evaluation of a variety of biliary disorders.56,57 IDUS probes operate at a high frequency, and produce detailed images of the bile duct wall and adjacent structures. During ERCP, the IDUS catheter can be easily and safely placed into the bile duct via a transpapillary route.58-60 These small caliber probes are placed over a guidewire, and can be positioned in the bile duct without the need for sphincterotomy.

Sonographic features 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.58 IDUS has consequently emerged as an adjunct to ERCP in the evaluation of biliary strictures. The accuracy of these criteria in patients with biliary strictures ranges from 83% to 90%.60-62

Although IDUS does not provide tissue diagnoses, the characterization of biliary structures provided by IDUS can be used in combination with other diagnostic approaches to develop appropriate therapeutic strategies. However, IDUS is limited in the repeated evaluation of strictures, because the presence of a previously placed biliary stent affects its diagnostic yield.47 IDUS can provide the local staging to select patients with cholangiocarcinoma who benefit from surgical resection.63,64 Recently, Stavropoulos et al62 reported that IDUS increased the accuracy of ERCP in distinguishing between benign and malignant strictures from 58% to 90%. This high rate of diagnostic accuracy using intraductal ultrasonography has been confirmed by others.60,65

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.48

4. Probe-based confocal laser endomicroscopy (pCLE)

Confocal laser endomicroscopy (CLE) is a novel imaging technique which utilizes focal laser illumination to scan one focal plane in the selected imaged lesion and provides a microscopic view of the surface epithelium and up to 250 μm of the lamina propria creating a “virtual biopsy” of the area of interest.66

To obtain a high contrast image, 1-5 mL of 10% fluorescein sodium is given intravenously 1-2 minutes prior to image acquisition.67,68 The contrast material diffuses through the capillaries and stains the extracellular matrix of the surface epithelium. The nuclei do not absorb the contrast and appear dark. This difference in contrast allows architectural analysis of the surface mucosa and aids in differentiating normal mucosa from neoplastic tissue. The pCLE images of normal CBD shows a thin black band (<20 μm) and normal vessels (thin and regular).69 Glands are not visible in benign cases. Malignant strictures display irregular vessels without contrast in the CBD wall, a large thick black band (>20 μm). Currently there are two devices which allow CLE of the surface mucosa, one for using upper endoscope and colonoscope (GastroFlex UHD miniprobe) and the other for pancreatobiliary duct during ERCP (CholangioFlex miniprobe, Mauna Kea Technologies, Paris, France).

In a pilot study of 14 patients with indeterminate biliary strictures, Meining et al67 used pCLE to differentiate malignant from benign strictures based on the presence of large, irregular micro-vessels with a sensitivity, specificity, and overall diagnostic accuracy for detection of neoplasia were 83%, 88%, and 86%, respectively. In this initial clinical experience, followed by 1-year follow-up to confirm benignity findings, the overall accuracy of pCLE was found to be superior to conventional biliary brushings cytology and forceps biopsy.
Meining et al’s studies proposed imaging criteria of pCLE for diagnosing malignancy in indeterminate biliary strictures. Criteria include loss of reticular pattern of epithelial bands of less than 20 μm; detection of irregular epithelial lining, villi, or glandlike structures; tortuous, dilated, and saccular vessels with inconsistent branching; and presence of “black areas” of more than 60 to 80 μm (locally decreased uptake of fluorescein).

In a recent multicenter study of probe-based CLE (used with cholangioscopy or ERCP) in 89 patients with indeterminate biliary strictures, CLE was found to provide a significantly higher accuracy for the diagnosis of malignant biliary strictures than achieved by ERCP with tissue acquisition alone (90 vs. 73%). This accuracy appears to be particularly enhanced by visually targeting mucosa via cholangioscopy as opposed to fluoroscopically guided catheter delivery of the CLE probe, although differences did not reach statistical significance (83 vs. 73%, respectively). There were no CLE-related adverse events.

In 2012, a uniform classification of biliary and pancreatic pCLE findings (“Miami classification”) for indeterminate strictures was developed. The set of image interpretation criteria were tested through blinded consensus review of 112 randomized pCLE videos from 47 patients, and interobserver variability was assessed in 42 patients. The characteristics most suggestive of malignancy included the following: thick white bands (>20 μm), or thick dark bands (> 40 μm), or dark clumps or epithelial strictures. These provided respective sensitivity, specificity, PPV, and NPV of 98%, 67%, 71%, and 97% compared with 45%, 100%, 100%, and 69% for standard tissue sampling methods.

However, pCLE for differentiation of biliary strictures 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 and interobserver agreement of pCLE in the evaluation of biliary strictures need further study.

5. 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 pancreaticobiliary strictures. FISH analysis detects chromosomal polysomy by using fluorescent probes, whereas DIA technique quantifies nuclear DNA via special stains to assess the presence of aneuploidy.

FISH is a technique that utilizes fluorescently labeled DNA probes to detect cells of chromosomal abnormalities (abnormal loss or gain of chromosomes or chromosomal loci). Levy et al found that FISH improved sensitivity 14% to 24% when routine cytology was negative. Fritcher et al found that patients with abnormal FISH results were 77 times more likely to have carcinoma than those with normal FISH results. 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. A recent report studied the additional value of including deletion of 9p21 (p16) in the diagnostic criteria of FISH for malignant biliary strictures. This addition significantly improved the sensitivity of FISH from 47% to 84%. Benign strictures in patients with primary sclerosing cholangitis may manifest chromosomal abnormalities and showed lower specificity of FISH than that of routine cytology. However, the sensitivity of FISH for malignancy in this setting is still higher than that of routine cytology at 72%. As FISH increases the sensitivity of brush cytology of indeterminate biliary strictures at the expense of a lower specificity, it should be reserved for patients with high pretest probability for malignant strictures.

DIA is a specialized technique of cytologic analysis that quantifies abnormalities of nuclear DNA (aneuploidy or tetraploidy) by using spectrophotometric principals. Using these techniques, small numbers of tumor cells can be analyzed in
contrast to flow cytometry where a larger number of cells are required for analysis. Fritcher et al found DIA had a higher sensitivity (44.8%) than cytology. However, they reported that DIA showed significantly lower specificity (89.1%) and found that DIA was not a significant independent predictor of malignancy. The Mayo Clinic has examined the use of DNA histograms for detecting aneuploidy, but with disappointing results. In a series of 100 patients (56 with malignancy and 44 with a benign stricture), the sensitivity of routine cytology was only 18%. When digital image analysis of the DNA histograms was employed, there was an increase in the diagnostic sensitivity to 39%. Overall, the accuracy of digital image analysis was not thought to be significantly better than routine cytology.

Conclusions

Accurate diagnosis of biliary strictures is essential in therapeutic planning, both to avoid unnecessary surgery for benign strictures and to indicate surgery and/or radiochemotherapy in case of malignant strictures. However, the diagnosis remains challenging due to the difficulties to access biliary strictures, visualize the intraductal lesion, and acquire an adequate tissue specimen.

There seems little doubt that cholangioscopy and targeted intrabiliary sampling will find an established clinical role in the diagnosis of biliary disease. 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). However, the 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.

The addition of image-enhancing techniques such as pCLE to cholangioscopy may further enhance the distinction between benign and malignant tissue in the future. FISH may improve the diagnostic sensitivity of routine brush cytology without compromising specificity and be gaining clinical usage. Those newer imaging and ancillary cytologic techniques may improve the diagnostic accuracy of biliary strictures. However, more data are needed before their use can be widely advocated.

It remains to be established whether its wider integration into the diagnostic algorithm for indeterminate strictures reduces the overall number of diagnostic interventions, and allows earlier diagnosis and definitive management. Ongoing studies will further improve the diagnosis of biliary strictures with refinement of endoscopic techniques and ancillary diagnostic procedures.

References

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